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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 ბაზებიდან.

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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THE ROLE OF CELL THERAPY IN THE COMPREHENSIVE TREATMENT OF CHRONIC HEPATITIS C-RELATED LIVER CIRRHOSIS

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Abstract.

Background: Despite the high efficacy of direct-acting antiviral (DAA) therapy for chronic hepatitis C virus (HCV) infection, a considerable proportion of patients continue to exhibit significant structural liver damage, including advanced fibrosis and cirrhosis. Therefore, the search for additional therapeutic approaches aimed at enhancing liver regeneration and improving hepatic functional status remains highly relevant.

Objective: To evaluate the clinical efficacy of fetal stem hepatocyte transplantation as part of a comprehensive treatment strategy for liver cirrhosis associated with chronic hepatitis C.

Materials and Methods: A prospective comparative study was conducted involving 106 patients with HCV-related liver cirrhosis. Patients were divided into two comparable groups of 53 individuals each. The main group received direct-acting antiviral therapy combined with fetal stem hepatocyte transplantation, whereas the control group received antiviral therapy alone. All participants underwent comprehensive clinical, laboratory, and instrumental examinations, including transient liver elastography. Treatment efficacy was assessed using changes in Child–Pugh and MELD scores over a 12-month follow-up period. Statistical analysis was performed using parametric and non-parametric methods.

Results: Baseline Child–Pugh and MELD scores did not differ significantly between the groups. After 12 months of follow-up, the Child–Pugh score was significantly lower in the main group compared with the control group (7.11 ± 0.91 vs. 7.81 ± 1.13 points, respectively; $p=0.002$). Similarly, the MELD score was significantly lower in the main group than in the control group (17.9 ± 2.11 vs. 19.1 ± 2.21 points, respectively; $p=0.004$). Repeated-measures analysis of variance demonstrated a statistically significant effect of both follow-up duration and treatment modality on Child–Pugh ($\eta^2=35.9\%$ and $\eta^2=25.0\%$, respectively) and MELD scores ($\eta^2=23.3\%$ and $\eta^2=18.2\%$, respectively; $p<0.001$).

Conclusion: The addition of fetal stem hepatocyte transplantation to standard antiviral therapy contributes to a more pronounced improvement in liver functional status in patients with HCV-related cirrhosis compared with antiviral therapy alone. These findings support the potential role of cell-

based therapies as a promising adjunctive treatment option for liver cirrhosis and highlight the need for further studies to evaluate their long-term efficacy and safety.

Key words. Chronic hepatitis C, liver cirrhosis, cell therapy, fetal stem hepatocytes, cell transplantation, Child–Pugh score, MELD score, regenerative medicine.

Introduction.

Liver cirrhosis resulting from chronic hepatitis C virus (HCV) infection remains one of the most important healthcare problems worldwide. Chronic HCV infection is characterized by persistent inflammatory activity and progressive liver injury, leading to impaired liver function, fibrosis, and ultimately cirrhosis. According to the World Health Organization, liver cirrhosis is one of the leading causes of mortality and represents a major burden among chronic liver diseases. Despite the widespread use of direct-acting antiviral (DAA) agents, which provide high rates of sustained virological response, pronounced structural liver changes, including fibrosis and cirrhosis, persist in a considerable proportion of patients. This highlights the need for additional regenerative treatment approaches [1,2].

Current treatment strategies for liver cirrhosis are mainly aimed at slowing disease progression and preventing complications. However, these approaches do not ensure complete restoration of damaged liver tissue. Therefore, regenerative medicine and cell-based therapies have attracted considerable attention as promising therapeutic strategies [3,4].

Fetal hepatic stem cells possess high proliferative activity, differentiation potential, and the ability to preserve the functional properties of hepatocytes. Their therapeutic use is believed to stimulate liver regeneration, improve the hepatic microenvironment through the secretion of growth factors and cytokines, and reduce chronic inflammatory activity. Experimental studies have demonstrated the regenerative potential of fetal-derived cells in restoring damaged liver tissue and maintaining hepatic function [5,6].

In recent years, increasing evidence has demonstrated the effectiveness of different types of cell therapy for chronic liver diseases. Several studies have reported improvements in liver biochemical parameters, reduction of clinical manifestations, and better quality of life following cell-based therapy [7-9].

