Complex Treatment of Erectile Dysfunction with Vascular Factor Deficit by Use of Pluripotent Fetal Stem Cells

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Abstract

Objective: To study the effect of combined therapy including fetal stem cells (FSCs) on different components of erections.

Material and methods: During a period of 2014-2015 years 19 patients with mixed type erectile dysfunction and mandatory vascular factor documented by pharmacodopplerography were under study in Cell Therapy Center EmCell. The program of examination for patients in the Main Group (MG) and Control Group (CG) included the scales of International Index of Erectile Function (IIEF) questionnaire, urine analysis, tests for total and free testosterone, Sex Hormone Binding Globulin (SHBG), Free Androgen Index (FAI), blood glucose and glycosylated Hemoglobin (HbA1c) testing, lipidogram findings, pharmacodopplerography of cavernous vessels, study of cortical and diencephalan components of erection by use of clinical methods and the questionnaires of State-Trait Anxiety Inventory – (STAI) and Beck Depression Inventory (BDI).

Conclusion: combined use of vardenafil and cryopreserved suspensions containing pluripotent FSCs extracted from fetal liver, brain and placenta promotes favorable effect on all components of erections.

Keywords: Erectile function; Complex therapy; Combined use of fetal stem cells; Medicinal preparations

Abbreviations: ED: Erectile dysfunction; T: Testosterone; NO: Nitric monoxide; PDE5: Phosphodiesterase 5; CVOD: Corporal veno occlusive dysfunction; ICB: Intracavernous block; DM: Diabetes mellitus; FSCs: Fetal stem cells; IIEF: International index of erectile function; SHBG: Sex hormone binding globulin; FAI: Free androgen index; STAI: State-trait anxiety inventory; BDI: Beck depression inventory; DMSO: Dimethyl sulfoxide; PgEI: Prostaglandin E1; ici: Intracavernous injections; EDV: End diastolic velocity; PSV: Peak systolic velocity; MSCs: Mesenchymal stem cells; PB: Proximal bypass; ACE: Angiotensin converting enzyme; DNA: De-oxy ribonucleic acid; DNMTs: DNA methyl transferases; HA1c: Hemoglobin A1c, also called Glycated Hemoglobin

Introduction

One can hardly overestimate a significance of erections for support of normal copulative cycle and sexual harmony in particular. Options of modern medicine in correction of Erectile Dysfunction (ED) have been greatly expanded owing to studying some fine mechanisms of erection maintenance since the end of the 20th century and at the beginning of this century.

The following milestones of contemporary andrology are likely to be outlined which effectively facilitate a solution of the problem of ED:

- establishing the options of intracavernous pharmacotherapy [1]
- development of concept on the role of Testosterone (T) in promotion of normal erections [2]
- identifying a significant value of Nitric Monoxide (NO) in neuromuscular conduction and the role of endothelial dysfunction which surmounted a creation of the principally new group of medicines-the inhibitors of Phosphodiesterase 5 (PDE5), these medicines widespread use helped in erections stimulation [3]

Thus, our contemporary ideas about promotion for the mechanisms of erection are based on classification of all factors affecting male erectile function into the executive structures and regulatory mechanisms. The vessels and nerves of penis, cavernous sinuses and tunica albuginea are referred to as the main executive structures. These anatomic and histologic units assure erection on a physical level, and must maintain definite physical and chemical properties for this [4,5]. These structures adequate functioning will be possible if regulatory mechanisms work appropriately and are coordinated:

- Cortical and diencephalic processes.
- Hormonal processes (testosterone in particular).
- Spinal cord centers, afferent and efferent parts in neurological circuit of erectile reflex (S2-S4).
- Prostate gland function.

Inventions of modern andrology have developed a wide panel of medicinal and medication free methods to promote influence on the functional level. The above mentioned list includes: various hormonal drugs; preparations which effectively influence anxiodepressive component; medications for improvement of nervous conduction; physiotherapy and acupuncture methods and, finally, the inhibitors of...
PDE5 – which influence the endothelial cascade of executive structures directly.

The principal mechanisms of normal erection maintenance and likely methods to influence those mechanisms are summarized in the Table 1.

Consequently, existing methods of conservative treatment of ED are not likely to be effective enough if we deal with affection of executive structures (vessels in particular) which are especially important for erections maintenance.

