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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии
საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებშიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman (Кириллица)**, для текста на грузинском языке следует использовать **AcadNusx**. Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - <http://www.spinesurgery.ru/files/publish.pdf> и http://www.nlm.nih.gov/bsd/uniform_requirements.html. В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректур авторам не высылаются, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of 3 centimeters width, and 1.5 spacing between the lines, typeface - **Times New Roman (Cyrillic)**, print size - 12 (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf

In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

**Articles that Fail to Meet the Aforementioned
Requirements are not Assigned to be Reviewed.**

ავტორთა საყურადღებო!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე, დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx**. შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემავსებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრაფიის ფოტოსურათები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შედეგების ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფხიხლებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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IMPACT OF STEM CELL THERAPY ADDED TO GUIDELINE-DIRECTED MEDICAL THERAPY ON QUALITY OF LIFE IN PATIENTS WITH ISCHEMIC CARDIOMYOPATHY

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Abstract.

Background: Despite substantial advances in guideline-directed medical therapy (GDMT), many patients with ischemic cardiomyopathy (ICM) and heart failure with reduced ejection fraction (HFrEF) continue to experience persistent symptoms and impaired quality of life. Regenerative cell therapy has emerged as a promising adjunctive treatment; however, its clinical effectiveness remains under active investigation.

Aim: To evaluate the association between adjunctive autologous bone marrow-derived mononuclear stem cell therapy and quality of life in patients with ischemic cardiomyopathy receiving contemporary guideline-directed medical therapy.

Materials and Methods: This prospective non-randomized controlled study included 54 patients with ischemic cardiomyopathy and HFrEF (left ventricular ejection fraction $\leq 40\%$). Twenty-seven patients underwent autologous bone marrow-derived mononuclear stem cell transplantation in addition to optimized GDMT, while 27 patients received optimized GDMT alone. Quality of life was assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ) at baseline and after 12 months. Within-group comparisons were performed using the Wilcoxon signed-rank test, and between-group comparisons using the Mann-Whitney U test.

Results: After 12 months, patients receiving adjunctive stem cell therapy demonstrated significantly greater improvement in overall MLHFQ score than patients treated with optimized GDMT alone. Significant improvements were also observed across several MLHFQ domains, particularly those related to physical functioning, mobility, daytime fatigue, daily activities, sexual activity, and memory and concentration. These benefits were observed in patients receiving optimized contemporary GDMT, including widespread use of angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors.

Conclusion: Adjunctive autologous bone marrow-derived mononuclear stem cell therapy was associated with greater improvement in quality of life than optimized guideline-directed medical therapy alone in patients with ischemic cardiomyopathy and HFrEF. These findings suggest that regenerative cell therapy may provide additional patient-reported benefits when added to contemporary pharmacological treatment. However, because of the prospective non-randomized design, relatively small sample size, and single-center setting, the results should be interpreted with appropriate caution and require confirmation in larger multicenter randomized controlled trials.

Key words. Ischemic cardiomyopathy, heart failure with reduced ejection fraction, autologous bone marrow-derived

mononuclear cells, stem cell therapy, quality of life, Minnesota living with heart failure questionnaire.

Introduction.

Heart failure (HF) remains one of the leading causes of mortality, disability, and recurrent hospitalizations worldwide. Despite substantial advances in the treatment of cardiovascular diseases, due to an aging population, the growing number of myocardial infarction survivors, and improved survival rates among patients with cardiovascular disorders [1-12].

Ischemic cardiomyopathy (ICM) is one of the most common causes of HF and is characterized by post-infarction myocardial remodeling, progressive deterioration of left ventricular systolic function, and progressive clinical deterioration [12]. Despite advances in myocardial revascularization techniques and optimal medical therapy, a considerable proportion of patients continue to experience persistent HF symptoms, reduced exercise capacity, and impaired quality of life [12,13-17].