Cell therapy is of particular interest in patients with decompensated liver cirrhosis, for whom conventional therapeutic options remain limited. A potential advantage of this approach is its ability to influence not only the clinical manifestations of the disease but also the regenerative processes within damaged liver tissue.

Despite these encouraging findings, the long-term efficacy and safety of cell therapy remain subjects of ongoing scientific debate. Further clinical studies with extended follow-up are required to establish its role in the treatment of liver cirrhosis [10,11].

Aim of the study. To comparatively evaluate the clinical efficacy of fetal hepatic stem cell transplantation as part of combination therapy in patients with liver cirrhosis associated with chronic hepatitis C virus infection.

Materials and Methods.

The study included 106 patients with a confirmed diagnosis of liver cirrhosis secondary to chronic hepatitis C virus (HCV) infection who were followed up at the Aktobe Hepatology Center and the Department of Cell Therapy of the Medical Center, Marat Ospanov West Kazakhstan Medical University.

This was a prospective, comparative, non-randomized study. All patients who met the inclusion criteria were offered fetal hepatic stem cell transplantation in addition to standard antiviral therapy. The study group consisted of patients who provided written informed consent for cell therapy (n=53). The control group included patients who declined fetal hepatic stem cell transplantation and received only standard antiviral therapy with direct-acting antiviral agents (n=53). Before treatment, baseline demographic and clinical characteristics were assessed. No statistically significant differences were found between the groups with regard to age, sex, disease duration, comorbidities, or baseline severity of liver cirrhosis, indicating that the groups were comparable at study entry.

The diagnosis of chronic hepatitis C was established based on clinical and anamnestic data, detection of anti-HCV antibodies by enzyme-linked immunosorbent assay (ELISA), and identification of HCV RNA by polymerase chain reaction (PCR). The stage of liver fibrosis was assessed by transient elastography using a FibroScan® 502 device.

The inclusion criteria were age between 18 and 65 years, liver cirrhosis secondary to chronic hepatitis C, and receipt of antiviral therapy according to the current clinical guidelines of the Republic of Kazakhstan. The exclusion criteria included liver cirrhosis of other etiologies, HIV coinfection, active tuberculosis, malignant diseases, psychiatric disorders, alcohol or drug dependence, pregnancy, and lactation.

The baseline demographic and clinical characteristics of the patients are presented in Table 1. Baseline analysis demonstrated that the study and control groups were comparable with respect to age, sex, body mass index, disease duration, and the pattern of comorbidities, allowing an appropriate comparison of the therapeutic interventions.

Before treatment, the severity of liver disease was similar in both groups. No statistically significant differences were observed between the study and control groups in the baseline Child–Pugh and MELD scores or in other demographic and clinical characteristics.

From the time of enrollment, all patients received antiviral therapy according to the Clinical Protocol "Chronic Viral Hepatitis C in Adults" of the Ministry of Health of the Republic of Kazakhstan (No. 118, October 23, 2020). The treatment regimen consisted of sofosbuvir plus daclatasvir administered for 24 weeks.

In addition, all patients received the same standard treatment for liver cirrhosis according to the Clinical Protocol "Liver Cirrhosis in Adults" (No. 135, April 29, 2021), including ursodeoxycholic acid, medications for the prevention and treatment of hepatic encephalopathy, diuretics, and other drugs when clinically indicated. Thus, the only difference between the groups was the administration of fetal hepatic stem cell transplantation in the study group.

Fetal hepatic stem cell transplantation was performed according to Protocol No. 10, "Transplantation of Fetal Stem Cells," approved by the Expert Council of the Republican Center for Health Development of the Ministry of Health and Social Development of the Republic of Kazakhstan on September 30, 2015. The procedure was performed by a certified specialist in surgery and transplantation within the framework of the state-guaranteed medical care program and compulsory social health insurance. Patients were hospitalized in the Department of Cell Therapy of the Medical Center, Marat Ospanov West Kazakhstan Medical University.

Fetal hepatic stem cells were obtained from fetal tissue collected after medically indicated termination of pregnancy unrelated to the present study. Liver tissue was isolated from fetuses at 17–22 weeks of gestation under laboratory conditions. Tissue procurement, processing, cryopreservation, and storage were performed at the Cell Bank of the Medical Center, Marat Ospanov West Kazakhstan Medical University, in accordance with the current legislation of the Republic of Kazakhstan and the approved institutional protocol.