Both insufficiency of arterial inflow (for example, stenosis of arteries) and Corporal Veno Occlusive Dysfunction (CVOD), in particular, belong to such conditions which are related to disturbances of intracavernous block (ICB) owing to a decreased elasticity of sinuses in cavernousum of penis; as well as disruption of physicochemical properties of tunica albuginea and/or aberrant vascular outflow [6-8].

Eventually, overall variety of different methods sustains 2 principal defects:

- Low effect on organic disturbances of ED, for example, in CVOD [9] and in cases of Diabetes Mellitus (DM) [10]; which demands surgery treatment resulting in stubborn psychological discomfort.
- Non-satisfactory long-term follow-up effect: unfortunately, even if effects are reached this frequently demands a continuous maintenance therapy for erections which is likely to be psychologically and economically unfavourable.

As it was mentioned earlier, chronic application of PDE5 inhibitors is a promising exception and such treatment use contributes to recovery of erections giving the patients a chance for medicines-free sexual life in 30-35% of cases [11-14]. Nevertheless, such follow-up treatment effectiveness is not enough and demands searching for the new methods with contemporary solution of this problem.

Increased therapeutic and follow-up effectiveness are likely to be the principal goals for optimal treatment of ED. Treatment by use of Fetal Stem Cells (FSCs) is one of challenging and future-oriented directions. FSCs therapy induces its influence both on a functional level of erections maintenance: cavernous endothelium, nerve receptors, afferent and efferent pathways and, especially, this treatment effects the components on the structural level – smooth muscle tissues and tunica albuginea of penis in particular [15]. It is noteworthy that despite the effect on all functional components nowadays is possible by use of medicinal and non-medicinal methods; there is still a lack of methods to induce non-surgical influence on the smooth muscles, and collagen of tunica albuginea, especially [5]. Therefore, approach by use of stem cell treatment (methods of regenerative biotechnology medicine) is likely to be progressive in the context of the “window of opportunity” along with a conservative treatment.

Currently accumulated data about stem cells use both on animal models and in clinical practice prove that biotechnology medicine is perspective in treatment of various chronic diseases, and vascular disorders in particular. Thus, according to Sytenko, administration of pluripotent FSCs by use of intracavernous injections to the rats revealed a significant elevation of a count of cavernous smooth muscle cells. This therapy is likely to exert positive influence on the quality of erections [15]. In accordance with observations of Klunnyk et al. additional positive action of FSCs on morphology-functional properties of the left ventricle myocardium was established as a result of stem cells transplantation along with a standard treatment; moreover, cells fixed influence on a structural component of the myocardium was documented in the study [16,17]. Also there are interesting data after Smikodub et al. in regard to FSCs use in treatment of complications including vascular and those induced by type 2 Diabetes Mellitus (DM) [18].

The aim of our study was investigation on effective use of FSCs in combined treatment of vascular disturbances of erections. Enhancing conservative efficacy and a long-term follow-up effect in treatment of ED was the principal purpose of this work.

**Material and Methods**

19 patients with ED of combined genesis were under study at Cell Therapy Center EmCell during a period of 2014-2015 years. Mixed type ED included mandatory vascular factor which was recorded by pharmacodopplerography studies. Investigation profile of the patients included the scales of International Index of Erectile Function (IIEF) questionnaire, urine analysis, tests for total and free testosterones, Sex Hormone Binding Globulin (SHBG), Free Androgen Index (FAI), blood glucose and glycosylated Hemoglobin (HbA1c) tests, lipogram findings, pharmacodopplerography of cavernous vessels, study of erections cortical and diencephalon components by use of the questionnaires of State-Trait Anxiety Inventory-(STAI) and Beck Depression Inventory (BDI).

All patients were allocated into 2 groups: the Main Group (MG) including 9 male patients and their average age made up 53.4 ± 2.1 years