Current guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction (HFrEF) includes angiotensin receptor-neprilysin inhibitors (ARNIs), beta-blockers, mineralocorticoid receptor antagonists (MRAs), and sodium-glucose cotransporter-2 (SGLT2) inhibitors. Although these therapies significantly reduce mortality and hospitalization rates, disease progression and deterioration of myocardial function continue to occur in a substantial number of patients [10,12].

In the Republic of Kazakhstan, the management of patients with chronic HF is based on the national clinical protocol for the Diagnosis and Treatment of Chronic Heart Failure (2022), developed based on the European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure. According to these recommendations, guideline-directed medical therapy for patients with HFrEF should include renin-angiotensin system inhibitors (preferably ARNIs), beta-blockers, MRAs, and SGLT2 inhibitors. Despite the substantial prognostic benefits achieved with contemporary pharmacological treatment, many patients continue to experience progressive myocardial remodeling, persistent HF symptoms, and deterioration in quality of life, highlighting the need for additional therapeutic approaches [10,12].

Heart transplantation remains the most definitive treatment option for end-stage HF. However, the shortage of donor organs, high treatment costs, and limited accessibility substantially restrict its widespread application [12]. Consequently, there is a continued search for novel therapeutic strategies aimed at restoring damaged myocardium and improving functional outcomes in patients with advanced cardiac disease.

Cell-based therapy has emerged as one of the most promising areas of regenerative cardiovascular medicine. Transplanted cells are believed to exert beneficial effects through paracrine signaling, stimulation of angiogenesis, attenuation of myocardial fibrosis, and favorable modulation of left ventricular remodeling processes [5,8,9].

Over the past decade, numerous clinical studies have investigated the use of different cell therapy approaches in patients with ischemic cardiomyopathy. The TAC-HFT trial demonstrated improvements in quality of life, six-minute walk distance, and reduction in infarct scar size following administration of mesenchymal stem cells [9]. Similar findings were reported in the POSEIDON and TRIDENT studies, which confirmed the safety of stem cell therapy and suggested its potential beneficial effects on myocardial function and overall clinical status [5,8].

Encouraging results have also been reported with CD34+ cell therapy in patients with ischemic cardiomyopathy. Previous studies demonstrated improvements in left ventricular ejection fraction, exercise tolerance, and neurohormonal markers following treatment [14,16]. However, results from large multicenter trials remain inconsistent. For example, the SCIENCE trial confirmed the safety of allogeneic mesenchymal stromal cell therapy but failed to demonstrate significant improvements in major clinical and echocardiographic outcomes compared with the control group [17].

Despite the growing body of evidence, the clinical efficacy of stem cell therapy in ischemic cardiomyopathy remains a matter of ongoing debate. Most published studies have focused on echocardiographic parameters, left ventricular remodeling, and biomarkers of heart failure. In contrast, the impact of stem cell therapy on patient-reported quality of life has received far less attention, particularly with respect to detailed analysis of individual domains of the Minnesota Living with Heart Failure Questionnaire (MLHFQ).

Therefore, further investigation of the effects of autologous stem cell therapy combined with guideline-directed medical therapy on quality of life in patients with ischemic cardiomyopathy and heart failure with reduced ejection fraction remains highly relevant.

Aim of the study.

To evaluate the effect of autologous stem cell therapy combined with guideline-directed medical therapy on quality of life in patients with ischemic cardiomyopathy and heart failure with reduced ejection fraction.

Study objectives.

To assess changes in the total score and individual domains of the Minnesota Living with Heart Failure Questionnaire (MLHFQ), and to compare quality-of-life outcomes between patients with ischemic cardiomyopathy receiving autologous stem cell therapy in addition to guideline-directed medical therapy and those receiving guideline-directed medical therapy alone.

Materials and Methods.

Study Design:

A prospective non-randomized controlled study was conducted to evaluate the effect of autologous stem cell therapy combined

with guideline-directed medical therapy on quality of life in patients with ischemic cardiomyopathy and heart failure with reduced ejection fraction. The study was performed between February 2023 and February 2024 at the Center for Cell Technologies and Transplantation of the National Scientific Medical Center (Astana, Republic of Kazakhstan). The study protocol was approved by the Local Bioethics Committee of Marat Ospanov West Kazakhstan Medical University (Protocol No. 1, January 24, 2023). Written informed consent was obtained from all participants before enrollment, and the study was conducted in accordance with the principles of the Declaration of Helsinki.