All fetal tissue donors provided written informed consent for the use of biological material for therapeutic and research purposes before the medical procedure. The decision to terminate pregnancy was made independently of any potential use of fetal tissue and was not related to the present study.

All participants were fully informed about the nature of cell therapy, its potential benefits, and possible risks and provided written informed consent for treatment and participation in the study.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the Convention on Human Rights and Biomedicine. The study protocol was approved by the Local Bioethics Committee of Marat Ospanov West Kazakhstan Medical University (Protocol No. 10).

Cryopreserved fetal hepatic stem cells were thawed in a temperature-controlled water bath at 37°C for 5 min. Cell viability was assessed using 0.2% trypan blue exclusion. Equal volumes of the cell suspension and trypan blue solution were mixed, and viable cells were counted using a Goryaev counting chamber. Cell viability after thawing was required to be at least 70%.

Fetal hepatic stem cells were administered intravenously as a single infusion of 1 mL of cell suspension containing 6×10^6 cells, diluted in 20 mL of 0.9% sodium chloride solution.

A peripheral intravenous catheter was inserted under aseptic conditions, and the cell suspension, matched for the recipient's ABO blood group and Rh factor, was infused using an infusion pump at a rate of 40–50 drops/min. The average infusion time was 30–40 min.

During the first, second, and third months of therapy (weeks 4, 8, and 12 of antiviral treatment), patients received pangenotypic direct-acting antiviral therapy consisting of sofosbuvir 400 mg once daily and daclatasvir 60 mg once daily according to the Clinical Protocol "Chronic Viral Hepatitis C in Adults" (No. 118, October 23, 2020). All patients also received standard treatment for liver cirrhosis, including hepatoprotective therapy, prevention of hepatic encephalopathy, and diuretics, while patients in the study group additionally underwent fetal hepatic stem cell therapy. Antiviral treatment continued for 24 weeks. Cell therapy was administered monthly during the first three months and subsequently every three months. Hospitalization for cell therapy was performed at the Department of Cell Therapy, Medical Center, Marat Ospanov West Kazakhstan Medical University.

All patients underwent comprehensive clinical and laboratory evaluation before treatment and throughout the follow-up period. Clinical manifestations, complete blood count, biochemical parameters, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, albumin, alkaline phosphatase (ALP), and gamma-glutamyl transferase (GGT), coagulation parameters, and abdominal ultrasonography findings were assessed.

The severity of liver cirrhosis and liver function were evaluated using the Child–Pugh and Model for End-stage Liver Disease (MELD) scoring systems. The Child–Pugh score included serum bilirubin, albumin, international normalized ratio (INR), ascites, and hepatic encephalopathy. The MELD score was calculated using serum bilirubin, creatinine, and INR values.

The safety of cell therapy was monitored throughout the study by recording all adverse events, infusion-related reactions, and possible complications.

Statistical analysis was performed using STATISTICA version 25. Data distribution was assessed using the Shapiro–Wilk and Kolmogorov–Smirnov tests. Normally distributed variables were expressed as mean $\pm$ standard deviation ($M \pm SD$), whereas non-normally distributed variables were presented as median (interquartile range, Me [Q1–Q3]). Paired data were compared using the paired Student's t-test or the Wilcoxon signed-rank test, as appropriate. Categorical variables were analyzed using McNemar's test. A P value <0.05 was considered statistically significant.

Results.

Fetal hepatic stem cell transplantation was generally well tolerated. No serious adverse events related to the administration of the cell product were observed. No anaphylactic reactions, hemodynamically significant disorders, severe allergic reactions, or other complications requiring discontinuation of therapy or intensive medical treatment occurred during the infusion or in the early post-infusion period.

During the 12-month follow-up period, no infectious complications related to cell therapy, transmission of infectious diseases, immunological complications, or other delayed adverse events associated with fetal hepatic stem cell transplantation were recorded.

All patients completed the study according to the protocol. No patient discontinued treatment because of adverse events associated with cell therapy.

It should be noted that all patients achieved a sustained virological response after completion of direct-acting antiviral therapy, confirming the high efficacy of current treatment regimens for chronic hepatitis C. Therefore, the differences observed between the study groups could not be attributed to differences in antiviral efficacy and most likely reflected the effect of adding fetal hepatic stem cell transplantation to standard therapy.

A repeated-measures analysis of variance (ANOVA) was performed to evaluate the effects of follow-up duration and

Table 1. Baseline demographic and clinical characteristics of patients with liver cirrhosis secondary to chronic hepatitis C virus infection.

