DECUBISON

Prospective multicenter randomized controlled low-interventional post-registration study

Final report

Nutricia

2021

Study Title	Prospective multicenter randomized controlled low-interventional post-registration study to assess the clinical efficacy of the specialized enteral tube nutrition composition Nutrison Advanced Cubison as a part of complex Pressure Ulcers (PU) therapy versus standard enteral tube nutrition products
Protocol Code	DECUBISON (DEcubitus observation study with CUBISON)
Protocol version	1.0
Protocol Date	17 MAY 2021
Active ingredient	Not applicable
Study Product	Nutrison Advanced Cubison 500ml (further could be called SP – Study Product) (5.5 g of protein/ 104 kkal /100 ml) (РЕГ. № RU.77.99.32.004.R.001267.05.20 of 22.05.2020), manuf. N.V. Nutricia, Eerste Stationsstraat 186 2712 HM Zoetermeer (Netherlands (not a medicinal product)
Study Phase	Post registration randomized controlled low-interventional study
Study population	60 patients, admitted to hospitals with stroke, traumatic brain injury, with tube feeding and diagnosed pressure ulcers stages 2-3 in two groups.
Study location	Russian Federation
Study sponsor	JSC Nutricia Advance (OGRN 1025001816256) 143421, Moscow Region, Krasnogorsky District, 26th km of the Baltiya Highway, Riga Land business center, build. B Authorized person: **Tatyana Novikova, MD** Medical Manager, M.D. Danone Specialized Nutrition CIS phone: +7 (916) 561 56 97 email: tatyana.novikova@danone.com
Study objectives	Primary objective: • To study the efficacy of the study product in the complex therapy of pressure ulcers in patients with tube feeding. Secondary objectives: • Study of the influence of the investigational product on the trophological status of the patients for certain blood parameters, • To study the effect of the study product on the incidence of infectious complications of pressure ulcers in study patients, • Study of the effect of the investigational product on the duration of the stay of the research patients in the ICU. In the course of the research, additional research objectives can be refined and supplemented.
CTMS	Enrollme.ru®
Principal Investigator	**Diana Nevzorova, MD, PhD** Chief specialist of the Ministry of Health of Russia for palliative care Director of the Federal Scientific and Practical Center for Palliative Care +7(909) 162-3635 Gyn_Nevzorova@mail.ru
Organization engaged by the Sponsor for the study conduct	Enrollme.ru LLC (OGRN 1187746457249) 121205, Moscow, territory of the Skolkovo Center, Nobel Str., 7 Authorized person: Mikhail Getman, PharmD, PhD CEO phone: +7(915)322-7080 email: mikhail.getman@enrollme.ru

1. Content

2. Tables and Figures

3. Study Summary

Study title: Prospective multicenter, randomized, controlled, low-intervention, post-registration study evaluating the clinical efficacy of a specialized tube feeding product Nutrizone Edvanst Cubison in the treatment of pressure ulcers in comparison with standard tube feeding.

Protocol version and date: DECUBISON v.1.0 dated May 17, 2021

Rationale for the study:

Pressure ulcers are a type of injury in which destruction of the skin and underlying tissues occurs under conditions where the skin area is under constant pressure for a period of time, causing tissue ischemia, interruption of tissue nutrition and oxygen supply, and ultimately leading to tissue necrosis.

In the United States, about 1–3 million people develop pressure ulcers each year, and 60,000 people die each year from complications caused by them. In the United States, between 1990 and 2000, pressure ulcer prevalence has been reported ranging from 10% to 18% in emergency care, 2.3% to 28% with long-term care, and up to 29% with home care, and 0% up to 6% in the rehabilitation system. Pressure ulcers impair the quality of life of patients due to pain, painful treatments and prolonged hospital stays. In addition, they lead to the death of some patients.

In the European Union, the prevalence of pressure ulcers ranges from 8.3% in Italy to 22.9% in Sweden. In Portugal, the United Kingdom and Belgium, the study rate was 12.5%, 21.8% and 21.1%, respectively, and the overall prevalence in all five countries was 18.1%.

A large number of studies are devoted to studying the effect of patient nutrition on the occurrence and treatment of pressure ulcers. Several studies, including the US National Long-term Treatment of Pressure Ulcers Study, have shown that weight loss and malnutrition were associated with a higher risk of pressure ulcers. Other work, through a systematic review and meta-analysis, investigated the benefits of nutritional support in patients at risk of developing pressure ulcers and demonstrated the effectiveness of oral and enteral nutritional support in preventing pressure ulcers.

Based on a systematic comprehensive review of peer-reviewed published studies of pressure ulcers from 1998 to January 2008, NPUAP and EPUAP developed and published clinical guidelines for the prevention and treatment of pressure ulcers (2009). Evidence-based guidelines, especially those focusing on nutrition for older people, emphasize that despite much research, there is still a need to identify and seek out the most effective ways to manage malnutrition.

A meta-analysis of research data has shown that giving patients a high-calorie (250-500 kcal) high-protein supplement is associated with a 25% reduction in pressure ulcers in at-risk individuals compared with routine care. There is also evidence of the effectiveness of supplementation in increasing the rate of healing of pressure ulcers, with the duration of the intervention being at least 4 weeks before complete healing. Such research confirms not only the importance of additional energy and protein, but also the beneficial effects of arginine and micronutrient supplementation (zinc and antioxidants).

One of the successful products specially created for the treatment of pressure ulcers and taking into account the results of research is the high-protein, energy-rich, ready-to-use enteral tube feeding food product Nutrison Advanced Cubison. It is a complete enteral nutritional supplement with an innovative nutrient composition for patients with chronic wounds, including pressure ulcers, or at increased risk of developing them.

The study of the benefits of oral and enteral supplements of the Nutrison Advanced Cubison / Cubitan family compared with a standard dietary approach was carried out in a 12-week randomized controlled trial. As a result, after 12 weeks in the study group of specialized nutrition, a higher healing rate was observed according to the results of the PUSH scale compared to the standard diet, and the decrease in the surface area of the pressure ulcer was significantly higher in patients already at 8 weeks.

Taking into account the available data, it seems expedient to continue studying the unique combination of nutrients that make up the study food product Nutrison Advanced Cubison in order to develop the most effective nutritional protocols for patients at risk for the treatment and prevention of pressure ulcers.

To organize the recruitment of patients, account for screening parameters and collect research data, a temporary network of physicians and researchers will be created, as well as a network database based on the digital technology of research management developed by Enrollmi.ru LLC (a member of the Skolkovo project).

Study sponsor: JSC Nutricia (OGRN 1025001816256)

Objectives of the study: The main objective of the study is to study the effect of the investigational product (PI) in the complex therapy of pressure ulcers in patients receiving tube feeding. Among the additional objectives of the study is to study the effect of the study product on the trophological status of study patients by some blood parameters, on the incidence of infectious complications of pressure ulcers in study patients and the duration of intensive care. Potential adverse events will also be investigated and described.

Study design: A prospective, multicenter, randomized, low-intervention, post-marketing, comparative study.

Study location: Russian Federation

Study population: The study will enroll 60 patients who meet the inclusion / exclusion criteria of both sexes 25 - 75 years old equally in two groups.

Duration of observation: up to 28 days from the date of Visit 1.

Data Sources: Electronic CRFs and Adverse Event Report Forms completed by the investigating physician during visits will be used to collect data. The study comprises screening, 2 visits and daily pressure ulcer observation.

4. Ethics

The DECUBISON study was prepared and conducted in accordance with statutory, regulatory, industry standards and applicable ethical requirements. Among the main criteria that define a prospective observational study are the following:

- the research is carried out for a scientific purpose;
- the study must have a program (protocol, plan) of the study, in which, in particular, interaction with medical professionals and / or organizations in which the study is conducted and the Organizer must be defined;
- the research protocol must be approved by the scientific department of the company, which must control the conduct of the research;
- the research protocol must be submitted to the ethics committee for review;
- the research should not stimulate the recommendation, prescription or sale of the investigational product;
- a condition for the inclusion of a patient in a non-interventional study is to obtain his / her voluntary informed consent in writing;
- Study results should be analyzed, a summary of results published within a reasonable time frame, and a final report received by all observer physicians participating in the program. If the survey results are relevant to the assessment of the utility's risk indicators, the final report should be sent immediately to the appropriate regulatory body.

The DECUBISON study protocol and design met these criteria.

4.1. Ethics review

The study was approved by the decision of the Independent Interdisciplinary Committee on the Ethical Review of Clinical Trials, Extract from Minutes No. 10 of the meeting of the Independent Interdisciplinary Committee on the Ethical Review of Clinical Trials on June 11, 2021 (protocol version 1.0).

The copy is attached.

Независимый междисциплинарный Комитет
по этической экспертизе клинических исследований

125468, Москва, Ленинградский пр-т, 51, тел. 8 (915) 346-30-30

Выписка из протокола № 10
заседания
Независимого междисциплинарного Комитета
по этической экспертизе клинических исследований
от 11.06.2021

Присутствовали: председатель Вольская Е.А., члены Комитета Береснева С.Л., Малый А.Ю., Маричева Л.Б., Мельцтер М.Ю., Миронова С.Е., Тимофеева И.Г.

Заседание состоялось в формате телеконференции.

Слушали: Рассмотрение вопроса об одобрении исследования «Проспективное многоцентровое рандомизированное малоинтервенционное пострегистрационное исследование по оценке клинической эффективности специализированного продукта для зондового питания Нутризон Эдванст Кубизон в комплексной терапии пролежней в сравнении со стандартным зондовым питанием» (ДЕКУБИЗОН) (организатор исследования - ООО «Нутриция», оператор электронной платформы исследования - ООО «Энроллми.ру»).

Представленные документы:

1. Мастер файл исследования DECUBISON v.1.0 от 17.05.2021 г. на 71 листе.
2. Форма Информационного листка пациента и информированного согласия на участие пациента в исследовании и обработку персональных данных на 7 листах.

Постановили: Одобрить исследование «Проспективное многоцентровое рандомизированное малоинтервенционное пострегистрационное исследование по оценке клинической эффективности специализированного продукта для зондового питания Нутризон Эдванст Кубизон в комплексной терапии пролежней в сравнении со стандартным зондовым питанием» (ДЕКУБИЗОН) (организатор исследования - ООО «Нутриция», оператор электронной платформы исследования - ООО «Энроллми.ру»).

Ответственный секретарь **Береснева С.Л.**

Выписка выдана 24.06.2021

Независимый междисциплинарный
Комитет по этической экспертизе
клинических исследований

5. Study management

The initiator and sponsor of the DECUBISON study is Nutricia LLC (OGRN 1025001816256).