Sample Size Calculation:

The minimum required sample size was calculated before study initiation using the Snedecor–Cochran formula for comparison of two independent means. The calculation was based on a two-sided significance level (α) of 0.05 and a statistical power of 80%, corresponding to a constant (C) of 7.85. The expected standard deviation (SD) of the primary outcome was 7.7 based on preliminary study assumptions, and the anticipated clinically meaningful difference between the treatment and control groups was used as the expected effect size. According to these assumptions, the minimum required sample size was 21.7 participants per group. To compensate for potential losses during the 12-month follow-up period, the calculated sample size was increased by 25%, resulting in a final enrollment target of 27 patients in each group (54 patients in total).

Study Population:

A total of 54 patients aged 40–71 years with established ischemic cardiomyopathy, previous myocardial infarction occurring at least 28 days before enrollment, and heart failure with left ventricular ejection fraction (LVEF) $\leq 40\%$ were included. Eligible patients had undergone myocardial revascularization or had no hemodynamically significant coronary artery stenoses. Exclusion criteria included non-ischemic cardiomyopathies, LVEF $>40\%$, acute myocardial infarction within 28 days before enrollment, malignant neoplasms, psychiatric disorders, hematologic or bone marrow diseases, and severe comorbid conditions limiting study participation.

Patient Allocation:

Patients who provided informed consent for autologous stem cell transplantation were assigned to the intervention group (Group 1), whereas patients who declined the procedure but agreed to participate in follow-up comprised the control group (Group 0). Each group included 27 patients. All participants were followed for 12 months according to the study protocol.

Stem Cell Therapy Protocol:

Patients allocated to the intervention group underwent autologous bone marrow-derived mononuclear stem cell transplantation according to the Clinical Protocol Transplantation of Autologous Stem Cells approved by the Ministry of Health of the Republic of Kazakhstan (2016).

Following written informed consent, approximately 220 mL of bone marrow was aspirated from the posterior iliac crest under sterile operating room conditions using a standardized aspiration technique. The harvested bone marrow was immediately

transferred under sterile conditions to a specialized cell technology laboratory, where the mononuclear cell fraction was isolated. The isolated mononuclear cell fraction subsequently underwent approximately 3 hours of pre-cultivation in a humidified incubator containing 5% CO₂ before transplantation [11].

Before administration, viable mononuclear cells were counted and suspended in 200 mL of sterile physiological saline. The cell suspension was administered intravenously through a peripheral vein at a controlled infusion rate of approximately 50 mL/h over approximately 3 hours. Patients were monitored throughout the infusion procedure and during the early post-infusion period according to institutional clinical practice.

Cell processing was performed under sterile laboratory conditions according to institutional laboratory procedures and the national Clinical Protocol for Transplantation of Autologous Stem Cells. Laboratory quality control was performed according to institutional laboratory procedures and the national clinical protocol. All procedures for bone marrow harvesting, laboratory processing, and cell administration were performed in accordance with the national clinical protocol and standardized institutional procedures throughout the study.

Guideline-Directed Medical Therapy:

Patients in both groups received contemporary guideline-directed medical therapy (GDMT) for heart failure with reduced ejection fraction according to the Clinical Protocol for the Diagnosis and Treatment of Chronic Heart Failure of the Ministry of Health of the Republic of Kazakhstan (2022), developed in accordance with the 2021 European Society of Cardiology Guidelines.

At baseline, 90.7% of patients received angiotensin receptor-neprilysin inhibitors (ARNIs), whereas 9.3% remained on angiotensin-converting enzyme inhibitors. Beta-blockers and mineralocorticoid receptor antagonists were prescribed in 100% of patients, sodium-glucose cotransporter-2 inhibitors in 90.7%, loop diuretics in 94.4%, statins in 92.6%, aspirin in 70.4%, and non-vitamin K oral anticoagulants in 37.0% according to individual clinical indications.