Parameter	Main group	Control group
Age, years ($M \pm SD$)	49,39 $\pm$ 8,92	50,74 $\pm$ 10,60
Height, cm ($M \pm SD$)	168,02 $\pm$ 8,46	166,41 $\pm$ 10,81
Body mass index (BMI), kg/m ² ($M \pm SD$)	27,06 $\pm$ 4,03	27,80 $\pm$ 4,41
Body weight before treatment, kg ($M \pm SD$)	76,14 $\pm$ 15,00	76,96 $\pm$ 15,54
Disease duration, years	12 [10–14]	12 [10–15]
Male, n (%)	43 (79,6)	34 (63,0)
Female, n (%)	11 (20,4)	20 (37,0)
Arterial hypertension, n (%)	23 (42,6)	28 (51,9)
Type 2 diabetes mellitus, n (%)	16 (29,6)	12 (22,2)
Obesity (BMI ≥ 30 kg/m ²), n (%)	10 (18,5)	17 (31,5)
Coronary artery disease, n (%)	4 (7,4)	9 (16,7)
Chronic pancreatitis, n (%)	10 (18,5)	4 (7,4)
Chronic gastritis, n (%)	18 (33,3)	19 (35,2)
Cholelithiasis and/or previous cholecystectomy, n (%)	12 (22,2)	12 (22,2)
Impaired glucose tolerance, n (%)	10 (18,5)	9 (16,7)
Chronic bronchitis, n (%)	3 (5,6)	8 (14,8)

Note: Continuous variables are presented as mean $\pm$ standard deviation ($M \pm SD$), categorical variables as n (%). Disease duration is presented as the median [interquartile range].

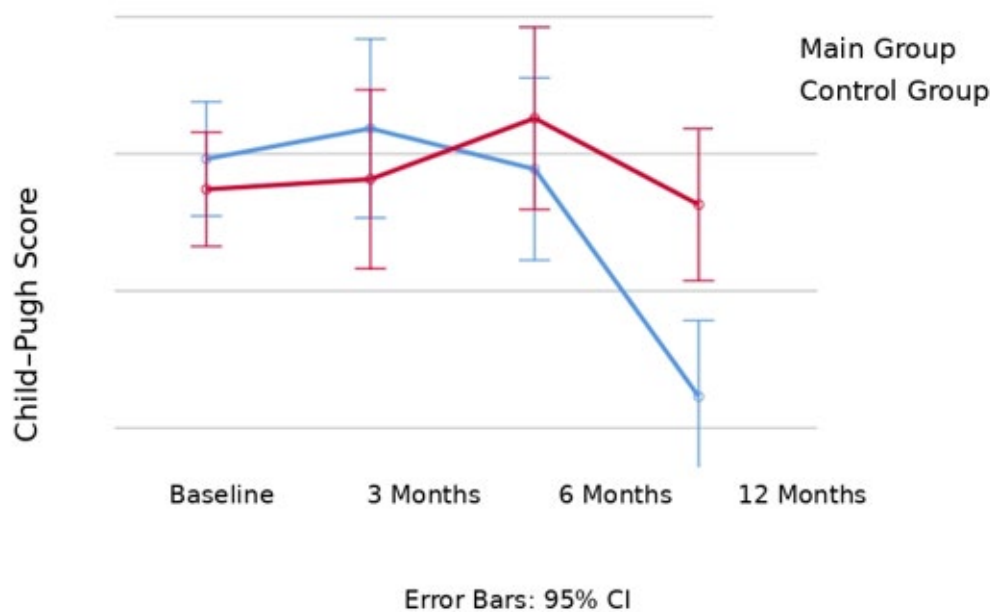


Figure 1. Effect of follow-up duration and treatment modality on the Child-Pugh score.