Contract Research Organization - Enrollme.ru LLC (OGRN 1187746457249)

Task	**Nutricia**	**Enrollme.ru**
Study documentation	Approves	Develops
Obtaining ethical review	-	Gains approval from the Independent Committee on the Ethical Review of Clinical Research
Training of the Sponsor's representative to work with Enrollme.ru CTMS	Appoints a representative responsible for work in IS Enrollmi.ru	Trains Sponsor’s representatives to work with electronic forms of documents in Enrollme.ru CTMS
Centers recruitment and start-up	Searches and recruits medical researchers	Provides technical support for the registration of doctors in Enrollme.ru CTMS
Contracts	-	Concludes contracts, maintains paperwork, closes contracts, pays research grants
Centers training	-	Trains researchers to work with electronic forms of documents in Enrollme.ru CTMS
Centers’ relations	-	Communicates with researchers, centers, provides assistance and technical support (ensuring operability and troubleshooting)
Enrollment of patients	-	Controls the enrollment of patients into the study and adherence to the enrollment deadlines
Study monitoring	If necessary, monitors the study with a visit to the research center, including control of CRFs and the compliance of the data with primary medical documentation	Performs remote control, makes queries to the data and closes CRFs for editing
Use of Enrollme.ru CTMS	Uses Enrollme.ru CTMS for the entire period of the study	Provides technical support (ensuring operability and troubleshooting) during the study
Data management	-	Cleaning of the database, preparation of datasets for statistical analysis

Task	**Nutricia**	**Enrollme.ru**
Statistics Report	Approves	Statistical analysis of the data, prepares a Statistical Report
Final report of the study	Approves	Prepares the Final Study report
RESPONSIBLE PERSONS	JSC Nutricia Advance (OGRN 1025001816256) 143421, Moscow Region, Krasnogorsky District, 26th km of the Baltiya Highway, Riga Land business center, build. B Authorized person: Tatyana Novikova, MD Medical Manager, M.D. Danone Specialized Nutrition CIS phone: +7 (916) 561 56 97 tatyana.novikova@danone.com	Enrollme.ru LLC (OGRN 1187746457249) 121205, Moscow, territory of the Skolkovo Center, Nobel Str., 7 Authorized person: Mikhail Getman, PharmD, PhD CEO phone: +7(915)322-7080 email: mikhail.getman@enrollme.ru

Study centers

Location	**Number**
Moscow	2
Samara	1
Bryansk	1

	Study group leader	Location	Hospital
1	Vaskovskaya Inga	Moscow	GBUZ GKB named after VV Vinogradov DZM
2	Morev Andrey	Moscow	Sechenov University, Federal Scientific and Practical Center PMP
3	Usov Aleksey	Samara	Hospital named after V.D. Seredavin
4	Vorontsov Alexey	Bryansk	GAUZ Bryansk city hospital №1

6. Study objectives

Primary objective:

- To study the efficacy of the study product in the complex therapy of pressure ulcers in patients with tube feeding.

Secondary objectives:

- Study of the influence of the investigational product on the trophological status of the patients for certain blood parameters,
- To study the effect of the study product on the incidence of infectious complications of pressure ulcers in study patients,
- Study of the effect of the investigational product on the duration of the stay of the research patients in the ICU.

7. The study process

7.1.The study design

The Russian Prospective multicenter, randomized, low-intervention, post-registration study evaluating the clinical efficacy of a specialized product for tube feeding Nutrison Advanced Cubison in the complex therapy of pressure ulcers in comparison with standard tube feeding provides the following methodology.

Doctors are recruited to the study in accordance with the standard algorithm used in Enrollme.ru CTMS after registration and qualification by the Sponsor.

Researchers will screen patients according to inclusion / exclusion criteria. Taking into account the severity of the patient's condition, the difficulty in obtaining informed consent to participate in the study and the processing of personal data from the patient's legal representatives, registration of patients for the study in Enrollme.ru CTMS will be carried out in a blinded form without specifying the patient's personal data. The patient may be included in the study on the basis of 1) Informed consent to participate in the study and the processing of personal data signed by the patient himself before being included in the study or after gaining his ability to read and sign Informed consent, 2) Informed consent signed by the patient's legal representative. The signing and dating of the document is carried out on paper, for which the doctor prints out the document in 2 copies, invites the patient to get to know him and sign in case of consent, and the signed document remains stored in the archives of the doctor-researcher. The research physician must make sure that informed voluntary consent to medical intervention is formalized in accordance with the requirements of the Federal Law of 21.11.2011 N 323-FZ "On the basics of protecting the health of citizens in the Russian Federation."

The study will include 60 patients hospitalized with strokes or traumatic brain injury, who are on tube feeding and with the presence of pressure ulcers of 2-3 stages identified at baseline or during hospital stay. The patients will be randomly divided into two groups: a study group of 30 people and a control group of 30 people.

Inclusion in the study, observation and assessment of the effectiveness of nutritional support begins from the moment of registration of pressure ulcers in a patient with stable hemodynamics.

The duration of the tube feeding period: according to the patient's ability to switch to oral nutrition or if the patient is medically necessary to transfer the patient to parenteral nutrition.

Start appointments in any department of the hospital.

During the study, physicians-researchers will use electronic individual registration cards (CRF) and electronic reports on adverse events (ADR), automatically generated in the IS Enrollmi.ru for data collection.

In total, the study provides for screening and 2 visits (B0-B1-B2).

- Screening and visit 1 are carried out on the day of detection of a pressure ulcer of stage 2-3 in a patient after considering other criteria, assigning the patient to the study group and prescribing an appropriate diet (in person);

- Visit 2 is carried out after the removal of the pressure ulcer, but no more than 28 days from the date of the patient's inclusion (in person);

At each visit, the investigator fills out a Patient Record Form (CPF), a weekly observation diary.

If an adverse event is detected during the study, the investigator fills out an adverse event report (AER).

7.2.The study setting

The study will include 60 patients hospitalized with strokes or traumatic brain injury, who are on tube feeding and with the presence of pressure ulcers of 2-3 stages identified at baseline or during hospital stay. The patients will be randomly divided into two groups: a study group of 30 people and a control group of 30 people.

Group 1 (research): 30 adult patients aged 30-75 years are randomized to a study group and receive a specialized tube feeding product Nutrison Advanced Cubison (20% protein energy 100 kcal, 5.5 g protein, 0.85 g arginine, 38 mg of vitamin C and 2 mg of zinc) in a volume not exceeding 1.5 liters / day and, if necessary, to replenish nutritional needs based on the total daily intake of 30-35 kcal / kg / day and 1.2-1.5 g of protein / kg body weight / day according to the recommendations for nutritional support for patients with pressure ulcers 1 during the entire observation period. Provided that 1.5 liters of the test product is insufficient to replenish the nutritional needs, based on the proposed criteria, the patient will additionally receive the same food product as in the control group until the required calorie value is reached.

Group 2 (control): 30 patients aged 30-75 years are randomized to a control group and receive a standard (available in the clinic) tube feeding product (similar to the product in group 1) with a standard content of arginine, vitamins and minerals from calculating the total daily intake of 30-35 kcal / kg / day and 1.2-1.5 g protein / kg body weight / day according to the recommendations for nutritional support for patients with pressure ulcers during the entire observation period.

The nutritional value of enteral nutrition is the same in both groups.

To collect data and carry out communications in the course of the study, the IS Enrollmi.ru will be used.

The participation of physicians and patients in this study should not change the usual diagnostic and treatment procedures for enrolled patients, nor should it stimulate the prescription of the investigational product in cases where the rationale for such prescription is not clear.

The Study sponsor reserves the right to terminate the study ahead of schedule or terminate the powers of the doctor-researcher, or withdraw the patient's participation in the following cases:

- The impossibility of obtaining the expected results for the enrollment in the study as a whole or from a specific doctor-researcher.
- The emergence of information about the investigational product that may adversely affect or create uncertainty regarding the safety of research subjects or limit the achievement of research objectives for administrative reasons.
- Violations of the protocol, terms of the contract, applicable legal requirements that may negatively affect the course of the study, the use of its results, or have administrative consequences.

Inclusion, non-inclusion and exclusion criteria

Patients must meet all of the following eligibility criteria for study entry:

- Age 25 - 75
- Patients diagnosed with stroke / TBI and who are on tube feeding
- Presence of pressure ulcers of 2-3 stages
- Informed voluntary consent to medical intervention is formalized in accordance with the requirements of the Federal Law of 21.11.2011 N 323-FZ "On the basics of protecting the health of citizens in the Russian Federation."

A patient cannot be included in the study or should be excluded from the study if he meets at least one of the following exclusion / exclusion criteria:

- Hemodynamically unstable patients
- Severe renal impairment (GFR <30 ml / min)
- Moderate or severe liver failure (Child-Pugh Class B or C)
- Oncological diseases (lasting more than 5 years)
- Hypersensitivity to any component of the test food mixture
- Inclusion in clinical interventional research
- Uncertainty of the investigator about the willingness or ability of the subject to comply with the protocol requirements
- Any other medical or non-medical reasons that, in the opinion of the physician, may prevent the patient from participating in the study.

Reasons for discontinuing a study in a patient:

- If, during the study, the investigating physician identifies events in the patient that meet at least one criterion of non-inclusion / exclusion, such a patient should be excluded from the study;
- Deterioration of the patient's condition, requiring his transfer to parenteral nutrition;
- Transfer of the patient to another hospital;
- Complications that could be caused by the tube feeding product;
- Withdrawals for safety reasons: If the reason for the patient's withdrawal from the study is an AE or a laboratory abnormality, that specific event or analysis should be reported in the Adverse Events Report. If a patient drops out of the study due to an AE, the investigator should make every effort to clearly indicate its outcome.
- Refusal of the patient (his legal representative) from further participation in the study or the provision of medical care. At the same time, the exclusion of a patient from the study should not affect the nature of his therapy.
- Death of the patient.

7.3. Randomization

Patients are randomized to study and control groups according to an end-to-end algorithm using a Mersenne vortex random number generator. Regardless of the center and the research doctor, the next enrolled patient is automatically assigned to one or the other group after the research doctor decides to include the patient. The information about the distribution of the patient becomes known to the doctor and the patient.

If a patient is dropped from the study, their randomization number is returned to the general pool of numbers.

7.4. Endpoints

The protocol provided for the following endpoints.

Primary endpoints:

- Changes in the area of pressure ulcers in both groups during the study;
- The proportion of patients in both groups with a decrease in the area of the pressure ulcer by 20% or more by the date of completion of observations;
- Changes in the Pressure Ulcer Scale for Healing (PUSH) values in both groups during the study.

Secondary endpoints:

- Duration of treatment for pressure ulcers in study patients;
- Frequency and duration of infectious complications of pressure ulcers in study patients;
- Blood albumin at the beginning and at the end of observations;

- Blood lymphocytes at the beginning and at the end of observations;
- C-reactive protein at the beginning and at the end of observations.

In the course of the statistical analysis, other research data of clinical significance were additionally processed (section "Plan of statistical analysis»).

8. Quality control

Before the start of the study, Enrollme.ru specialists trained medical researchers on the following issues:

- Research protocol
- Criteria for inclusion / exclusion / exclusion
- How to work with Enrollme.ru interfaces
- Procedure for obtaining informed consent from the patient
- The procedure for filling out electronic KFMs
- Inquiries and verification of completed CRFs

Enrollme.ru provided participants with a User Guide containing a step-by-step presentation of the Enrollme.ru algorithms that should be used during the study.

In the event of technical problems during the study, Enrollme.ru provided a prompt 48-hour response to identified problems.

Continuous quality control of the study is carried out in accordance with the Data Management Plan. Research progress was monitored remotely; there were no face-to-face visits to research centers. Subject to control:

- Recruitment of research doctors
- Patient recruitment, patient signing informed consent, recruitment schedules
- Compliance with the schedule of visits to each patient
- Contents of completed records of each patient at each visit

Requests to the CRF data were made by authorized employees of Enrollme.ru.

Data quality control before closing the database includes:

- Completeness and integrity of the database,
- Missing or inaccurate data, requests for data, their correction,
- Combining several databases in the case of using several versions of the KFM,
- Annotating data fields,
- Creating a master copy of the database,
- Formation of data sets for analysis and their rechecking.

All actions with the research base are recorded in the information system.

9. Statistical analysis plan

Primary and secondary analyzes are represented by descriptive statistics. All continuous variables are summed using the following parameters: n (sample size of available patients), mean, standard deviation, median, 25th and 75th percentiles, maximum and minimum. Results will be presented for analysis populations of patients and study groups. The critical p-value and confidence intervals will be calculated as two-sided. The study will assume a statistical significance level of 0.05 (two-sided testing, all p-values will be rounded to three decimal places).

Continuous variables are described using the arithmetic mean, standard deviation, 95% confidence intervals, median, upper and lower quartiles.

Categorical variables are presented as frequency percentages.