Throughout the study, patients in both groups received optimized guideline-directed medical therapy according to current national and European recommendations. Therefore, the differences observed between the study groups reflect the additional effect of autologous stem cell therapy beyond optimized background pharmacological treatment.

Outcome Assessment:

Quality of life was assessed using the Minnesota Living with Heart Failure Questionnaire (MLHFQ), consisting of 21 items scored on a six-point Likert scale (0–5), with higher scores indicating poorer quality of life. Assessments were performed at baseline and after 12 months of follow-up. Both the total MLHFQ score and changes in individual questionnaire domains were analyzed.

Statistical Analysis:

Statistical analysis was performed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean ± standard deviation (SD).

Normality of data distribution was assessed before comparative analyses. Within-group comparisons were performed using the Wilcoxon signed-rank test, whereas between-group comparisons were conducted using the Mann–Whitney U test. Categorical variables were analyzed using Fisher's exact test. All statistical tests were two-sided, and a p-value <0.05 was considered statistically significant. The analyses of individual MLHFQ domains were considered exploratory and were performed to provide additional descriptive information regarding specific aspects of quality of life.

Results.

Baseline Characteristics:

At baseline, the study groups were comparable with respect to the main demographic and clinical characteristics. The mean age of the participants was approximately 59 years. Males predominated in both groups, which is consistent with the epidemiological characteristics of ischemic cardiomyopathy. No statistically significant differences were observed between the groups regarding age, sex distribution, anthropometric parameters, smoking status, or baseline left ventricular ejection fraction (Table 1).

Quality of life outcomes: total MLHFQ score:

Analysis of the total Minnesota Living with Heart Failure Questionnaire (MLHFQ) score demonstrated improvement in quality of life in both study groups after 12 months of treatment.

In the treatment group, the mean total MLHFQ score decreased from 77.1±5.7 to 70.6±2.5 points, indicating a reduction in heart failure symptom burden and an improvement in quality of life. Within-group analysis revealed a statistically significant improvement after 12 months of follow-up (p<0.001).

In the control group, the total MLHFQ score also decreased, from 79.0±6.2 to 77.5±7.7 points. However, the magnitude of improvement was considerably smaller than that observed in the treatment group. Although a statistically significant within-group change was detected (p=0.021), the overall improvement was less pronounced (Figure 1).

Intergroup analysis demonstrated significantly greater improvement in quality of life among patients who received stem cell therapy in addition to guideline-directed medical therapy (p=0.001).

The mean total MLHFQ score decreased by 6.48±4.63 points in the treatment group compared with 1.48±5.37 points in the control group (p<0.001), indicating a significantly greater improvement in patient-reported quality of life following combined stem cell and medical therapy.

Analysis of Individual MLHFQ Domains:

To provide a more detailed assessment of the impact of stem cell therapy on quality of life, all 21 domains of the MLHFQ were analyzed (Table 3).

The most pronounced improvements were observed in domains related to physical functioning, the need for daytime rest, mobility outside the home, sexual activity, and memory and concentration.

The largest reduction in mean scores was observed for item 10 (Δ=-0.85), reflecting the impact of disease on sexual activity.