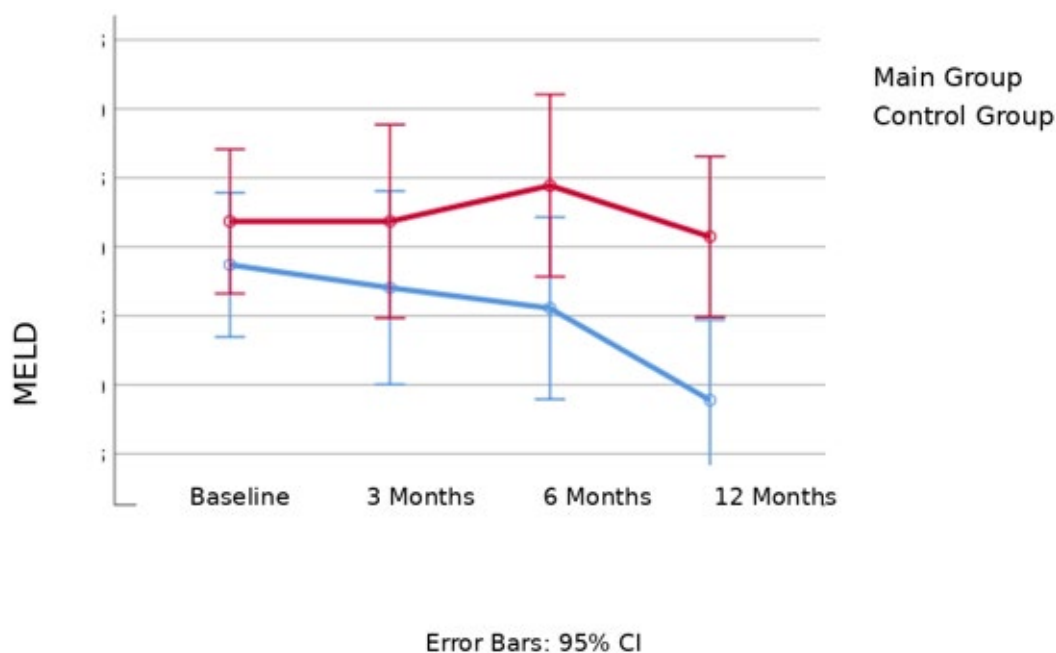


Figure 2. Effect of follow-up duration and treatment modality on the MELD score.

treatment modality (two groups) on the Child-Pugh score. The analysis demonstrated a statistically significant effect of follow-up time on the Child-Pugh score ($P < 0.001$), with an effect size of $\eta^2 = 35.9\%$. Treatment modality also had a significant effect on the Child-Pugh score ($P < 0.001$), accounting for 25.0% of the total variance ($\eta^2 = 25.0\%$). The corresponding model is presented in Figure 1.

At baseline, the mean Child-Pugh score was 7.98 ± 0.79 in the study group and 7.87 ± 0.75 in the control group, with no statistically significant difference between the groups ($P = 0.463$), confirming their baseline comparability. After 3 months of follow-up, the Child-Pugh score remained comparable between the groups (8.09 ± 1.17 vs. 7.91 ± 1.25 ; $P = 0.349$). Similarly, no

significant difference was observed after 6 months (7.94 ± 1.20 vs. 8.13 ± 1.26 ; $P = 0.452$). However, after 12 months, a statistically significant difference was detected. The mean Child-Pugh score decreased to 7.11 ± 0.91 in the study group compared with 7.81 ± 1.13 in the control group ($P = 0.002$). In addition, the 95% confidence intervals did not overlap, confirming the statistical significance of the observed difference.

Thus, no significant differences between the groups were observed during the first 6 months of follow-up. However, by month 12, the study group demonstrated a significantly greater improvement in the Child-Pugh score than the control group, suggesting a beneficial effect of fetal hepatic stem cell transplantation.

A repeated-measures analysis of variance (ANOVA) was also performed to evaluate the effects of follow-up duration and treatment modality (two groups) on the MELD score. Follow-up duration had a significant effect on the MELD score ($P<0.001$), explaining 23.3% of the total variance ($\eta^2 = 23.3\%$). Treatment modality also significantly influenced the MELD score ($P<0.001$), accounting for 18.2% of the variance ($\eta^2 = 18.2\%$). The corresponding model is shown in Figure 2.

At baseline, the mean MELD score was 18.8 ± 1.98 in the study group and 19.2 ± 1.89 in the control group, with no statistically significant difference between the groups ($P=0.268$), confirming their baseline comparability. After 3 months of follow-up, the MELD score remained comparable between the groups (18.7 ± 2.61 vs. 19.2 ± 2.58 ; $P=0.253$). Similarly, no statistically significant difference was observed after 6 months (18.6 ± 2.54 vs. 19.4 ± 2.34 ; $P=0.103$). However, after 12 months of follow-up, a statistically significant difference was found. The mean MELD score was 17.9 ± 2.11 in the study group compared with 19.1 ± 2.21 in the control group ($P=0.004$). The 95% confidence intervals did not overlap, confirming the statistical significance of the observed difference.