Replacement and restoration of missing data is not provided. All variables will be compared before and after a specified observation period. To test the significance of differences in normally distributed data, the corresponding varieties of analysis of variance will be used. For other distributions, the Wilcoxon test will be used.

The chi-square test or Fisher's exact test will be used to test the significance of differences in categorical data.

Analysis of the primary and secondary endpoints will be performed on the full dataset (ITT, intention-to-treat).

Переменные

№	Endpoint	Population	Method
1	Proportion of patients whose pressure ulcer was completely healed (%)	Treatment Control	Number of patients with healed pressure ulcer / total number of patients in the group * 100% Difference between groups
2	Duration of treatment for pressure ulcers in study patients (days)	Treatment Control	Average number of days to complete cure per group (cured patients only) Difference between groups
3	Average change in PUSH scores for pressure ulcer area over the observation period	Treatment Control	Mean difference in PUSH scores for pressure ulcer area between visit 2 and visit 1 in the group. Difference between groups
4	Change in the total values of the PUSH scale in both groups during the study	Treatment Control	Average PUSH score difference between visit 2 and visit 1 in the group. Difference between groups
5	Blood lymphocytes at the beginning and at the end of observations	Treatment Control	Average change in lymphocyte count between visit 2 and visit 1. Reliability of changes within each group (no need to compare between groups)
6	Blood albumin at the beginning and at the end of observations	Treatment Control	Mean change in albumin count between Visit 2 and Visit 1.

			Reliability of changes within each group (no need to compare between groups)
7	C-reactive protein at the beginning and at the end of observations	Treatment Control	Mean change in C-reactive protein between visit 2 and visit 1. Reliability of changes within each group (no need to compare between groups)
8	The proportion of patients in both groups with a decrease in the area of the pressure ulcer by 20% or more by the date of completion of observations	Treatment Control	The proportion of patients with a decrease in the area of the pressure ulcer by 20% or more during the observation period. Difference between groups
9	Average number of days until the pressure ulcer area is reduced by at least 20% by the date of completion of observations	Treatment Control	The average number of days until the area of the pressure ulcer is reduced by at least 20% by the date of completion of observations. Difference between groups
10	Change in the area of pressure ulcers in both groups during the observation period (in%)	Treatment Control	Mean value of changes in pressure ulcer area (in%) between visit 2 and visit 1. Difference between groups
11	The incidence of infectious complications of pressure ulcers in study patients	Treatment Control	The proportion of infectious complications of pressure ulcers in the group. Difference between groups

10. Demography and Disposition

Demography

	n	%	Mean	SD	Median	25 Quartile	75 Quartile	Min	Max
Total enrolled	67								
Dropped-out (deaths)	12								
All subjects (PP)	55								
Sex	55								
Male	15	27,27%							
Female	40	72,73%							
Age	55		60,3	14,1	64,0	53,0	72,0	29	75
Height	55		167,9	7,1	168,0	162,0	173,5	156	182
Weight	55		84,3	16,8	85,0	73,0	97,5	46	135
Treatment group	29								
Sex	29								
Male	7	24,14%							
Female	22	75,86%							
Age	29		59,9	13,9	63,0	53,0	70,0	30	75
Height	29		169,0	7,1	168,0	162,0	175,0	160	182
Weight	29		87,9	14,5	89,0	76,0	100,0	60	120
Control group	26								
Sex	26								
Male	8	30,77%							
Female	18	69,23%							
Age	26		60,8	14,7	67,0	50,3	72,8	29	75
Height	26		166,7	7,0	166,5	160,5	170,0	156	182
Weight	26		80,3	18,6	80,0	68,0	92,0	46	135

Comorbidities

ID	Pressure ulcer location	COVID Y/N	Comorbidities
3649	gluteal regions	No	Cerebral infarction in the basin of the branches of the right posterior cerebral artery Essential hypertension III, risk 4 Diabetes mellitus type 2. Individual target HbA1c level <8.0%. Metabolic alkalosis from 08/29/21 Diabetic distal sensory polyneuropathy. Diabetic microangiopathy: diabetic nephropathy. Chronic kidney disease C4 (CKD-EPI 25 mL / min / 1.73 m2). pressure ulcers both gluteal regions
3660	bridge of nose	Yes	Acute cerebrovascular accident (ACVA) Obesity grade 3 Community-acquired bilateral pneumonia Coronavirus infection COVID-19 Pressure ulcer bridge of the nose
3661	bridge of nose	Yes	ACVA, novel coronavirus infection COVID-19, community-acquired bilateral polysegmental pneumonia

			Gestational diabetes mellitus Multiple organ failure Pressure ulcer bridge of the nose
3663	sacrum	Yes	ACVA, novel coronavirus infection COVID-19, bilateral interstitial lung tissue infiltration Ischemic heart disease Dilated cardiomyopathy Obesity Diabetes mellitus type 2 Hypertension 2 gr, risk 4 Pressure ulcer sacrum
3672	buttock	Yes	ACVA ischemic in the left hemisphere, New coronavirus infection COVID-19 Ischemic heart disease Persistent atrial fibrillation Pressure ulcer buttock
3697	sacrum	No	Intracerebral hemorrhage 12 cm3 in the left hemisphere. Massive Subarachnoid hemorrhage (SAH). Cerebral edema. Traces of hemorrhagic contents in 3-4 ventricles. Hypertensive disease, grade III risk 4 COPD Pressure ulcer sacrum
3839	sacrum	Yes	CVA, new coronavirus infection COVID-19, right-sided upper lobe segmental bronchopneumonia Erysipelas Pressure ulcer sacrum
3840	bridge of nose	Yes	Traumatic brain injury (TBI). Subdural hematoma of the frontal region. Novel coronavirus infection COVID-19 Obesity grade 3 Pressure ulcer bridge of the nose
3841	bridge of nose	Yes	ACVA ischemic at left middle cerebral artery. Novel coronavirus infection COVID-19. Bilateral, polysegmental, interstitial infiltration. Atherosclerosis of the aorta and coronary arteries Pressure ulcer bridge of the nose
3842	bridge of nose	Yes	TBI from 09/20/2021 Contusion of the left parietal region. Novel coronavirus infection COVID-19, no virus identified. Community-acquired bilateral polysegmental pneumonia. Pressure ulcer bridge of the nose
3876	gluteal region on the left	No	Cerebral infarction due to unspecified blockage or stenosis of cerebral arteries (I63.5) Ischemic heart disease Postinfarction cardioslerosis of unknown age Paroxysmal form of atrial fibrillation, paroxysm of unknown age, tachyform. CAH2DS-VASc 9 points ХСН2Аст3ФК according to NYHA (FV) Hypertension III st, risk 4 Pressure ulcer of the gluteal region on the left
3987	sacrum	No	Myasthenia gravis. Bilateral polysegmental interstitial infiltration of lung tissue. ARDS DN 3 Hypertension 2 tbsp., Risk 4 Pressure ulcer sacrum
4036	sacrum	No	Intracerebral hemorrhage with the formation of an intracerebral hematoma, volume 10 cm3, total volume with perifocal edema up to 17.6 cm3, from 03.10.2021 (I61.2) Hypertension grade III, risk 4 (I11.9) Ischemic heart disease. lipodermatosclerosis. Closed chest injury. Multiple fractures of 4-5-6-7 ribs on the left. P / traumatic left-sided pneumonia on the left. Left shoulder contusion. Left shoulder bruise. Superficial sedimentation of the area of the left knee joint and left lower leg. (S22.40) Pressure ulcer of the sacrum
4092	sacrum	No	Recurrent cerebral infarction (atherombotic subtype according to TOAST criteria) in the basin of the left middle cerebral artery of unknown age Hypertension grade III, risk 4. Blockade of the anterior branch of the left bundle branch. Acquired heart disease Minor mitral insufficiency. Minor tricuspid valve insufficiency. Bladder atony, chronic urinary retention. (I63.3) Pressure ulcer of the sacrum
4093	sacrum, calcaneal areas	No	Cerebral infarction caused by thrombosis of cerebral arteries. Cerebral infarction in the basin of the right middle cerebral artery. Left-sided mild hemiparesis (I63.3) Atherosclerosis of cerebral vessels (I67.2) Atherosclerotic heart disease. Cardiosclerosis (I25.1) Unspecified diabetes mellitus with neurological complications. Diabetes mellitus type 2. Insulin independent. Diabetic macropathy (E14.4 *) Permanent atrial fibrillation (I48.1)

			Alimentary constitutional obesity (E66.8) Nontoxic single nodular goiter (E04.1) Pressure ulcers of the sacrum, heel areas
4137	bridge of nose	No	ACVA ischemic at left middle cerebral artery Atherosclerosis of the aorta and coronary arteries Hypertension 3 tbsp, risk 4 Type 2 diabetes mellitus Pressure ulcer bridge of the nose
4140	bridge of nose	Yes	ACVA ischemic at left middle cerebral artery. New coronavirus infection COVID-19 (PCR test positive from 03/10/2021). Community-acquired bilateral interstitial pneumonia Diabetes mellitus type 2 Pressure ulcer bridge of the nose
4141	bridge of nose	Yes	ONMK ischemic. Community-acquired bilateral polysegmental interstitial pneumonia. Novel coronavirus infection, no virus identified Pressure ulcer bridge of the nose
4150	sacrum	No	Aneurysmal brain disease, PSA aneurysm. Stroke by hemorrhagic type, subarachnoid hemorrhage Arterial hypertension 3 tbsp Myocardial hypertrophy of the left recumbency Encephalopathy 2 degree stetohepatosis retinal angiopathy decubitus sacrum
4323	sacrum	No	Multifocal cerebral infarction in the basin of the left middle cerebral artery from 23.10.2021. Right-sided hemiparesis. Sensomotor aphasia. (I63.5) Hypertension grade III, risk 4 (I11.9) Pressure ulcer sacrum
4348	sacrum	No	ACVA, ischemic stroke localized in the basin of the right middle cerebral artery, left-sided coarse hemiparesis Arterial hypertension 3 tbsp Vascular atherosclerosis Pressure ulcer sacrum
4351	sacrum	No	Early recovery period of stroke, ischemic stroke, bulbar disorders Arterial hypertension 3 tbsp encephalopathy decubitus sacrum
4369	sacrum	No	Brain infarction in the basin of the right middle cerebral artery with hemorrhagic impregnation from 10/25/2021. Hypertension 2 tbsp., 3 stages. Risk 4. Persistent form of atrial fibrillation. Risk on the CHA2DS2VASc scale - 4 points. Varicose veins of the lower extremities. Gallbladder polyps Pressure ulcer sacrum
4370	sacrum	No	Cerebral infarction in the basin of the right middle cerebral artery from 24.10.21 Left-sided hemiparesis. Left-sided hemihypesthesia. Dysarthria. (I63.5) IHD: atherosclerotic cardiosclerosis (I25.9) Hypertensive heart disease, grade III, screech4 (I11.9) Obesity (E66.9) Pressure ulcer sacrum
4389	sacrum	No	TBI, marginal fracture of the body of the 2nd thoracic vertebra, horizontal fracture of the 3rd thoracic vertebra with damage to the spinal cord bilateral lung contusion right hemotarax open fracture of the condyle of the right humerus with displacement fracture of the pelvis decubitus sacrum
4453	bridge of nose	Yes	ACVA ischemic in the basin of the right middle cerebral artery dated 20.10.2021. Novel coronavirus infection COVID-19, no virus identified Hypertension 2 gr., Risk 4 Pressure ulcer bridge of the nose
4457	heel	Yes	ACVA ischemic in Vertebrobasilar basin (VBB) from 01.11. Novel coronavirus infection COVID-19, no virus identified. Community-acquired bilateral lung tissue infiltration Glaucoma Pressure ulcer heel
4458	scapula	Yes	Subarachnoid hemorrhage from 01.11. Novel coronavirus infection COVID-19, no virus identified. Community-acquired bilateral polysegmental pneumonia. Ischemic heart disease