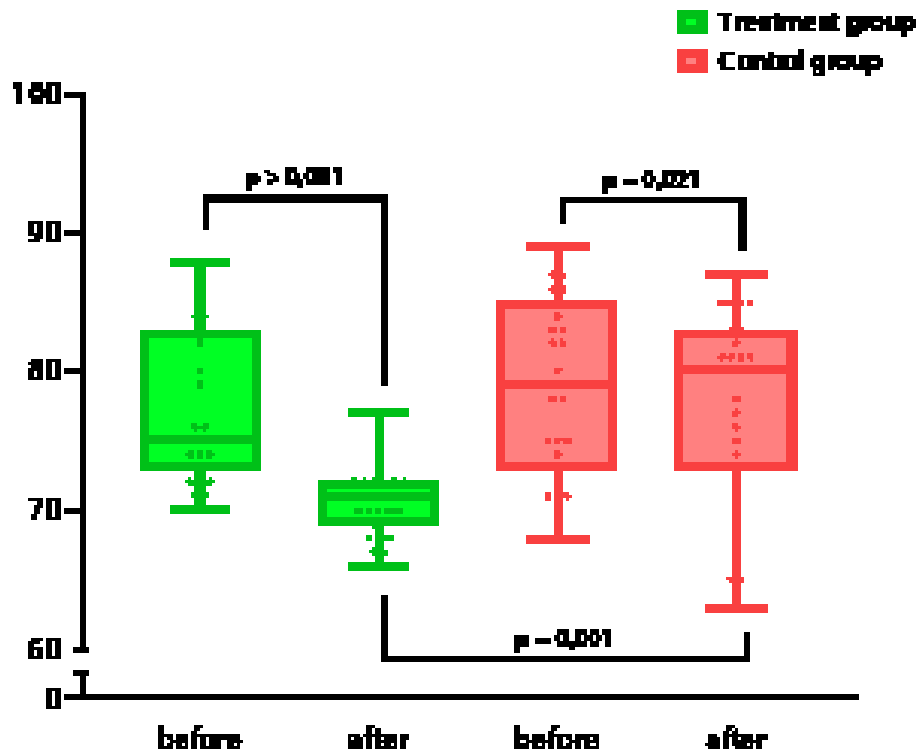


Figure 1. Changes in the total MLHFQ score after 12 months of treatment.

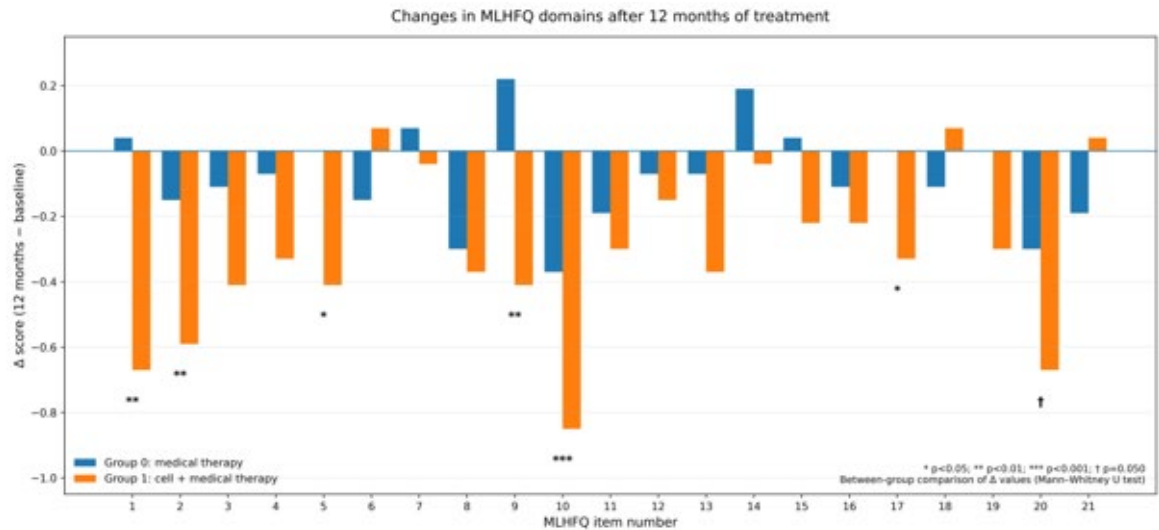


Figure 2. Comparative changes in the 21 MLHFQ domains between study groups after 12 months of follow-up.

Table 1. Baseline clinical and demographic characteristics of the study population.