<table>
<thead>
<tr>
<th>Mechanisms</th>
<th>Causes of disturbances</th>
<th>Correction methods</th>
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<tbody>
<tr>
<td>Cortical-diencephalic</td>
<td>Depression</td>
<td>Psychotherapy</td>
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<td></td>
<td>Anxiety</td>
<td>Pharmacotherapy</td>
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<td></td>
<td>Insomnia</td>
<td>Acupuncture</td>
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<td></td>
<td>Intoxication</td>
<td>Detoxication</td>
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<td>Endocrine</td>
<td>Diabetes Mellitus</td>
<td>Hormonotherapy</td>
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<td></td>
<td>Androgenic deficiency</td>
<td>Adaptogens</td>
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<td></td>
<td>Hyperprolactinemia</td>
<td>Herbal (vitamin) therapy</td>
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<td>Vascular</td>
<td>Diabetes Mellitus</td>
<td>PDE 5 inhibitors, Intracavernous pharmacotherapy, Physical therapy, NO-metabolism optimization Surgical treatment</td>
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<td>Atherosclerosis</td>
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<td>Endarteritis</td>
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<td></td>
<td>Varicose syndrome (dysplastic connective tissue syndrome)</td>
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<tr>
<td>Neurogenic</td>
<td>Demyelination diseases</td>
<td>Pharmacotherapy</td>
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<td></td>
<td>Stroke</td>
<td>Acupuncture</td>
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<td></td>
<td>Neuropathies</td>
<td>Physical therapy</td>
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<td>Surgical treatment</td>
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Table 1: Principal mechanisms of erection maintenance and methods of correction.
The patients received combined treatment for the vascular factor of ED using a course therapy by vardenafil medication in daily therapeutic dose of 10 mg, and complex regenerative therapy with FSCs extracted from fetal liver, brain and placenta.

The patients in the Control Group (CG) which included 10 men with average age of 54.2 ± 1.8 years were suggested only a course of treatment by vardenafil in the same dose (10 mg/day, every day, over a period of 3 months).

In complex regenerative therapy we used a cryopreserved suspension containing pluripotent FSCs harvested from the cadaveric fetal tissues of 7-12 weeks gestation and acquired as a result of legal abortions pursuant to family planning and social reasons. All donors of abortive material were practically healthy women and revealed negative test results for hemic infections. Bioethical principles have been strictly adhered over all stages of our study. Biotechnology process of suspension preparing included: extraction of cells from different growth zones of fetus (liver, brain, heart and soft tissues of the embryo) as well as assessment of cell viability, programmed cryopreservation, bacteriology and virology studies. Directly before FSCs injection, a defrost for cryopreserved suspensions was performed by use of water bath thawing at 37°C and viable stem cells were evaluated.

Cryopreservation was performed under the protection of 5% Dimethyl Sulfoxide (DMSO) using 3-phase program for cryopreservation with an initial rate of 1°C/min and initialization for crystals formation. Cell viability was assessed immediately before administration using trypan blue staining. Counting was carried out simultaneously in the Goryaev chamber and 1450001 TC10 TM Automated Cell Counter was used for processing. Cell viability prior to freezing remained 83.0 ± 3.0%. After storage in a low-temperature cryobank at (–196°C) and subsequent heating in a water bath at temperature of +37.5 ± 0.12°C stem cells viability made up 74.8 ± 1.03% in the least.

In regenerative therapy of the patients in the MG we administrated 3 types of suspensions containing FSCs. One preparation included FSCs extracted from fetal liver which we administered both via drip-feed Intravenous (i.v.) infusions and by use of Intracavernous Injections (i.ci) to the patients. Intracavernous injection was made during artificial erections induced by i ci Prostaglandin E1 (PGE1) in a dose of 10-20 mcg. The dose of PGE1 was individually selected under control of pharmacodopplerography and the rate of End Diastolic Velocity (EDV) was the main criterion for injection, which had to be 5 cm/s and less at the moment of FSCs administration. Such an approach facilitated the maximal temporary isolation of the cavernosum which was an optimal condition for topic implantation of FSCs. The 2nd medication included FSCs that were obtained from fetal brain and the 3rd preparation in suspension was made of FSCs extracted from placenta accordingly. The 2nd and 3rd medications were administered subcutaneously into abdominal periumbilical area.

Embryonic material containing FSCs was harvested in the surgery room in conformity with aseptic and antisepsic rules. Extracted FSCs suspensions were later exposed to cryopreservation inside of the programmed freezing chamber Sylab Icecube series 14 S (Australia, 2012). After that suspension was placed into the test tubes in volume of 0.3-1.0 mL to be cryopreserved.

Such a cryopreservation technique allows unlimited period of storage for FSCs suspension and enables conducting intensive safety screening for infections with definition of quality and quantity parameters of a suspension.