			Pressure ulcer scapula
4459	left buttock	Yes	ACVA on GT in the left hemisphere from 8.11.2021. Novel coronavirus infection COVID-19, no virus identified. Community-acquired bilateral polysegmental interstitial infiltration. Hypertension 2 tbsp., Risk 4 Pressure ulcer buttock
3583	sacral region	No	CVD, Consequences of ACVA from 29.06.21 IHD LDC: a permanent form of atrial fibrillation. Obesity 2 gr Pressure ulcer sacrum
3640	sacrum	No	Cerebral infarction in the basin of the vertebro-basilar arterial system from 08.16. Hypertension grade III, risk 4. Atherosclerosis BCA. Anemia Chronic cerebral ischemia Pressure ulcers of the sacrum.
3713	left heel area	No	Cerebrovascular disease. The consequences of the earlier ACVA. IHD CH 2 class Type 2 diabetes mellitus Obesity 2 gr Heel pressure ulcer
3726	rib cage	No	Spontaneous non-traumatic intracerebral hematoma in the left hemisphere of the brain of unknown age. Edematous dislocation syndrome. Bilateral pneumonia. pressure ulcers of the head and trunk. Hypertension III gr, risk 4 Pressure ulcer chest
3777	gluteal regions	No	heart attack in the PSMA pool of unknown age. Left-sided hemiplegia. Paresis of gaze to the left. IHD: Atherosclerotic cardiosclerosis. Essential hypertension III, risk4 Hypovolemia. Electrolyte disturbances. Ultrasound signs of occlusive deep vein thrombosis of the left lower Pressure ulcer gluteal region
3980	sacrum	No	ACVA, ischemic stroke from 09/14/2021 undifferentiated Arterial hypertension 3 пк Ischemic heart disease, atherosclerotic cardiosclerosis, CHF 1 cl Chronical bronchitis decubitus sacrum
3985	sacrum	Yes	ACVA ischemic VBB. Novel coronavirus infection COVID-19. Community-acquired bilateral polysegmental interstitial pneumonia. Ischemic heart disease Pressure ulcer sacrum
4069	sacral region	No	ONMK unspecified type 2 diabetes mellitus Arterial hypertension 2 degrees Pressure ulcer sacrum
4070	sacral region	No	ischemic stroke Arterial hypertension 3 tbsp Pressure ulcer sacrum
4100	sacral region	No	CVD. ACVA from 09/29/2021. GB 3 stage 3 art risk 4 SSO Pressure ulcer sacrum
4115	sacrum	No	I63.5 Cerebral infarction in the basin of the left middle cerebral artery from 05.10.21 I11.9 Hypertension grade III risk 4 E11.8 Type 1 diabetes mellitus Pressure ulcer sacrum
4116	sacrum	No	Cerebral infarction in the basin of the left posterior cerebral artery from 07.10.2021 (atherothrombotic subtype according to TOAST) right-sided light hemiparesis, right-sided hemihypesthesia, dysarthria. Diabetes mellitus type 2. Diabetic Macropathy Hypertensive disease grade 3 grade III risk of CVC 4 Obesity due to excess intake of energy resources. BMI 35. Pressure ulcer sacrum
4138	bridge of nose	Yes	ACVA of hemorrhagic type in the right parietal region. New coronavirus infection COVID-19 (PCR positive from 09/20/2021). Community-acquired bilateral polysegmental pneumonia.

			Hypertension 2 gr, risk 3 Pressure ulcer bridge of the nose
4139	sacrum	Yes	Massive subarachnoid hemorrhage (SAH). New coronavirus infection COVID-19 (PCR test positive from 10/10/2021). Bilateral polysegmental interstitial infiltration. Hypertension 2 gr, risk 3 Pressure ulcer sacrum
4142	sacrum	No	ACVA of IT VBB Ischemic heart disease Pressure ulcer sacrum
4293	sacrum	No	Cerebral infarction in the left parietal lobe in the LSMA pool of unknown age. Right-sided hemiparesis. Sensomotor aphasia (I63.5) Diabetes mellitus type 2. (E11.7) Hypertension grade III, risk4 (I11.9) Community-acquired left-sided upper lobe pneumonia. (J18.9) IHD: Atherosclerotic cardiosclerosis. Permanent form of atrial fibrillation. (I25.9) Obesity grade III Pressure ulcer sacrum
4322	heel areas	No	Cerebral infarction in the basin of the left middle cerebral artery from 16.10.2021 (I63.5) Dyslipidemia (E78.9) Hypertension stage III, risk 4. (I11.9) Diabetes mellitus type 2. Pressure ulcer calcaneal area
4324	sacrum	No	Cerebral infarction in the right parietal lobe in the basin of the right middle cerebral artery and in the left occipital lobe in the basin of the left posterior cerebral artery. TOAST cardioembolic subtype. Left-sided moderate hemiparesis. Permanent atrial fibrillation, tachysystole Ischemic heart disease. Postinfarction cardiosclerosis. CA stenting. Chronic heart failure 2A tbsp. NYHA III FC. Pulmonary edema. Right-sided small hydrothorax. Pulmonary hypertension 2 tbsp. Cardiomegaly, atherosclerosis of the aorta and coronary arteries Diabetes mellitus type 2. Individual target HbA1c level <7.5%. Diabetic macropathy. Autoimmune thyroiditis Mild iron deficiency anemia. Pressure ulcer sacrum
4329	sacral region	No	Progressive encephalopathy against the background of conformational changes in protein structures. Tetraparesis. Pathological patterns "GPEDS". Neurogenic bladder. Type 2 diabetes mellitus Pressure ulcer sacrum
4345	sacrum	Yes	ACVA. New coronavirus infection COVID-19, virus identified (PCR test positive from 10/14/2021) Pressure ulcer sacrum
4346	sacrum	Yes	ACVA of IT. New coronavirus infection COVID-19, virus identified (PCR test positive from 10/20/2021) Obesity Pressure ulcer sacrum
4347	sacrum	Yes	ACVA. Novel coronavirus infection COVID-19, no virus identified. Community-acquired bilateral polysegmental pneumonia. Obesity 3 tbsp. Pressure ulcer sacrum
4350	right buttock	Yes	ACVA of IT in VBB (20.10.2021). Novel coronavirus infection COVID-19, no virus identified. Bilateral polysegmental interstitial pneumonia Pressure ulcer buttock
4454	scapula	Yes	ACVA of IT LSMA dated 10/15/2021. New coronavirus infection COVID-19 (PCR test from 10/19/2021 is determined). Community-acquired bilateral polysegmental interstitial pneumonia. small uterine fibroids adenomyosis anemia pressure ulcer scapula
4455	sacrum	No	Cerebral edema, meningitis upper lobe pneumonia decubitus sacrum
4456	sacrum	Yes	ACVA in the left hemisphere of the GM. New coronavirus infection COVID-19 (PCR test from 10/26/2021 is determined) Ischemic heart disease

	Hypertension 3 gr, risk 4 Pressure ulcer sacrum

Deaths

Due to the negative development of the underlying and concomitant diseases, 12 (twelve patients) dropped out of the study due to death. None of the deaths were attributed to a direct or indirect cause attributable to the use of the study product in the judgment of the treating physicians.

The study death cases declaration

Patient ID	Sex	Age (years)	Group	Underlying disease	Date Enrolled	Date of Death	Cause of death
3520	female	70	Control	Acute cerebrovascular accident (ACVA)	27/07/2021	29/07/2021	COVID-19
3552	male	71	Control	ACVA, ischemic stroke localized in the area of the right posterior cerebral artery, left-sided rough hemiparesis	02/08/2021	14/08/2021	Poststroke vascular embolism
3621	male	75	Trial	Cerebral infarction in the basin of the left middle cerebral artery from 03/08/2021. Atherothrombotic type. Right-sided hemiplegia. Motor aphasia.	21/08/2021	27/08/2021	Poststroke vascular embolism
3662	female	59	Trial	Stroke, new coronavirus infection COVID-19, bilateral pneumonia	04/09/2021	08/09/2021	COVID-19
3664	female	50	Trial	ACVA, new coronavirus infection COVID-19	04/09/2021	26/09/2021	COVID-19
3912	female	62	Control	Early recovery period of stroke, ischemic stroke, bulbar disorders	01/10/2021	13/10/2021	Poststroke vascular embolism
4164	male	73	Control	Stroke, ischemic stroke of 14/09/2021 undifferentiated	20/10/2021	24/10/2021	Undeclared
4452	male	58	Control	Ischemic stroke of 24/10/2021	10/11/2021	17/11/2021	Recurrent stroke
3601	male	72	Trial	Stroke, lacunar ischemic stroke in PSMA, dysarthria, dysphagia	16/08/2021	24/08/2021	Cardiovascular event
3807	female	71	Control	ACVA. Novel coronavirus infection COVID-19, no virus identified	22/09/2021	15/10/2021	COVID-19
4149	female	73	Control	ACVA unspecified, DEP	19/10/2021	30/10/2021	Undeclared
4358	male	18	Control	TBI, cerebral edema	29/10/2021	13/11/2021	COVID-19, pneumonia

11. Efficacy study

11.1. Summary on efficacy

№	Endpoint	Treatment group	Control group	Proven Yes/No
1	Proportion of patients whose pressure ulcer was completely healed (%)	62,07%	34,62%	Yes
2	Duration of pressure ulcers complete healing (days)	21,28 days	24,44 days	Yes
3	Average change in PUSH scores for pressure ulcer area over the observation period	-3,24	-2,46	No
4	Change in the total values of the PUSH scale in both groups during the study	-7,00	-5,23	No
5	Blood lymphocytes at the beginning and at the end of observations	7,31	6,73	No
6	Blood albumin at the beginning and at the end of observations	4,66	2,54	No
7	C-reactive protein at the beginning and at the end of observations	-63,32	-74,42	No
8	The proportion of patients in both groups with a decrease in the area of the pressure ulcer by 20% or more by the date of completion of observations	86.21%	69.23%	No
9	Average number of days until the pressure ulcer area is reduced by at least 20% by the date of completion of observations	16,03 days	20,27 days	Yes
10	Change in the area of pressure ulcers in both groups during the observation period (in%)	-76,87%	-51,25%	Yes
11	The incidence of infectious complications of pressure ulcers in study patients	0,00%	7,69%	No

11.2. Proportion of patients whose pressure ulcer was completely healed (%)

At the end of the observation, the total number of patients in the study and control groups in whom the pressure ulcer was completely healed was calculated.