Variable	Group 1 (n=27)	Group 0 (n=27)	p-value
Age, years	58.63±7.81	59.44±4.99	0.910
Male sex, n (%)	26 (96.3)	25 (92.6)	1.000
Height, cm	169.63±8.20	168.89±7.77	0.896
Weight, kg	89.07±13.96	82.56±16.24	0.051
BMI, kg/m ²	31.00±4.96	28.75±4.71	0.062
Baseline LVEF, %	30.52±6.89	32.44±5.54	0.327
Smoking, n (%)	9 (33.3)	13 (48.1)	0.406

Table 2. Changes in the total MLHFQ score during 12 months of follow-up.

Variable	Group 1 (n=27)	Group 0 (n=27)	p-value
MLHFQ before treatment, points	77.11±5.67	78.96±6.15	0.290
MLHFQ at 12 months, points	70.63±2.51	77.48±7.67	<0.001
Δ MLHFQ (post-treatment – baseline), points	-6.48±4.63	-1.48±5.37	<0.001
Within-group p-value (Wilcoxon test)	<0.001	0.021	

Table 3. Changes in individual domains of the Minnesota Living with Heart Failure Questionnaire.

MLHFQ Item	Clinical Meaning of the Domain	Δ Group 0	Δ Group 1	Between-Group p-value (Δ)	Within-Group p-value Group 0	Within-Group p-value Group 1
1	Leg swelling	0.04	-0.63	0.008	0.808	0.003
2	Need for daytime rest	-0.15	-0.59	0.007	0.206	<0.001
3	Difficulty climbing stairs	-0.11	-0.41	0.061	0.405	<0.001
4	Limitation of household activities	-0.07	-0.33	0.134	0.480	0.013
5	Limitation of mobility outside the home	0.00	-0.41	0.002	1.000	<0.001
6	Sleep disturbance	-0.15	0.07	0.286	0.285	0.617
7	Limitation of social interaction with friends and relatives	0.07	-0.04	0.636	0.527	0.782
8	Reduced ability to work / reduced income	-0.30	-0.41	0.563	0.021	<0.001
9	Limitation of hobbies, sports, and leisure activities	0.37	-0.41	<0.001	0.035	0.005
10	Sexual dysfunction	-0.37	-0.85	0.010	0.012	<0.001
11	Limitation of usual daily activities	-0.19	-0.30	0.397	0.059	0.021
12	Shortness of breath	-0.07	-0.15	0.627	0.480	0.157
13	Hospitalization due to heart failure	-0.07	-0.37	0.072	0.414	0.018
14	Fatigue / weakness	0.19	-0.04	0.265	0.132	0.782
15	Financial burden of medical treatment	0.04	-0.22	0.057	0.705	0.014
16	Side effects of medications	-0.11	-0.22	0.284	0.083	0.014
17	Feeling like a burden to family members	0.00	-0.33	0.027	1.000	0.013
18	Loss of control over the disease	-0.11	0.07	0.212	0.248	0.593
19	Anxiety / worry	0.00	-0.30	0.209	1.000	0.154
20	Memory and concentration problems	-0.30	-0.67	0.050	0.021	<0.001
21	Depressive mood	-0.19	0.04	0.104	0.096	0.655

Substantial improvements were also detected for item 1 ($\Delta=-0.67$), item 20 ($\Delta=-0.67$), and item 2 ($\Delta=-0.59$), representing symptoms of heart failure and their influence on everyday life.

Significant improvements were additionally observed in items 3, 5, 8, and 9, with reductions ranging from -0.37 to -0.41 points. These findings suggest a positive effect of stem cell therapy on functional capacity, symptom burden, and daily activity levels in patients with ischemic cardiomyopathy.

In the control group, changes in most questionnaire domains were less pronounced. The greatest improvements were observed for items 8 and 20 ($\Delta=-0.30$), as well as item 10 ($\Delta=-0.37$). Nevertheless, the magnitude of change across nearly all MLHFQ domains remained lower than that observed in the treatment group.

Comparative analysis of all 21 MLHFQ domains demonstrated consistently greater improvements. The largest between-group differences were observed in domains related to physical functioning, limitations in daily activities, and subjective perception of heart failure symptoms (Figure 2).

Safety:

No procedure-related complications or serious adverse events related to stem cell therapy were observed during the study period.

Discussion.