Suspensions for application satisfied the following requirements:
- fetal liver suspension contained 1.5 × 10^6/mL-3.61×10^6/mL of nucleated stem cells;
- fetal brain suspension contained not less than 3.14×10^6/mL, respectively;
- stem cell suspension of fetal placenta-not less than 5.29×10^6/mL;
- Spec. gravity of viable fetal stem cells made up not less than 70%
- Volume of a suspension per one injection was not less than 1 mL of fetal liver stem cells; fetal brain and placenta suspensions were in volume not less than 0.5 mL per administration.

Storage of all suspensions was in liquid nitrogen at the minimal temperature of (-196°C).

The test-tubes containing suspensions were retrieved from liquid nitrogen and defrosted by water bath thawing at temperature 37.5°C to reach a liquid phase immediately before FSCs application. All subsequent procedures were undertaken in the conditions of indoor temperature and following all aseptic standards. Time between retrieving at indoor temperature and suspension use did not exceed 10 minutes. All patients made their informed consent prior to treatment using FSCs.

The adjuvant therapy was adjusted in case of presence of erections disorders in the patients caused by cortical-diencephalic factors, for example, we applied the medications of vitamalatonin, melitor, stimuloton, afobazol, acupuncture and rational psychotherapy etc. (for anxiodepressive factors and insomnia); for androgen deficiency the patients were suggested hormonal replacement therapy (nebido, omnadren medicines etc.) provided reproductive function was not important for the patient.

Therefore, our main goal was to examine the role of vascular factor in development of ED and likelihood of additional FSCs positive influence on combined therapy effectiveness.

**Results and Discussion**

All study groups were compared and homogeneously correlated in regard to the age of the patients and clinical characteristics. Average age of the patients in the MG was 53.4 ± 2.1 yrs., CG constituted 54.2 ± 1.8 years (р>0.05). The values of cavernous circulation prior to treatment were not significantly different by arterial and venous phases – after comparative analysis of peak systolic and end diastolic velocities (PSV and EDV) which is demonstrable in the Tables 3 and 4 (р>0.05). The average score by IIEF scale in the MG patients made up 15.3 ± 0.6, whereas the same score in the CG constituted 15.5 ± 0.5 (р>0.05). Among the patients of the MG endocrine component was fixed in 8 out of 9 patients, and, furthermore, 5 among them revealed a sub-compensation phase of type 2 DM (HAI<7.5); cortical-diencephalic components of ED (anxiodepressive factors and insomnia) in accordance with the STAI and BDI scales were reported by 7 patients of this group.

Characteristic features of the patients in the CG were similar: an endocrine factor was recorded in 7 patients of the CG; DM – was remarkable for 4 patients; anxiodepressive factors and insomnia in 7 patients. Subsequently, the above correlation between the MG and CG patients is likely to be significant and clinically correct.

Since the principal objective of our study was to investigate FSCs effect on the vascular factor of ED; correction of endocrine and cortical-diencephalic impairment was conducted both for the patients of the...
MG and CG (as it has been mentioned above).

The data according to IIEF scale compared between the groups are shown in the Table 2.

Analysis of data in the Table 2 demonstrates improvement of sexual function over 27% in the MG and over 17% in the CG; it is noteworthy that positive changes in the MG patients were more significant (p<0.01 in the MG versus p<0.05 in the CG); moreover, there is also a significance of likely changes after treatment (p<0.05).

Subsequently, a clinical analysis of treatment effects in the above groups under study has already demonstrated additional positive influence of regenerative therapy on treatment of ED in the patients if compared to the standard approach in therapy of ED. The comparative characteristics of cavernous circulation of the MG and CG in a process of treatment are described in the Tables 3 and 4 accordingly:

Patients of the MG who were administered combined treatment revealed improved inflow on average over 20%, whereas the same value increased by 10% in the patients of the CG.

Results described in the Table 1 prove the evidence about the following:

- All groups under study being statistically homogenous in regard to hemodynamic parameters are correlated in accordance with the values baseline (p>0.05) and this comparison between the groups is correct.

- Deeper positive effects of stem cell therapy along with administration of a course of vardenafil (p<0.05 on the right and p<0.01 on the left) if compared to isolated use of vardenafil in a treatment course (p<0.05 on the right and p>0.05 on the left, respectively).