Table 1. Number and share of patients with completely healed pressure ulcer

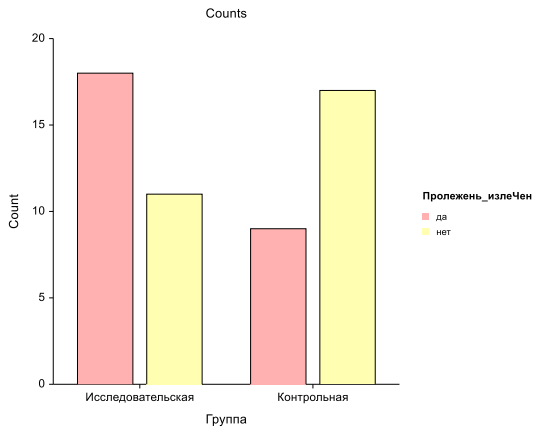
Group	Yes Count	No Count	Total Count	Proportion
Treatment	18	11	29	62,07%
Control	9	17	26	34,62%

Two-Sided Tests of the Difference (P1 - P2)
H0: P1 = P2 vs. Ha: P1 ≠ P2

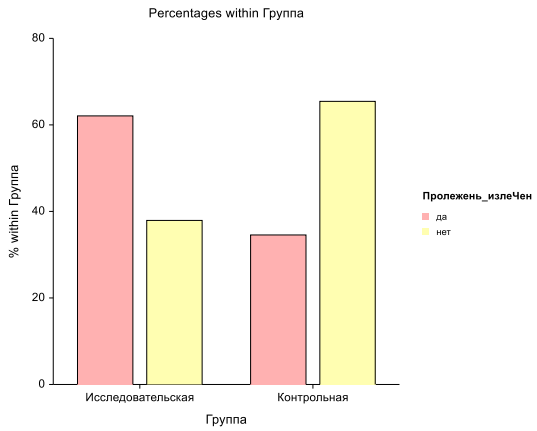
Test Statistic Name	p1	p2	Difference p1 - p2	Test Statistic Value	Prob Level	Reject H0 at α = 0,05?
Wald Z	0,6207	0,3462	0,2745	2,033	0,0420	Yes
Wald Chi-Square	0,6207	0,3462	0,2745	4,134	0,0420	Yes
Mantel-Haenszel	0,6207	0,3462	0,2745	2,015	0,0439	Yes

In the treatment group, the pressure ulcer was completely healed in 18 subjects out of 29 subjects in the group (62.07%), in the control group - in 9 subjects out of 26 subjects in the group (34.62%) (Table 1). Statistical testing was performed using a two-sided method. The significance of the differences between the groups was confirmed (p≈0.04).

Picture 1. Number of patients with completely healed pressure ulcer by group



Picture 2. Share of patients with completely healed pressure ulcer by group (%)



Despite the obtained result, it should be noted that the reliability of differences is at the borderline level and requires confirmation in a larger experiment.

11.3. Duration of pressure ulcers complete healing (days)

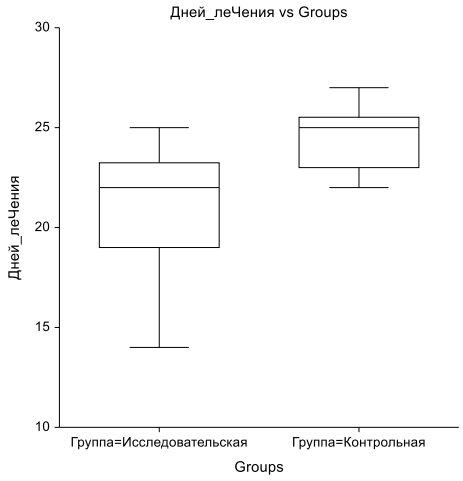
For patients in whom the pressure ulcer was completely healed, the duration of treatment was calculated (Table 2).

Table 2. Duration of complete healing in the treatment and control groups

Group	Duration of complete healing in the treatment and control groups (days). Intergroup comparison		
	n	Mean	Median
Treatment	18	21,28	22
Control	9	24,44	25
Difference and 95% CI	-3,16 days 95% CI for difference: -4,9 до -1,4		
Parametric	0,005** 0,001**		
Non-parametric	0,004**		
Power	от 0,83 до 0,94		

In the treatment group, the pressure ulcer was completely healed in 18 subjects on average in 21.28 days, and in the control group in 9 subjects on average in 24.44 days. Statistical testing was carried out by parametric and non-parametric methods. The significance of the differences between the groups was convincingly confirmed.

Picture 3. Number of days for complete healing in the treatment and the control groups



11.4. Average change in PUSH scores for pressure ulcer area over the observation

The PUSH scale for pressure ulcers of various locations includes a point scale for the area of the pressure ulcer. The change in pressure ulcer area scores between study visits was calculated and the difference between study groups was assessed. The results are shown in Table 3.

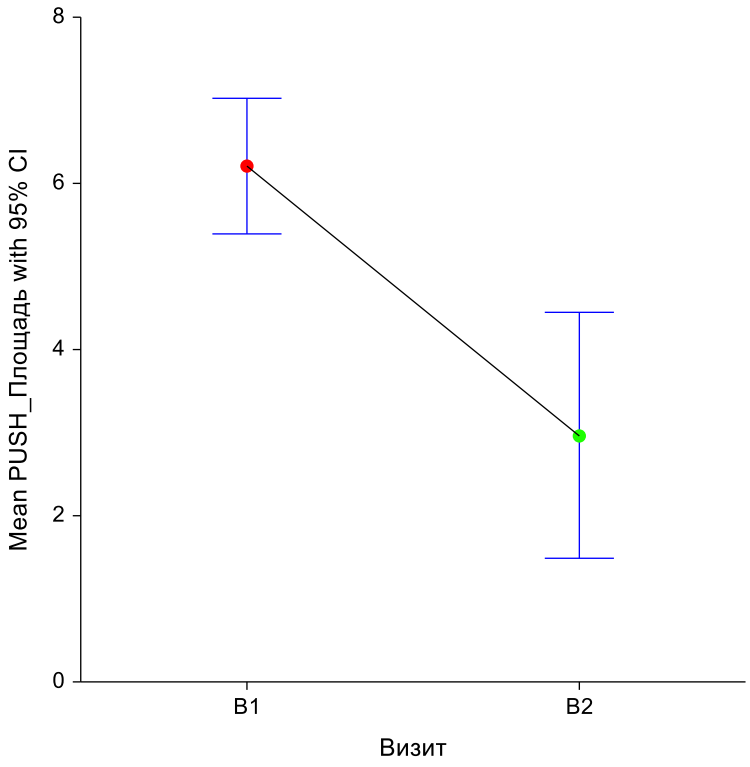
Table 3. Change of the PUSH score for the pressure ulcer area

PUSH area score. Intergroup comparison									
Группы	Visit 1			Visit 2			V2-V1		
	n	Mean	Median	n	Mean	Median	n	Mean	Median
Treatment	29	6,206897	5	29	2,965517	0	29	-3,241379	-4
Control	26	6,423077	6,5	26	3,961539	3	26	-2,461539	-1
Parametric method	p>0.05			p>0.05			p>0.05		
Non-parametric method	p>0.05			p>0.05			p>0.05		
Power	pwr < 0.7			pwr < 0.7			pwr < 0.7		

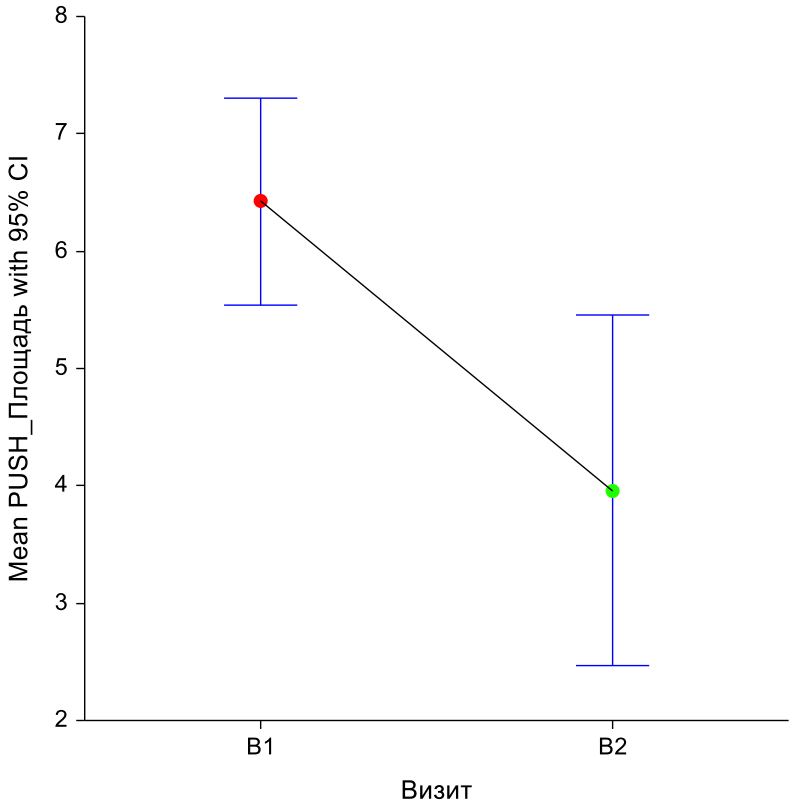
The significance of intragroup changes between visits was proven (p <0.001). At the same time, the significance of the mean values in the intergroup comparison at neither visit 1, nor at visit 2 was not proven (p> 0.05).

In the treatment group, the mean difference in scores between visits was -3.24, and in the control group, -2.46. Statistical testing was carried out by parametric and non-parametric methods. Differences between groups were not significant.

Picture 4. Average change in PUSH scores for pressure ulcer area, treatment group



Picture 5. Average change in PUSH scores for pressure ulcer area, control group



11.5. Change in the total values of the PUSH score in both groups during the study

The sum of the PUSH scores for pressure ulcers of different localization is the sum of the scores for the area, for the amount of exudate and for the type of tissue. The change in the total scores of the scale between study visits was calculated and the difference between the study groups was assessed. The results are presented in the table 4.

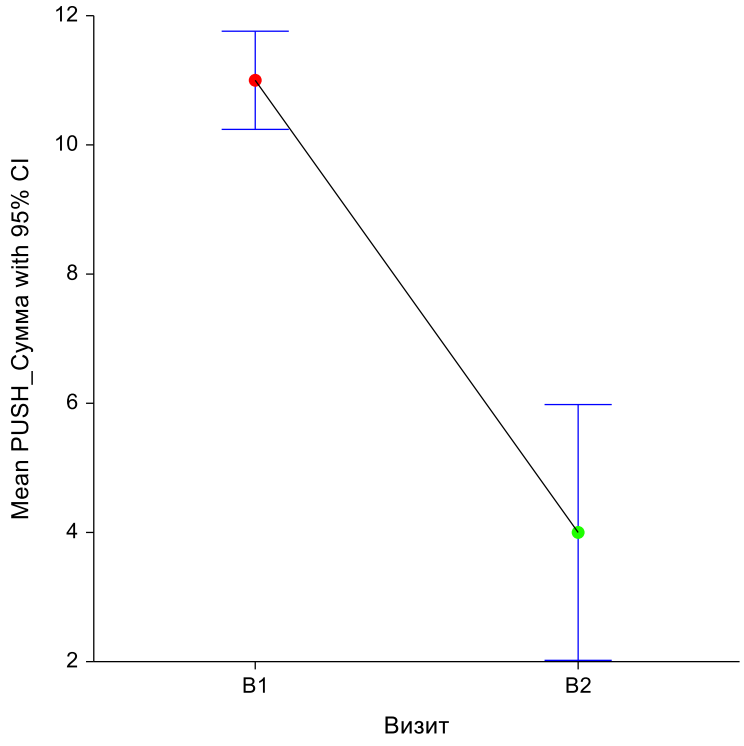
Table 4. Change in the total values of the PUSH score

Total values of the PUSH score. Intergroup comparison									
Group	Визит 1			Визит 2			B2-B1		
	n	*Mean*	*Median*	*n*	*Mean*	*Median*	*n*	*Mean*	*Median*
Treatment	29	11,00	10	29	4,00	0	29	-7,00	-9
Control	26	10,92	11	26	5,69	5	26	-5,23	-4
Parametric method	p>0.05			p>0.05			p>0.05		
Non-parametric method	p>0.05			p>0.05			p>0.05		
Power	pwr < 0.7			pwr < 0.7			pwr < 0.7		