Thus, no significant differences between the groups were observed during the first 6 months of follow-up. However, by month 12, the study group demonstrated a significantly greater reduction in the MELD score than the control group, indicating an improvement in liver function and suggesting the additional clinical benefit of fetal hepatic stem cell transplantation.

Discussion.

The present study demonstrated that the addition of fetal hepatic stem cell transplantation to the comprehensive treatment of patients with liver cirrhosis secondary to chronic hepatitis C resulted in a greater improvement in liver function compared with antiviral therapy alone. These findings are based on changes in the Child–Pugh and MELD scores, which are widely accepted indicators of liver disease severity and prognosis.

Our results showed that statistically significant differences between the groups became evident only during long-term follow-up. After 12 months, the mean Child–Pugh score was significantly lower in the study group than in the control group (7.11 ± 0.91 vs. 7.81 ± 1.13 ; $P=0.002$), indicating an improvement in liver function. Similar findings were obtained for the MELD score, which was also significantly lower in patients who received cell therapy than in those receiving standard treatment alone (17.9 ± 2.11 vs. 19.1 ± 2.21 ; $P=0.004$). The absence of significant differences during the first months of follow-up and the appearance of a significant effect after 12 months may indicate that the regenerative effects of cell therapy require time to become clinically evident.

Our findings are consistent with previous studies by Lee et al. (2021), Liu et al. (2022), Yang et al. (2023), and Yao et al. (2022), which demonstrated that different types of cell therapy improve liver function and clinical outcomes in patients with chronic liver diseases [7–9]. Similar conclusions were reported in the systematic review by Qi et al. (2014) and the meta-analysis by Zhu et al. (2021), both of which confirmed that cell therapy may improve liver function and reduce the severity of hepatic insufficiency in patients with liver cirrhosis of various etiologies [12,13].

The present findings also complement the results previously reported by our research group. In our earlier study, Astrakhanov et al. (2024) demonstrated that cell transplantation improved biochemical markers of liver function during the early follow-up period in patients with HCV-related liver cirrhosis. The current study extends these observations by demonstrating sustained improvement in the Child–Pugh and MELD scores after 12 months of follow-up [14].

The observed improvement in the Child–Pugh and MELD scores may be explained by the biological properties of fetal hepatic stem cells. Unlike many other cell types, fetal-derived cells possess a high proliferative capacity and a marked ability to differentiate. According to Yovchev and Oertel (2017), these cells are capable of participating in liver repopulation and replacing damaged hepatocytes [5]. In addition, fetal cells exert paracrine effects through the secretion of growth factors and anti-inflammatory cytokines that promote liver regeneration.

Another important mechanism may be the immunomodulatory activity of cell therapy. Bieback et al. (2012) reported that stem cells are able to reduce chronic inflammation, regulate immune responses, and attenuate liver injury [4]. Similar mechanisms have recently been described by Shafritz et al. (2023), who emphasized the role of cell therapy in controlling chronic inflammation and inhibiting liver fibrogenesis.

Improvement of liver function has important clinical implications beyond laboratory parameters. Trounson and McDonald (2015) suggested that even moderate improvement in liver function may reduce fatigue, increase physical activity, and improve patients' quality of life [15]. Therefore, the improvement in the Child–Pugh and MELD scores observed in the present study may also reflect better overall clinical status.

Another possible mechanism underlying the beneficial effects of cell therapy is the improvement of the liver's synthetic function. Miki (2019) demonstrated that cell therapy may restore hepatic protein synthesis [16]. Similar findings were reported by Yasen et al. (2019), who observed improved protein metabolism following fetal liver cell transplantation [17]. Restoration of the liver's synthetic capacity may therefore contribute to reduced disease severity and improved prognosis.

Previous studies have also suggested that cell therapy may have beneficial effects on portal hypertension and its complications. Nazhvani et al. (2020) reported that regenerative cell therapy reduced intrahepatic vascular resistance and improved hepatic microcirculation [18]. Lewis et al. (2021) suggested that restoration of liver architecture may reduce portal hypertension and decrease the risk of disease decompensation [19]. These mechanisms may also have contributed to the improvement in the Child–Pugh and MELD scores observed in the present study.