The present prospective non-randomized controlled study evaluated the association between autologous bone marrow-derived mononuclear stem cell therapy and quality of life in patients with ischemic cardiomyopathy and heart failure with reduced ejection fraction receiving contemporary guideline-directed medical therapy (GDMT). The principal finding was that patients treated with adjunctive stem cell therapy demonstrated significantly greater improvement in the overall Minnesota Living with Heart Failure Questionnaire (MLHFQ) score than those receiving GDMT alone. Furthermore, detailed evaluation of all 21 MLHFQ domains showed that the observed benefits extended beyond the overall questionnaire score and involved several aspects of physical functioning, daily activities, and patient well-being.

An important feature of the present study is that the observed improvements were achieved despite optimized contemporary pharmacological treatment. More than 90% of patients received angiotensin receptor-neprilysin inhibitors and sodium-glucose cotransporter-2 inhibitors, while all participants were treated with beta-blockers and mineralocorticoid receptor antagonists according to current national and European heart failure guidelines. Consequently, the additional improvement in quality

of life observed in the intervention group cannot be explained by inadequate background medical therapy alone and supports the potential complementary role of stem cell therapy when added to optimized GDMT.

The beneficial effects observed in the present study are generally consistent with previous clinical investigations evaluating regenerative therapies in ischemic cardiomyopathy. One of the landmark studies in this field, the TAC-HFT trial, demonstrated significant improvements in quality of life, six-minute walk distance, and reduction in myocardial scar size following transcatheter administration of mesenchymal stem cells [9]. These findings suggested that regenerative therapy may influence not only myocardial structure but also patients' perception of functional capacity and overall health status.

Comparable observations were reported in the POSEIDON trial, in which both autologous and allogeneic mesenchymal stem cells demonstrated favorable safety profiles together with improvements in clinical status among patients with ischemic cardiomyopathy [8]. Subsequently, pooled analysis of the POSEIDON and TAC-HFT cohorts demonstrated that therapeutic response was largely independent of patient age. Individuals older than 60 years achieved improvements in quality of life and functional capacity comparable with those observed in younger patients, supporting the applicability of stem cell therapy across a broad spectrum of patients with chronic heart failure [7].

The present findings are also in agreement with the TRIDENT study, which demonstrated that administration of higher doses of mesenchymal stem cells was associated with favorable changes in left ventricular function and clinical status [5]. Although our study was not designed to evaluate dose-response relationships or compare different cellular products, the significant improvement in patient-reported quality of life observed after autologous bone marrow-derived mononuclear cell transplantation further supports the concept that regenerative therapies may provide clinically meaningful benefits when administered alongside optimized pharmacological treatment.

In recent years, patient-reported outcomes have become increasingly important in cardiovascular clinical research because they directly reflect the patient's perception of treatment benefit. Accordingly, the CHART-1 trial incorporated MLHFQ assessment together with echocardiographic parameters and exercise capacity among its principal clinical endpoints [2]. The results of the present study support this comprehensive approach and emphasize that evaluation of novel regenerative therapies should include validated quality-of-life instruments in addition to conventional structural and functional cardiac parameters.

Despite encouraging findings reported by several clinical trials, the overall evidence regarding stem cell therapy for ischemic cardiomyopathy remains heterogeneous. Considerable differences exist among published studies with respect to patient selection, cell source, laboratory processing methods, administered cell dose, route of administration, primary endpoints, and duration of follow-up. These methodological variations should be considered when interpreting treatment effects and are likely to contribute to the inconsistent results observed across individual studies.

Nevertheless, not all clinical studies have demonstrated consistent therapeutic benefits. The CONCERT-HF trial confirmed the safety of mesenchymal stromal cells and c-kit-positive cardiac cells; however, improvements in major clinical outcomes were less pronounced than initially anticipated [3]. Similarly, the SCIENCE trial demonstrated an excellent safety profile of allogeneic adipose tissue-derived mesenchymal stromal cells but did not show significant improvements in left ventricular function, exercise capacity, or quality of life compared with placebo [17]. Taken together, these findings suggest that although stem cell therapy appears to be safe, its clinical efficacy remains dependent on multiple methodological and patient-related factors, including patient selection, cell characteristics, manufacturing procedures, delivery strategy, and treatment protocol.