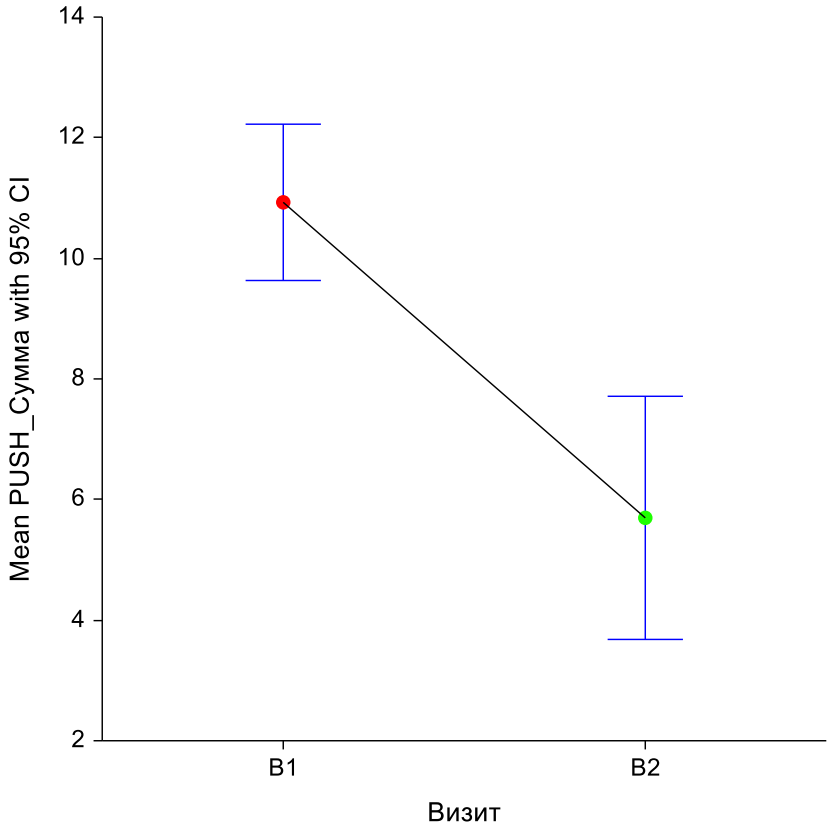
The significance of intragroup changes between visits was proven (p <0.001). At the same time, the significance of the mean values in the intergroup comparison was not proven at either visit 1 or visit 2 (p> 0.05)

During the assessment of changes in groups, in the treatment group, the average difference in total values between visits was -7.00, and in the control group -5.23. Statistical testing was carried out by parametric and non-parametric methods. Differences between groups were not significant.

Picture 6. Change of the total PUSH score, treatment group



Picture 7. Change of the total PUSH score, control group



11.6. Blood lymphocytes at the beginning and at the end of observations

At visits 1 and 2, the researchers recorded some blood test results, including the "Blood lymphocytes" indicator. The change in score between study visits was calculated and the difference between study groups was assessed. The results are presented in table 5..

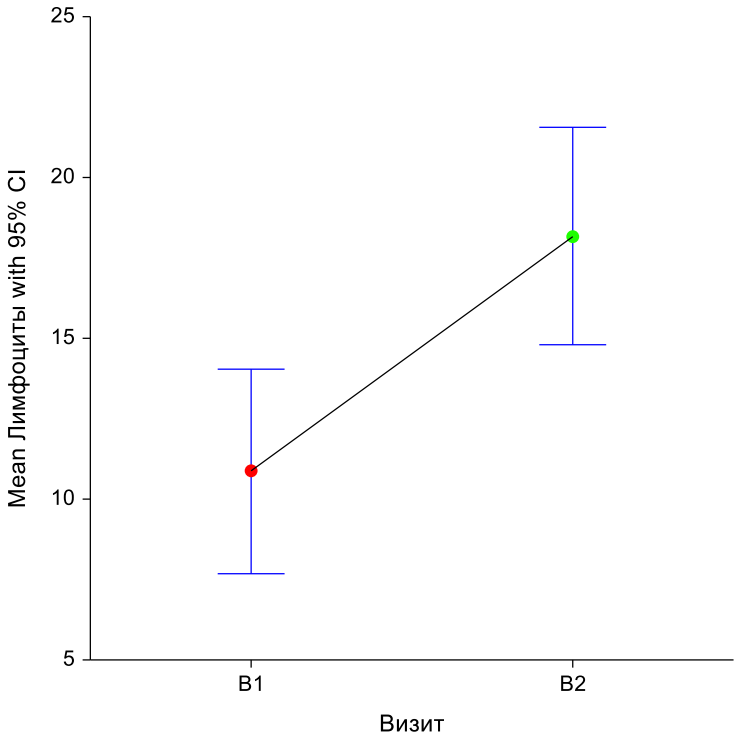
Table 5. Change of the blood lymphocyte count

Lymphocyte (intergroup)									
Group	Visit 1			Visit 2			V2-V1		
	n	*Mean*	*Median*	*n*	*Mean*	*Median*	*n*	*Mean*	*Median*
Treatment	29	10,86207	8	29	18,17241	19	29	7,310345	10
Control	26	8,461538	7.5	26	15,19231	14	26	6,730769	4
Parametric method	p>0.05			p>0.05			p>0.05		
Non-parametric method	p>0.05			p>0.05			p>0.05		
Power	pwr < 0.7			pwr < 0.7			pwr < 0.7		

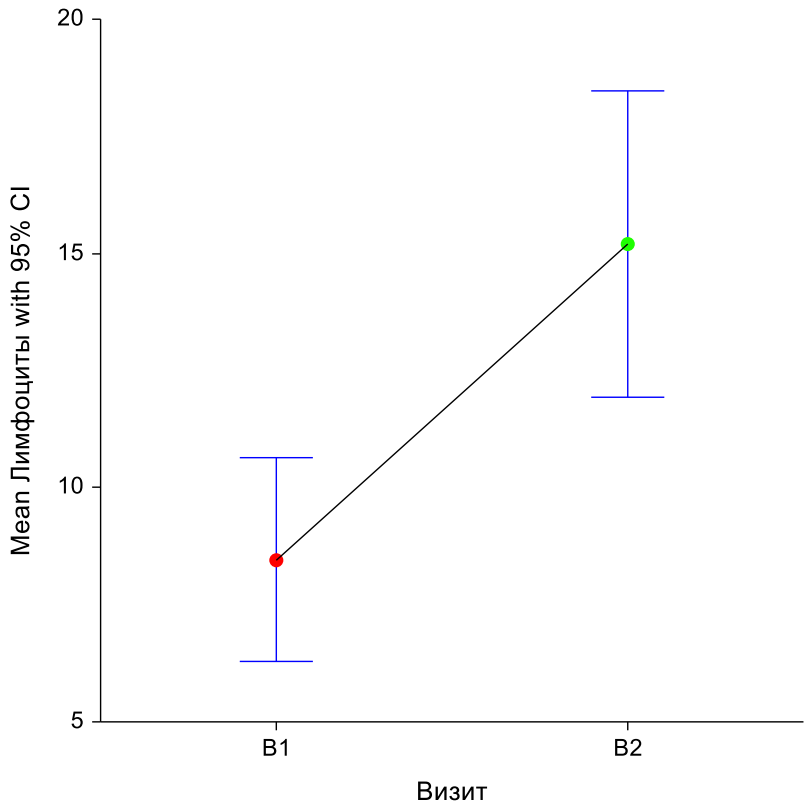
The significance of intragroup changes between visits was proven (p <0.01). At the same time, the significance of the mean values in the intergroup comparison was not proven at either visit 1 or visit 2 (p> 0.05)

During the assessment of changes in groups, in the treatment group, the average difference in the values of the indicator "blood lymphocytes" between visits was -7.31, and in the control group -6.73. Statistical testing was carried out by parametric and non-parametric methods. Differences between groups were not significant.

Picture 8. Change of the blood lymphocyte count, treatment group



Picture 9. Change of the blood lymphocyte count, control group



11.7. Blood albumin at the beginning and at the end of observations

At visits 1 and 2, the researchers recorded some blood test results, including the "Blood albumin" indicator. The change in score between study visits was calculated and the difference between study groups was assessed. The results are presented in the table 6.

Table 6. Change of the blood albumin count

Albumin (intergroup)									
Group	Visit 1			Visit 2			V2-V1		
	n	*Mean*	*Median*	*n*	*Mean*	*Median*	*n*	*Mean*	*Median*
Treatment	29	32,276	33	29	36,931	37	29	4,655	3
Control	26	34,000	32,5	26	36,538	34	26	2,538	3
Parametric method	p>0.05			p>0.05			p>0.05		
Non-parametric method	p>0.05			p>0.05			p>0.05		
Power	pwr < 0.7			pwr < 0.7			pwr < 0.7		

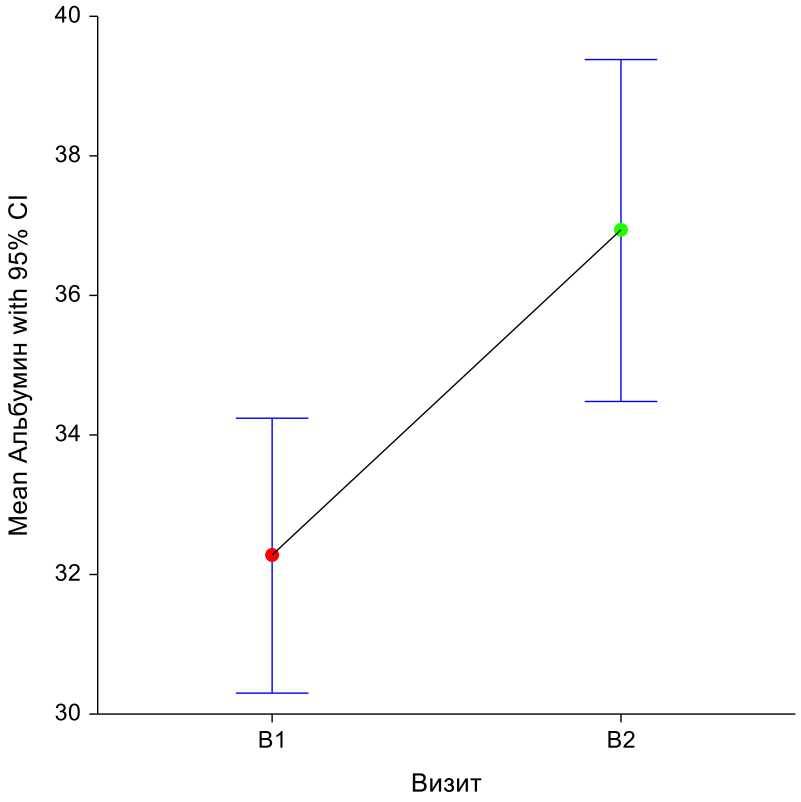
The significance of intragroup changes between visits was proven only for study group subjects, but was not proven for control group subjects (Table 7). At the same time, the reliability of the mean values in the intergroup comparison, neither at visit 1, nor at visit 2, was not proven (p> 0.05).

