

NJSC "Astana Medical University"

ANNOTATION

dissertation work of Zhankina Rano Amirkhanovna on the topic: "Possibilities of autotransplantation of mesenchymal stem cells in the treatment of male infertility", submitted for the degree of Doctor of Philosophy (PhD) in the specialty 8D10102 - "Medicine"

Relevance.

Infertility in marital marriage is the most important medical and social problem, attracting the attention of many researchers to the problem of reproductive health of the population [Glybochko P.V., Alyaev Yu.G., Chaly M.E. et al., 2013].

Infertility is defined as the inability to become pregnant after a year of regular, unprotected sexual intercourse. Infertility in married couples affects more than 180 million people worldwide [Winters B.R., Walsh T.J., 2014]. Of these cases, 20 - 50% are secondary to the male factor [M. Vander Borcht, C. Wyns, 2018].

The role of the male factor of infertility in marital marriage ranges from 18.8 to 39% [Filonenko T.G., 2013]. According to a number of studies, rates of male infertility in African and Central/Eastern European countries are quite high and range from 9 to 12%, respectively [Human Fertilization and Embryology Authority, 2013]. In the Republic of Kazakhstan, due to the lack of a register of male infertility, there is no information in the available literature.

Azoospermia is perceived as the absence of sperm in the spermogram and is approximately detected in 1% of men and in 10-15% of patients with infertility [Cocuzza M., 2013]. There are two forms of azoospermia: obstructive and non-obstructive [Hendriks S., Dancet E.A., Meissner A., 2014]. Married couples with non-obstructive azoospermia are clinically unable to have their own children and have the option of either adopting or using donor sperm. The advantages of assisted reproductive technologies, such as intracytoplasmic sperm injection and in vitro fertilization, have changed the approach to the management of such patients with non-obstructive azoospermia.

Thus, based on these premises, we came to the idea of developing a strategy for the treatment of non-obstructive azoospermia using mesenchymal stem cells.

From a practical point of view, the results of the work can serve as the basis for the use of a new cell-therapeutic approach in the treatment of non-obstructive azoospermia using mesenchymal stem cells.

The purpose of the study: To evaluate the effectiveness and therapeutic safety of the use of autologous bone marrow mesenchymal stem cells in the treatment of non-obstructive azoospermia.

Object of study:

This scientific study was based on the results of examination and treatment of 80 men diagnosed with "Non-obstructive azoospermia" aged 24 to 48 years. Clinical examination and treatment of patients was carried out at the following clinical sites: Ecomed LLP clinic; Center for Cell Technologies, Transplantation

and Management of the Institute of Fundamental and Applied Medicine of the National Scientific Medical Center JSC from 2019 to 2023. This contingent of patients has been repeatedly and unsuccessfully treated with various methods of conservative therapy by andrologists.

Before conducting the scientific study, the patient was provided with detailed information about the essence of the method of autotransplantation of bone marrow mesenchymal stem cells, the technology of implementation, possible risks, pain, and complications of cell therapy.

Research objectives:

1. Assess the surgical safety of using mesenchymal stem cells in patients with non-obstructive azoospermia.
2. To evaluate the regenerative effect of mesenchymal stem cells on the process of spermatogenesis in patients with non-obstructive azoospermia.
3. Conduct a comparative analysis of the hormonal profile of two groups of patients with non-obstructive azoospermia.
4. Develop an algorithm for diagnosis and treatment of patients with non-obstructive azoospermia.

Research methods:

1. CBC, BAM, biochemical blood test (ALT, AST, total and direct bilirubin, creatinine, urea);
2. coagulogram (APTT, PTI, INR, prothrombin time, fibrinogen);
3. hormonal profile (level of testosterone, LH, FSH, prolactin, inhibin B hormone);
4. study for tumor markers: CA 19-9, CYFRA, PSA (total and free), AFP, S-100, CEA, SCCA, CA 72-4;
5. Y-chromosome microdeletion and karyotyping;
6. spermogram assessment;
7. Ultrasound of the scrotum;
8. Ultrasound of the bladder, prostate gland, residual urine volume;
9. myeloexfusion of bone marrow;
10. flow cytometry;
11. study of the phenotype and isolation of mesenchymal stem cells;
12. micro-TESE
13. conservative therapy
14. assessment of effectiveness after 6, 9, 12 months (evaluation of spermogram; change in hormonal profile (levels of testosterone, FSH, inhibin B, prolactin)
15. statistical processing SPSS.

Scientific novelty:

1. For the first time in the Republic of Kazakhstan, the method of autotransplantation of bone marrow mesenchymal stem cells was used in men with non-obstructive azoospermia, which was manifested by an improvement in the hormonal profile (decreased FSH levels, normalized testosterone levels, increased inhibin B levels).
2. The stimulating effect of autologous bone marrow mesenchymal stem cells in patients with secondary non-obstructive azoospermia was manifested by the appearance of sperm in the ejaculate.

Practical significance:

The use of mesenchymal stem cells from autologous bone marrow is safe and, due to the regenerative effect, promotes the appearance of sperm in patients with non-obstructive azoospermia in the ejaculate.