Another important consideration is the design of the present study. Patient allocation was based on informed consent to undergo stem cell transplantation rather than random assignment. Although the intervention and control groups were comparable with respect to baseline demographic and clinical characteristics, the possibility of selection bias cannot be completely excluded. Consequently, the present findings should be interpreted as demonstrating an association between adjunctive stem cell therapy and improved quality of life rather than establishing a definitive causal relationship. Confirmation of these findings in adequately powered randomized controlled trials remains necessary.

An additional aspect of interest concerns the potential influence of sex on treatment response. Florea et al. reported comparable improvements in left ventricular ejection fraction, quality of life, and functional status among both male and female patients following mesenchymal stem cell administration [6]. In the present study, only three women were enrolled, reflecting the epidemiological characteristics of advanced ischemic cardiomyopathy. Although no significant imbalance in sex distribution was observed between the study groups, the limited number of female participants precluded meaningful sex-specific analyses.

A particular strength of the present study is the comprehensive evaluation of all 21 domains of the Minnesota Living with Heart Failure Questionnaire. While most previous investigations have primarily focused on changes in the overall MLHFQ score, domain-specific analyses have been reported less frequently. Our findings demonstrated that the greatest improvements occurred in domains related to physical functioning, the need for daytime rest, mobility outside the home, sexual activity, daily activities, and memory and concentration. These observations provide a more detailed understanding of how regenerative therapy may influence everyday functioning from the patient's perspective and represent one of the distinctive methodological features of the present investigation.

Study Limitations.

Several limitations should be acknowledged when interpreting the results of this study. First, the investigation was conducted as a prospective non-randomized controlled study, and allocation to the intervention group depended on patients' willingness to undergo stem cell transplantation. Although baseline

characteristics were comparable, the possibility of residual selection bias cannot be completely excluded. Second, the sample size was relatively small, and the study was performed at a single center, which may limit the generalizability of the findings. Third, the follow-up period was limited to 12 months and therefore did not allow evaluation of long-term clinical outcomes such as mortality, recurrent hospitalizations, or sustained treatment effects. Fourth, quality of life was assessed using a single disease-specific instrument, the Minnesota Living with Heart Failure Questionnaire, although this questionnaire is one of the most extensively validated and widely used tools for patients with heart failure. Finally, the present study was not designed to investigate the biological mechanisms responsible for the observed clinical improvements. Future multicenter randomized controlled trials with larger study populations and longer follow-up periods are warranted to further clarify the clinical role of stem cell therapy in patients with ischemic cardiomyopathy.

Overall, the present findings suggest that autologous bone marrow-derived mononuclear stem cell therapy may provide additional patient-reported benefits when administered alongside optimized contemporary guideline-directed medical therapy in patients with ischemic cardiomyopathy and heart failure with reduced ejection fraction. However, these findings should be interpreted within the context of the non-randomized study design and require confirmation in larger randomized controlled trials before definitive conclusions regarding clinical efficacy can be established.

Conclusion.

In this prospective non-randomized controlled study, adjunctive autologous bone marrow-derived mononuclear stem cell therapy was associated with significantly greater improvement in quality of life compared with optimized guideline-directed medical therapy alone in patients with ischemic cardiomyopathy and heart failure with reduced ejection fraction. Improvements were observed not only in the overall Minnesota Living with Heart Failure Questionnaire score but also across multiple domains reflecting physical functioning, daily activities, and patient well-being.

The findings suggest that autologous stem cell therapy may provide additional patient-reported benefits when administered alongside contemporary guideline-directed medical therapy. However, because of the non-randomized design, relatively small sample size, and single-center setting, these results should be interpreted with appropriate caution. Larger multicenter randomized controlled trials with longer follow-up are required to confirm the clinical effectiveness of this therapeutic approach and to further define its role in the management of ischemic cardiomyopathy.

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