Table 7. Intragroup comparison: albumin count

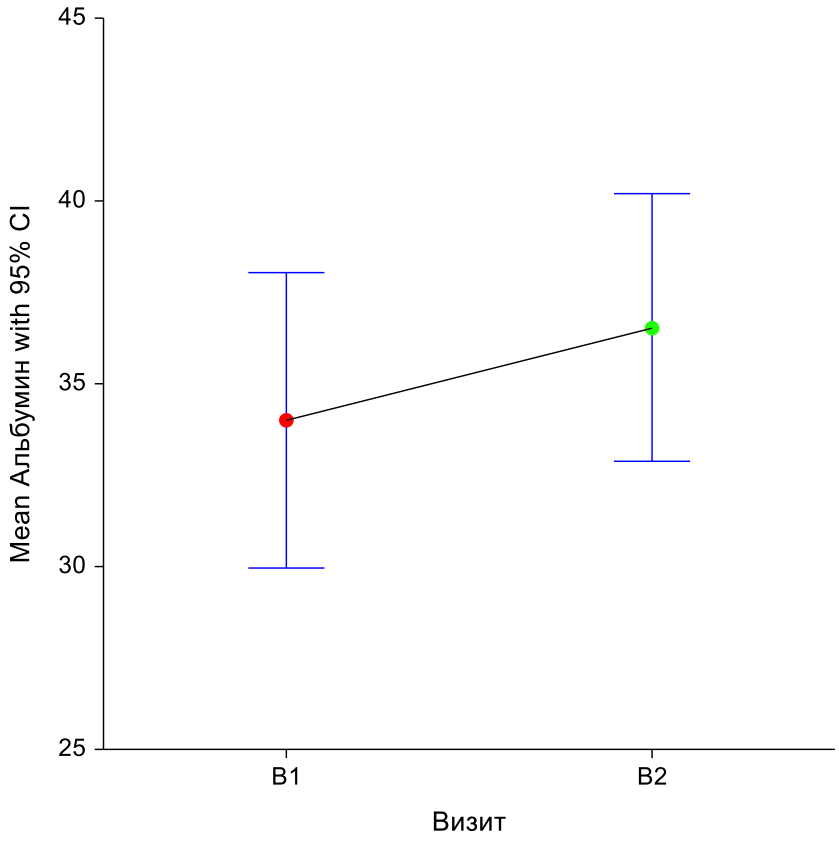
Albumin (Intragroup - paired)							
Group	Visit 1		Visit 2		Significance paired difference		
	n	*Mean*	*n*	*Mean*	*t-test*		*Wilcoxon*
Treatment	29	32,276	29	36,931	p=0,002**	pwr=0,90	p=0,004***
Control	26	34,000	26	336,538	p=0,1032	pwr=0,37	p=0,100

During the assessment of changes in groups, in the treatment group, the average difference in blood albumin values between visits was -4.66, and in the control group, -2.54. Statistical testing was carried out by parametric and non-parametric methods. Differences between groups were not significant.

Picture 10. Change of the blood albumin count, treatment group



Picture 11. Change of the blood albumin count, control group



11.8. C-reactive protein at the beginning and at the end of observations

At Visits 1 and 2, the researchers recorded some blood test results, including the C-reactive protein score. The change in score between study visits was calculated and the difference between study groups was assessed. The results are presented in table 8.

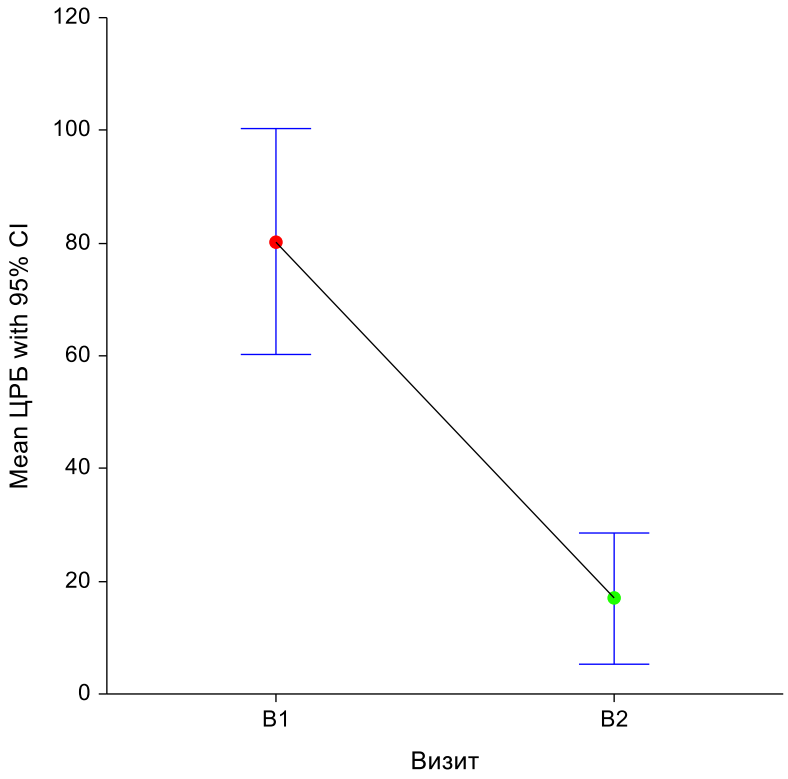
Table 8. Change of the C-reactive protein count

C-reactive protein (intergroup)									
Group	Visit 1			Visit 2			V2-V1		
	n	*Mean*	*Median*	*n*	*Mean*	*Median*	*n*	*Mean*	*Median*
Treatment	28	80,250	77	28	16,928	7,5	28	-63,321	-63,5
Control	26	94,731	86,5	26	20,308	16,5	26	-74,423	-66,5
Parametric method	p>0.05			p>0.05			p>0.05		
Non-parametric method	p>0.05			p>0.05			p>0.05		
Power	pwr < 0.7			pwr < 0.7			pwr < 0.7		

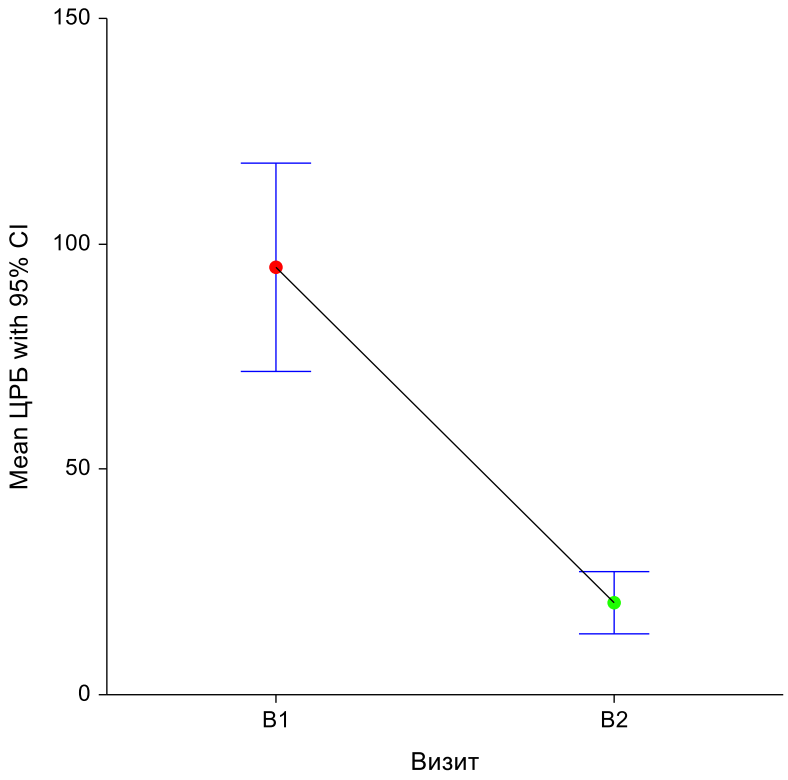
Intragroup changes between visits were proven to be significant (p <0.0001). At the same time, the significance of the mean values in the intergroup comparison was not proven at either visit 1 or visit 2 (p> 0.05)

During the assessment of changes in groups, in the treatment group, the average difference in the values of the C-reactive protein parameter between visits was -63.32, and in the control group -74.42. Statistical testing was carried out by parametric and non-parametric methods. Differences between groups were not significant.

Picture 12. Change of the C-reactive protein, treatment group



Picture 13. Change of the C-reactive protein, control group



11.9. The proportion of patients in both groups with a decrease in the area of the pressure ulcer by 20% or more by the date of completion of observations

To assess the dynamics of changes in the pressure ulcer, the researchers kept a daily diary of the patient and recorded the indicators of the wound area. In the course of data processing, the proportion of patients in each group with a decrease in the area of the pressure ulcer by at least 20% by the date of completion of observations was calculated. The results are presented in the table 9.

Table 9. Number and proportion of patients with a decrease in the area of the pressure ulcer by 20% or more

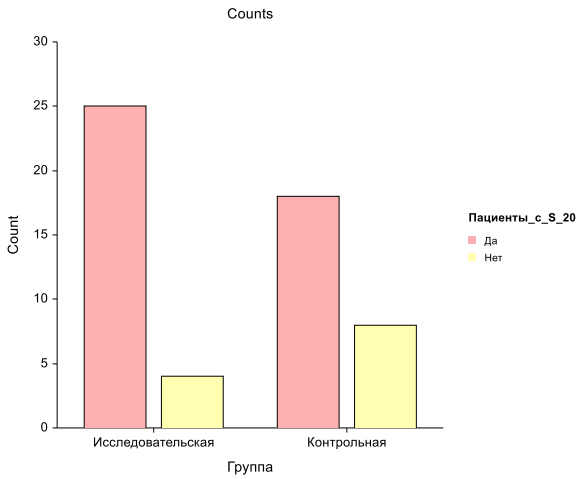
Group	Yes Count	No Count	Total Count	Proportion*
Treatment	25	4	29	86.21%
Control	18	8	26	69.23%

Two-Sided Tests of the Difference (P1 - P2)
H0: P1 = P2 vs. Ha: P1 ≠ P2

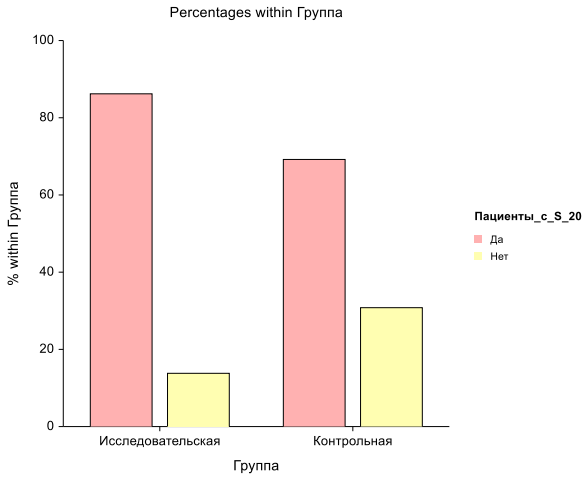
Test Statistic Name	p1	p2	Difference p1 - p2	Test Statistic Value	Prob Level	Reject H0 at α = 0,05?
Wald Z	0,8621	0,6923	0,1698	1,522	0,1280	No
Wald Chi-Square	0,8621	0,6923	0,1698	2,316	0,1280	No
Wald Chi-Square c.c.	0,8621	0,6923	0,1698	1,428	0,2321	No
Mantel-Haenszel	0,8621	0,6923	0,1698	1,508	0,1316	No
Fisher's Exact	0,8621	0,6923	0,1698	0,192	0,1924	No

In the treatment group, a decrease in the area of the pressure ulcer by at least 20% occurred in 25 subjects out of 29 subjects (86.21%), in the control group - in 18 subjects out of 26 subjects in the group (69.23%) (Table 9). Statistical testing was performed using a two-sided method. The significance of differences between groups was not confirmed (p> 0.05).

Picture 14. Number of patients with a decrease in the area of the pressure ulcer by 20% or more by group



Picture 15. Proportion of patients with a decrease in the area of the pressure ulcer by 20% or more by group



11.10. Average number of days until the pressure ulcer area is reduced by at least 20% by the date of completion of observations

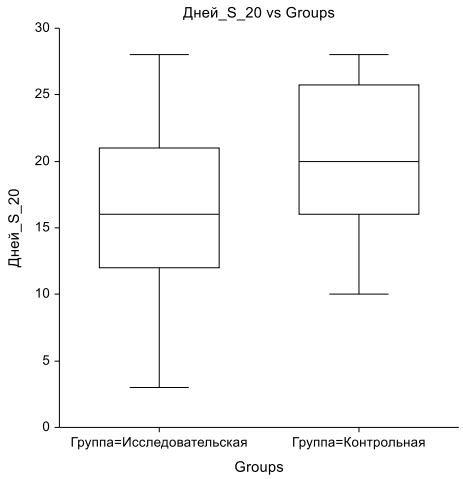
To assess the dynamics of changes in the pressure ulcer, the researchers kept a daily diary of the patient and recorded the indicators of the wound area. In the course of data processing, the number of days until the pressure ulcer area was reduced by at least 20% by the date of completion of observations was calculated for each patient meeting this criterion in each group. The results are presented in the table 10.