We suppose likely tendency could be explained by the following factors: arterial inflow depends on definite patency of afferent vessels (helicini e.g.); adequate regulation of vascular endothelium of corpora cavernosa; and on sufficient distensibility of smooth muscle structures in corpora cavernosa. Vardenafil action similarly to the other PDE-inhibitors is mainly directed to the endothelial biochemical conveying system (that is, on the functional level) whereas FSCs combined therapeutic use allows for making a breakthrough to the structural level of erections maintenance. Possible mechanisms of such effects are: maintenance of increased count of smooth muscle cells in the corpora cavernosa as well as neoangiogenesis formation of the new vessels.

Consequently, pluripotent FSCs use in complex treatment contributed to restriction of venous outflow over 10% in the MG; on the contrary, isolated use of vardenafil by the patients in the CG resulted in increase of outflow almost over 30% (negative dynamics).

Analysis of results in the Table 4 gives an evidence of statistic and hemodynamic uniformity of the groups which are compared (p>0.05); and such a comparison is likely to be reasonable.

At the same time, even though no significant difference was observed before and after treatment in both groups, special attention is drawn to

### Table 2: Values by IIEF scale in the patients of the MG and CG.

<table>
<thead>
<tr>
<th></th>
<th>MG (n=9)</th>
<th>CG (n=10)</th>
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<tbody>
<tr>
<td></td>
<td>Right</td>
<td>Left</td>
</tr>
<tr>
<td>PSV</td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>≥ 30 sm/s</td>
<td>23.9 ± 2.0</td>
<td>29.9 ± 0.9 p&gt;0.05; p&lt;0.05</td>
</tr>
<tr>
<td>≤ 5 cm/s</td>
<td>5.5 ± 0.6</td>
<td>4.6 ± 1.3 p&gt;0.05; p&lt;0.05</td>
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P: significant difference between the values baseline; p1: significant difference between the groups before and after treatment.

### Table 3: Dynamics of cavernous circulation (inflow, PSV, cm/s) according to dopplerography data during a treatment course with vardenafil along with FSCs therapy (MG, n=9), and during isolated use of vardenafil treatment course (CG, n=10).

<table>
<thead>
<tr>
<th></th>
<th>MG (n=9)</th>
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<tbody>
<tr>
<td></td>
<td>Right</td>
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<tr>
<td>EDV</td>
<td>Before treatment</td>
<td>After treatment</td>
</tr>
<tr>
<td>≤ 5 cm/s</td>
<td>5.5 ± 0.6</td>
<td>4.6 ± 1.3 p&gt;0.05; p&lt;0.05</td>
</tr>
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P: significant difference between the values baseline; p1: significant difference between the groups before and after treatment.
divergent tendencies in the MG and the CG: if after combined action of vardenafil and mesenchymal stem cells (MSCs) positive tendency is remarkable for the patients (restriction of outflow throughout both of corpora cavernosa) which can likely become significant at more meaningful statistical sampling; whereas in the course of vardenafil isolated use – increase of venous outflow (negative tendency) is observed simultaneously with elevation in arterial inflow (positive tendency).

Such a clinical pattern could be explained by the following: as it is known, vascular maintenance of sufficient erections is achieved at the expense of optimal balance between arterial inflow and venous outflow [19]. In its turn, venous outflow has both passive and active components. Passive component is maintained due to veins pressure to tunica albuginea by cavernous sinuses distended by inflowing blood at time of sexual desire – so called Intracavernous Block (ICB). An active component is reached by reflector spasm of distal circumflex capillary veins.

The mechanisms of Corporeal Venous-Occlusive Dysfunction (CVOD) could be subdivided as follows:

- Proximal Bypass (PB) – venous leakage throughout the aberrant veins.
- Disturbances related to ICB – related to insufficiency of inflow, disruption of distensibility of walls over cavernous sinuses and the changes of viscoelastic properties in tunica albuginea as a result of congenital or acquired damage – collagenopathy).
- Disorders of active reflector regulation of distal circumflex capillary veins [5,20].