This study has several limitations. The relatively small sample size and the 12-month follow-up period do not allow definitive conclusions regarding the long-term efficacy and safety of fetal hepatic stem cell transplantation. These limitations are consistent with previous reports by Shen et al. (2021) and El Baz et al. (2019), who emphasized the need for large randomized controlled trials with longer follow-up to define the role of cell therapy in the treatment of liver cirrhosis [9,10].

Overall, our findings support the potential value of fetal hepatic stem cell transplantation as an adjunct to standard

treatment in patients with liver cirrhosis secondary to chronic hepatitis C. The significant improvement in the Child–Pugh and MELD scores after 12 months suggest that this therapeutic approach may contribute to improved liver function and clinical outcomes.

Conclusion.

Fetal hepatic stem cell transplantation as part of comprehensive therapy improves liver function in patients with liver cirrhosis secondary to chronic hepatitis C, as demonstrated by favorable changes in clinical and prognostic indicators. These findings support the therapeutic potential of this approach and indicate the need for further large-scale studies to evaluate its long-term efficacy and safety.

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Conflict of Interest.

The authors declare no conflict of interest.

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Роль клеточной терапии в комплексном лечении цирроза печени, ассоциированного с хроническим вирусным гепатитом С

Актуальность: Несмотря на высокую эффективность противовирусных препаратов прямого действия при хроническом вирусном гепатите С (ХВГС), у значительной части пациентов сохраняются выраженные структурные изменения печени, включая фиброз и цирроз. В связи с этим актуальным является поиск дополнительных методов, способствующих регенерации печёночной ткани и улучшению функционального состояния печени.

Цель исследования: Провести сравнительную оценку клинической эффективности трансплантации фетальных стволовых гепатоцитов в составе комплексной терапии цирроза печени, ассоциированного с хроническим вирусным гепатитом С.

Материалы и методы: Проведено проспективное сравнительное исследование с участием 106 пациентов с циррозом печени в исходе ХВГС. Пациенты были распределены на две сопоставимые группы по 53 человека. Основная группа получала противовирусную терапию препаратами прямого действия в сочетании с трансплантацией фетальных стволовых гепатоцитов, контрольная группа — только противовирусную терапию. Всем пациентам проводили клиническое, лабораторное и

инструментальное обследование, включая транзитную эластографию печени. Эффективность лечения оценивали по динамике шкал Child-Pugh и MELD в течение 12 месяцев наблюдения. Статистическую обработку данных выполняли с использованием методов параметрического и непараметрического анализа.

Результаты: Исходно показатели Child-Pugh и MELD в группах статистически не различались. Через 12 месяцев наблюдения показатель Child-Pugh в основной группе составил $7,11 \pm 0,91$ балла против $7,81 \pm 1,13$ балла в контрольной группе ($p=0,002$). Значение MELD через 12 месяцев также было достоверно ниже в основной группе — $17,9 \pm 2,11$ против $19,1 \pm 2,21$ балла соответственно ($p=0,004$). Дисперсионный анализ выявил статистически значимое влияние как времени наблюдения, так и применяемой терапии на показатели Child-Pugh ($\eta^2=35,9\%$ и $\eta^2=25,0\%$ соответственно) и MELD ($\eta^2=23,3\%$ и $\eta^2=18,2\%$ соответственно; $p<0,001$).

Заключение: Включение трансплантации фетальных стволовых гепатоцитов в комплексную терапию пациентов с циррозом печени в исходе ХВГС способствует более выраженному улучшению функционального состояния печени по сравнению со стандартной противовирусной терапией. Полученные результаты подтверждают перспективность применения клеточных технологий в комплексном лечении цирроза печени и обосновывают необходимость дальнейших исследований для оценки их долгосрочной эффективности и безопасности.

Ключевые слова: хронический вирусный гепатит С, цирроз печени, клеточная терапия, фетальные стволовые гепатоциты, трансплантация клеток, Child-Pugh, MELD, регенеративная медицина.

უჯრედული თერაპიის როლი ქრონიკულ C ვირუსულ ჰეპატიტთან ასოცირებული ღვიძლის ციროზის კომპლექსურ მკურნალობაში

აქტუალობა: მიუხედავად პირდაპირი მოქმედების ანტივირუსული პრეპარატების მაღალი ეფექტურობისა ქრონიკული C ვირუსული ჰეპატიტის (HCV) მკურნალობაში, პაციენტთა მნიშვნელოვან ნაწილში კვლავ ნარჩუნდება ღვიძლის გამოხატული სტრუქტურული დაზიანებები, მათ შორის ფიბროზი და ციროზი. ამასთან დაკავშირებით აქტუალურია დამატებითი მეთოდების ძიება, რომლებიც ხელს შეუწყობს ღვიძლის ქსოვილის რეგენერაციას და მისი ფუნქციური მდგომარეობის გაუმჯობესებას.