The main provisions for defense:

1. Autotransplantation of mesenchymal stem cells is a safe and effective procedure in the treatment of men with secondary non-obstructive azoospermia.
2. Autotransplantation of bone marrow mesenchymal stem cells causes an improvement in the hormonal profile in men with secondary non-obstructive azoospermia: normalization of testosterone levels, increase in the level of inhibin B; decrease in FSH levels.
3. As a result of the use of autotransplantation of bone marrow mesenchymal stem cells, spermatogenesis is activated in patients with secondary non-obstructive azoospermia.

Conclusions:

1. the absence of complications over 6, 9 and 12 months or more of observation period after autotransplantation of bone marrow MSCs in patients with secondary non-obstructive azoospermia indicates the surgical safety of this method;
2. spermogram results in the main group against the background of autotransplantation of bone marrow MSCs indicate the regenerative effect of this method. According to the results of spermograms carried out after 12 months in the main group, 9 out of 40 patients revealed 1 million/ml sperm, which amounted to 22.5% and was a statistically significant difference both between groups ($p = 0.0012$) and within the group ($p=0.001$);
3. in a comparative analysis both in the main group and in the comparison group after 6, 9 and 12 months: testosterone levels after 6 months increased by 26.3% ($p = 0.093$), after 9 months by 12% ($p = 0.021$), after 12 months by 18.9% ($p=0.000$) compared with the comparison group. The FSH level decreased by 9.4% ($p=0.439$) after 6 months, by 5% ($p=0.204$) after 9 months, and by 18% ($p=0.001$) after 12 months compared with the comparison group. Levels of LH and prolactin in both groups after 6, 9 and 12 months did not change statistically significantly. The inhibin B level increased by 22.8% ($p=0.358$) after 6 months, by 66% ($p=0.002$) after 9 months, and by 83.2% ($p=0.000$) after 12 months compared to the comparison group;
4. An algorithm has been developed for the diagnosis and treatment of patients with secondary non-obstructive azoospermia using mesenchymal stem cells.

Practical recommendations:

1. A comprehensive examination with mandatory assessment of hormonal status is necessary.
2. Additional research is needed to repeat the experimental treatment in other centers treating male infertility.
3. Patients diagnosed with secondary non-obstructive azoospermia in the absence of effect from hormonal therapy should be offered autotransplantation of bone marrow MSCs.

Approbation of work:

The dissertation work was tested at an extended meeting of the Department of Urology and Andrology and the Department of Surgical Diseases with courses in angiosurgery and plastic surgery (Minutes No. 2 10/1 dated July 28, 2023).

The main results of the research and the provisions of the dissertation were reported in the speeches:

- at the XLIII International Scientific and Practical Conference at “EurasiaScience” February 15, 2022.
- at XII Global Science and Innovations 2021: Central Asia. International Scientific Practical Journal, Nur-Sultan, Kazakhstan, February.
- at the international conference “VII International Scientific and Practical Conference” Munich, Germany February 22 – 25, 2022
- at the XVII International Multidisciplinary Conference March (Madrid, 2022).

Publications:

Based on the materials of the study, 6 articles were published: one article was published in the journal Stem Cell Research and Therapy, which has the 90th percentile (Q1) and an article in the journal Urology, which has the 25th percentile (Q4) according to CiteScore in the Scopus database, 3 review articles in peer-reviewed domestic publications recommended by the Committee for Quality Assurance in Science and Education of the Ministry of Education and Science of the Republic of Kazakhstan and 1 article in a Russian journal. Also published 7 publications in the materials of international scientific and practical conferences (Kazakhstan, Russia, Canada, Madrid, Germany). There is 1 copyright certificate dated 05/22/2020 No. 10124.

The results of the work have been tested and implemented in uroandrological departments, in VFC in Astana.

Personal contribution of the dissertation student:

During the research, the dissertation candidate took part in determining the topic of the dissertation work, forming its methodological structure, formulating goals and objectives, collecting research materials, independently conducted a statistical analysis and summarizing the results obtained, carried out clinical and laboratory interpretation of patient data, and analyzed literary data on the topic of the dissertation work. .

The author acted as an assistant in bone marrow collection, cultivation, and changing nutrient media together with scientific consultant M.B. Askarov.

She independently supervised patients before and after autotransplantation for 3 years, and also, together with the andrologist at the Ecomed LLP clinic, Arman E., performed a testicular biopsy with the introduction of mesenchymal stem cells intratesticularly.

The author prepared and published research results in journals recommended by the Committee for Quality Assurance in Science and Education of the Ministry of Education and Science of the Republic of Kazakhstan, at international scientific and practical conferences and foreign publications.

Scope of structure and dissertation:

The dissertation consists of an introduction, literature review, description of materials and methods, own results and their discussion, conclusions, conclusions and bibliography, including 151 sources foreign (141) and domestic (10) authors.

The dissertation materials are presented on 79 pages of typewritten text and illustrated with 7 tables, 28 figures, 4 appendices (A, B, C, D).