Apparently, vardenafil and the other PDE5 inhibitors induce their influence on a passive mechanism of outflow restriction only at the expense of maintaining intense inflow; at the same time inclusion of FSCs to combined therapy option affords us to influence the other mechanisms of venous hemodynamics owing to the following aspects:

- Increase of number of smooth muscle cells due to FSCs – likely enhanced distensibility and passive component.
- Neoangiogenesis to optimize blood inflow in the new vessels which improves the passive component [21].
- Potential improvement of tunica albuginea properties by virtue of FSCs administration maintaining a passive component too.
- Improvement of electrophysiological properties of the neurons and nervous fibers which make provision for erections on account of administered brain FSCs which also enhance the active component.
- Optimization of testosterone metabolism maintained by application of placenta components [22] which contribute to desensitization of cavernous tissue to anti-erection; first of all, via adrenergic effects [23].

It must be emphasized that the study of regenerative therapy influence on neurogenic and hormonal mechanisms of erections maintenance was not regarded as a goal of this article. Therefore, we did not conduct evaluation of dynamics based on objective results of neurology erections maintenance (e.g. pallestesiometry or neuroelectromyography).

Simultaneously, positive influence of placenta preparations on testosterone metabolism – it was an objective of our previous research [22]. The principal purpose of this work was estimation of the role of vascular factor for erections and possibility to be managed by application of biotechnology methods of regenerative medicine. In future research it appears reasonable to launch a study on FSCs effects on the neurogenic factor of erections maintenance and likelihood of favorable effects after injecting pluripotent FSCs.

Certainly, this concept bears enough empiric character at present and it demands additional in-depth studies to support it with more representative samplings. Nevertheless, we suppose it is possible to take into consideration all statements of classical and regenerative methods in treatment of vascular factor of ED: especially, if we deal with mild arterial insufficiency and a treatment course by PDE5 inhibitors is likely to be enough for compensation treatment of ED in the patients. As far as moderate and several forms of vascular ED are concerned, particularly, if we deal with venous-occlusive pathology of erections, administration of FSCs for regenerative purpose can give effect by significant improvement of prognosis and this regenerative treatment using FSCs is likely to become a challenging therapy and alternative to surgery treatment of ED.

Finally, one must dwell upon a very important clinical aspect - a long-term follow up effectiveness in ED maintenance that is, maintaining pharmacology independent sexual life by such patients. Comparative analysis of sexual life between the patients of the groups under study was made over 3 and 6 months and the results proved that over 40% of patients in the MG could lead adequate sexual intercourse without pharmacological stimulation, in comparison with patients from the CG where only 25% of patients reported about such sexual ability. We refer such recorded results to more indepth and long-term structural action of FSCs over the vascular component of erections.

Studies have shown that significant variations in drug response to sildenafil are based on the genotypes of Angiotensin Converting Enzyme (ACE) I/D polymorphisms in patients with erectile dysfunction [24]. As the transcription of ACE is strongly associated with the levels of DNA methylation presenting at its promoter [25], aberrant expression of this gene might also lead to the erectile associated dysfunction. In addition, since DNA methyltransferases (DNMTs) as well as other histone modifiers deposit and maintain DNA methylation [26,27], ectopic levels of epigenetic modifiers might also cause erectile dysfunction. Therefore, investigation of the epigenetic markers and their related writers might shed light on a novel direction for the understanding and treatment of erectile dysfunction in patients.

Conclusions

1. Combined use of vardenafil along with cryopreserved suspensions containing PSCs extracted from fetal liver, brain and placenta in complex treatment of erectile dysfunction is likely to maintain and improve the arterial component of erections on average over 20%; which is twofold higher compared to isolated treatment by use of vardenafil (10%).

2. Influence of combined FSCs therapy on venous phase of cavernous circulation contributes to outflow restriction over 10%, whereas isolated vardenafil medicine use stipulates a negative tendency – outflow is reduced almost over 30%. Therefore, pluripotent FSCs in treatment of vascular factor of erectile dysfunction induce a balanced and favorable influence on both arterial and venous phases of erections.

3. Positive clinical effects of a combined approach to treatment of ED result in improvement of sexual function over 27% according to the results by IIEFs scale which is 1.6-fold higher
compared to isolated use of vardenafil medical drug (17%).

4. Stem cell therapy of vascular factor of ED supplies a long-term effect which is by 1.6 times better than with isolated use of PDE5 inhibitors (over 40% and 25% respectively).

Competing Interests

The paper is intended to be an original paper; all authors of the manuscript are practicing at Cell Therapy Center EmCell, Kyiv, Ukraine. The authors have approved the manuscript and do agree to its submission. There are no matters relevant to the conflict of interests among the authors who contributed to manuscript submission.

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