მიზანი: შეფასდეს ფეტალური ღეროვანი ჰეპატოციტების ტრანსპლანტაციის კლინიკური ეფექტურობა ქრონიკულ C ვირუსულ ჰეპატიტთან

ასოცირებული ღვიძლის ციროზის კომპლექსური მკურნალობის შემადგენლობაში.

მასალა და მეთოდები: ჩატარდა პროსპექტიული შედარებითი კვლევა, რომელშიც მონაწილეობდა HCV-თან ასოცირებული ღვიძლის ციროზის მქონე 106 პაციენტი. პაციენტები გადანაწილდნენ ორ შესადარებელ ჯგუფად, თითოეულში 53 პაციენტი. ძირითადი ჯგუფი იღებდა პირდაპირი მოქმედების ანტივირუსულ თერაპიას ფეტალური ღეროვანი ჰეპატოციტების ტრანსპლანტაციასთან ერთად, ხოლო საკონტროლო ჯგუფი მხოლოდ ანტივირუსულ თერაპიას. ყველა პაციენტს ჩატარდა კლინიკური, ლაბორატორიული და ინსტრუმენტული გამოკვლევები, მათ შორის ღვიძლის ტრანზიენტული ელასტოგრაფია. მკურნალობის ეფექტურობა შეფასდა Child-Pugh-ისა და MELD-ის სკალების დინამიკის მიხედვით 12-თვიანი დაკვირვების პერიოდში. სტატისტიკური ანალიზი განხორციელდა პარამეტრული და არაპარამეტრული მეთოდების გამოყენებით.

შედეგები: საწყის ეტაპზე Child-Pugh-ისა და MELD-ის მაჩვენებლები ჯგუფებს შორის სტატისტიკურად არ განსხვავდებოდა. 12-თვიანი დაკვირვების შემდეგ Child-Pugh-ის მაჩვენებელი ძირითად ჯგუფში შეადგენდა $7,11 \pm 0,91$ ქულას, ხოლო საკონტროლო ჯგუფში — $7,81 \pm 1,13$ ქულას ($p=0,002$). MELD-ის მაჩვენებელიც სარწმუნოდ დაბალი იყო ძირითად ჯგუფში — $17,9 \pm 2,11$, საკონტროლო ჯგუფში კი $19,1 \pm 2,21$ ქულა ($p=0,004$). დისპერსიულმა ანალიზმა აჩვენა როგორც დაკვირვების ხანგრძლივობის, ისე გამოყენებული თერაპიის სტატისტიკურად მნიშვნელოვანი გავლენა Child-Pugh-ის ($\eta^2=35,9\%$ და $\eta^2=25,0\%$, შესაბამისად) და MELD-ის მაჩვენებლებზე ($\eta^2=23,3\%$ და $\eta^2=18,2\%$, შესაბამისად; $p<0,001$).

დასკვნა: ფეტალური ღეროვანი ჰეპატოციტების ტრანსპლანტაციის დამატება სტანდარტულ ანტივირუსულ თერაპიასთან იწვევს ღვიძლის ფუნქციური მდგომარეობის უფრო გამოხატულ გაუმჯობესებას HCV-თან ასოცირებული ღვიძლის ციროზის მქონე პაციენტებში, ვიდრე მხოლოდ ანტივირუსული თერაპია. მიღებული შედეგები ადასტურებს უჯრედული ტექნოლოგიების პერსპექტიულობას ღვიძლის ციროზის კომპლექსურ მკურნალობაში და ამართლებს შემდგომი კვლევების ჩატარების აუცილებლობას მათი გრძელვადიანი ეფექტურობისა და უსაფრთხოების შესაფასებლად.

საკვანძო სიტყვები: ქრონიკული C ჰეპატიტი, ღვიძლის ციროზი, უჯრედული თერაპია, ფეტალური ღეროვანი ჰეპატოციტები, უჯრედების ტრანსპლანტაცია, Child-Pugh, MELD, რეგენერაციული მედიცინა.