Table 10. Average number of days until the pressure ulcer area is reduced by at least 20%, by group

Group	**Среднее количество дней до уменьшения площади пролежня по крайней мере на 20% Межгрупповое сравнение**		
	n	*Mean*	*Median*
Treatment	29	16,034	16
Control	26	20,269	20
Difference and 95% CI	- 4,23 95% ДИ от -7,60 до -0,87.		
Parametric	0,0146* 0,0135*		
Non-parametric	0,018*		
Power	pwr ~0,69		

In the treatment group, the average duration of treatment before reducing the area of the pressure ulcer by 20% or more was 16.03 days (25 patients), and in the control group - 20.27 days (18 patients). Statistical testing was carried out by parametric and non-parametric methods. The significance of the differences between the groups was convincingly confirmed.

Picture 16. Duration (days) until the pressure ulcer area is reduced by at least 20% by group



11.11. Change in the area of pressure ulcers in both groups during the observation period (in%)

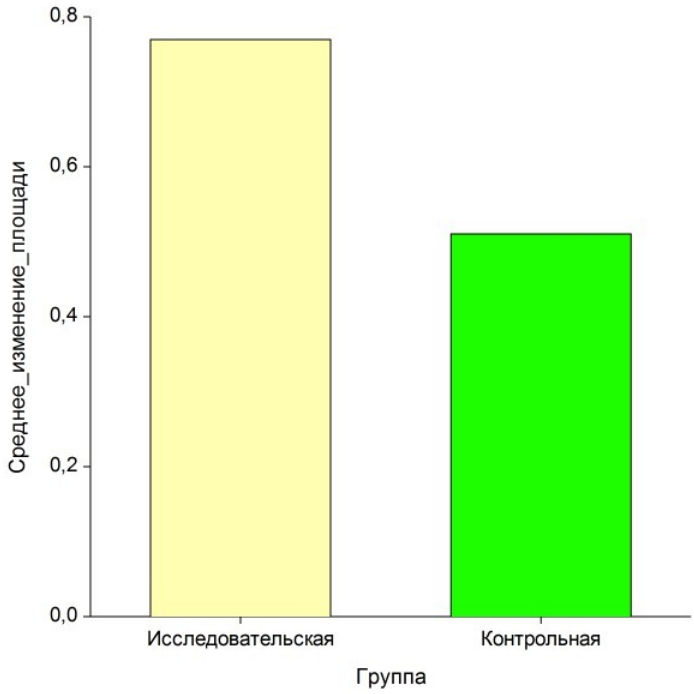
As one of the efficacy criteria, for all patients of each group, the average value of the change in the area of the pressure ulcer by the end of the observations was calculated. The results are presented in the table 11.

Table 11. Average pressure ulcer area changes during observation by group

Group	**Average pressure ulcer area changes during observation by group (proportion). Intergroup comparison**		
	n	*Mean*	*Median*
Treatment	29	0,7687241	1
Control	26	0,5124615	0,39
Difference and 95% CI	0,256. 95% ДИ разности от 0,059 до 0,453		
Parametric method	p=0,012* p=0,013*		
Non-parametric method	p=0,013*		
Power	pwr ~ 0,71		

The average change in the area of the pressure ulcer in the research group (29) was 76.87%, while in the control group (26) - 51.25%. Statistical testing was carried out by parametric and non-parametric methods. The significance of the differences between the groups was convincingly confirmed.

Picture 17. Average pressure ulcer area changes during observation by group



11.12. The incidence of infectious complications of pressure ulcers in study patients

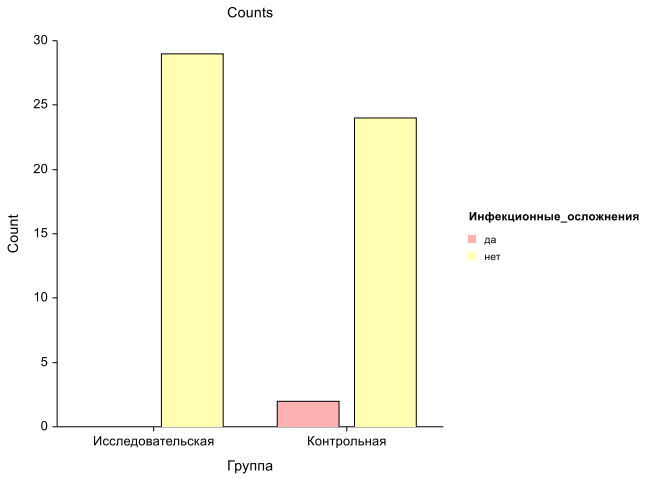
During the study, pressure ulcers were infected only 2 times in the control group. The processing results are presented in Table 12. At the same time, the reliability of the differences was not confirmed.

Table 12. Incidence of infectious complications by group

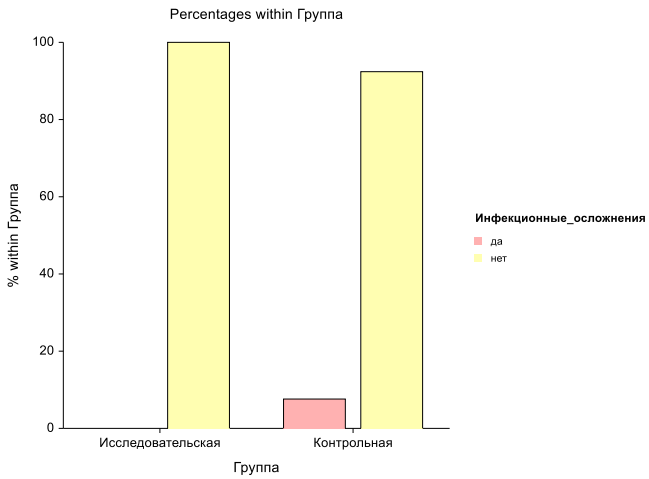
Group	Yes Count	No Count	Total Count	Proportion*
Treatment	0	29	29	p1 = 0,0000
Control	2	24	26	p2 = 0,0769

Test Statistic Name	p1	p2	Difference p1 - p2	Test Statistic Value	Prob Level	Reject H0 at α = 0,05?
Wald Z	0,0000	0,0769	-0,0769	-1,521	0,1281	No
Wald Chi-Square	0,0000	0,0769	-0,0769	2,315	0,1281	No
Wald Chi-Square c.c.	0,0000	0,0769	-0,0769	0,640	0,4237	No
Mantel-Haenszel	0,0000	0,0769	-0,0769	-1,508	0,1317	No
Fisher's Exact	0,0000	0,0769	-0,0769	0,219	0,2189	No

Picture 18. Number of infectious complications by group



Picture 19. Proportion of infectious complications by group



12. Safety study

The study generated 12 adverse event reports. All of them concerned the death of patients due to the severity of the condition and the negative development of the underlying and concomitant diseases. In no case were there any adverse events associated with tube feeding, neither in the study nor in the control groups.

13. Discussion

Based on a systematic comprehensive review of peer-reviewed published studies of pressure ulcers from 1998 to January 2008, NPUAP and EPUAP developed and published clinical guidelines for the prevention and treatment of pressure ulcers (2009) based on a comprehensive assessment of the importance of nutritional support for patients [1].

Among other things, arginine is known to be an essential amino acid and plays a role in the severe phase of diseases such as trauma, sepsis and / or pressure ulcers [2].

Arginine stimulates insulin secretion, accelerates wound healing and prevents pressure ulcers. It stimulates the transport of amino acids into tissue cells and supports the production of proteins in the cell. Arginine acts as a substrate for protein synthesis, cell proliferation, collagen deposition, T-lymphocyte function and contributes to a positive nitrogen balance. It is also a biological precursor of nitric oxide, which has potent vasodilator, antibacterial and angiogenic properties; all of these properties are essential for wound healing. In diabetes, nitric oxide synthesis is reduced in the wound environment, and since arginine is the only substrate for nitric oxide synthesis, it has been hypothesized that arginine supplementation can accelerate wound healing by increasing nitric oxide production [3].

Nutrison Advanced Cubison enteral tube feeding food is a complete enteral nutrition product with an innovative composition of nutrients, intended for patients with chronic wounds, including pressure ulcers, or an increased risk of their development. It is enriched with nutrients that play an important role in wound healing (arginine, vitamins A, C and E, other antioxidants and zinc) and contains micronutrients that are often lacking in many patients with an increased risk of pressure ulcers and long-term non-healing wounds, such as patients lying in the hospital and, in particular, in the intensive care units and intensive care, or the elderly [4].

The study of the benefits of oral and enteral supplements of the Nutrison Advanced Cubison / Cubitan family compared with a standard dietary approach was carried out in a 12-week randomized controlled trial [5]. It involved 28 elderly patients who were in the hospital with newly-onset pressure ulcers of II, III and IV degrees (0-1 month before the start of the study), who received additional nutritional support in the form of mixtures at the rate of 30 kcal / kg per day. The selected groups were matched for age, gender, nutritional status, oral regimen, type of feeding, and severity of pressure ulcers.

As a result of using the product, after 12 weeks in the study group of specialized nutrition, a higher healing rate was observed on the PUSH scale compared to the standard diet, and the reduction in the surface area of the pressure ulcer was significantly higher in patients already at 8 weeks.

In a comprehensive review of literature sources, it was shown that the use of arginine-containing nutritional support led to a significant reduction in the healing time of pressure ulcers, the proportion of patients with completely healed pressure ulcers, etc. [6].

In the course of the study DECUBIZON, we obtained convincing data on the efficacy and safety of the investigated product.

The most important are, in our opinion, the following endpoints. In the study group, compared with the control group, a greater number of patients had complete cure of the pressure ulcer: 18 subjects (62.07%) versus 9 (34.62%) in the control group. There was also a shorter average treatment time (for those patients who achieved complete cure): 21.28 days in the study group and 24.44 days in the control group.

Another important result was that in the research group, the average overall decrease in the area of pressure ulcers (in%) significantly exceeded the same value in the control group: -76.87% (research) and -51.25% (control).

However, it should be noted that, despite the difference in the change in the PUSH scale scores for the pressure ulcer area (-3.24 in the research group and -2.46 in the control group), the statistical significance of this difference was not achieved. This is probably due to the discreteness of the PUSH scale scores, in particular, expressed for large pressure ulcers, in contrast to the linear accounting for the percentage of healing.

Also, reliability was not achieved in the change in the total score of the PUSH scale by study groups (-7.00 in the study group and -5.23

An important indicator of the rate of healing of a pressure ulcer is the endpoints associated with a decrease in the area of the pressure ulcer by at least 20% of the original value.

The proportion of patients in each group who reached this endpoint differed across groups (86.21% in the study group and 69.23% in the control group), but these differences did not reach statistical significance.

At the same time, the significance of differences in terms of the average time to reach this endpoint in each group (16.03 days in the study and 20.27 days in the control) was successfully confirmed.

Changes in blood parameters (lymphocytes, albumin, c-reactive protein) generally did not reach statistical significance. This is understandable given the secondary importance of pressure ulcer therapy in relation to the treatment of the underlying disease and its effect on systemic parameters. At the same time, it should be noted that in the study group, changes in the "blood albumin" indicator reached significance between visits, in contrast to the control group.

The incidence of infectious complications of pressure ulcers was low and differences between the groups in this indicator could not be achieved.

We believe that the results of the DECUBIZON study are in agreement with the literature data, will successfully complement scientific data on the need for nutritional support and will play an important role in improving the quality of treatment for patients with severe neurological diseases, dysphagia and pressure ulcers resulting from a serious condition.

13.1. Literature references of the section

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