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CONTENT

COMPARISON OF THE QUALITY OF LIFE OF PATIENTS IN THE LOCALY ADVANCED BREAST CANCER FORMS AFTER SYSTEM AND INTRALYMPHATIC POLYCHEMOTHERAPY

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Abstract

In recent years, breast cancer (BC) is the most common cancer pathology and the most common cause of disability among women in developed countries. Finding the most effective ways of interaction between the patient and the doctor creates the preconditions for the necessary analysis of the treatment process from an objective and subjective point of view. Therefore, an important indicator to be taken into account is the quality of life of a patient.

To compare the indicators of a comprehensive assessment of the quality of life of patients to the adverse locally advanced forms (LA) of breast cancer before and after systemic intravenous polychemotherapy (SPCTx) and selective endolymphatic polychemotherapy (ELPCTx) in neoadjuvant mode.

The study was conducted on the basis of a random analysis of outpatient cards from 112 patients with LA BC T4A-DN0-3M0 who received a comprehensive antitumor treatment on the basis of the Donetsk regional antitumor center and the University Clinic of the Odessa National Medical University from 2000 to 2017, which was proposed a questionnaire at various stages of preoperative treatment. The first (control) group consisted of 65 patients (58 %) with inoperable forms of LA BC, which was performed in neoadjuvant mode by SPCTx. The second (study group) included 47 patients (42 %) with inoperable forms of LA BC, which was performed as a neoadjuvant course ELPCTx.

According to the integral indicators of quality of life and quality of health between patients in the control and study groups, there was no statistically significant difference. In a detailed analysis of the indicators of symptomatic scales, the difference between the groups did not exceed the critical. Based on the results of a study conducted among patients receiving endolymphatic chemotherapy in a neoadjuvant mode, the subjective evaluations of treatment in absolute numbers have better reference values without statistical superiority.

The study of the integrative indicator of quality of life and its discrete elements is an ergonomic and economical means of heuristic assessment of the health of patients in order to further develop more rational and convenient ways of solving urgent issues of modern oncology by increasing compliance and finding a compromise between the physician and the patient.

Keywords: locally advanced breast cancer, complex treatment, endolymphatic polychemotherapy, systemic polychemotherapy, quality of life.

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1. Introduction

Over the past decades, according to the registers of most countries of the world, breast cancer (BC) is the most widespread cancer and one of the most common causes of disability and mortality among women in the world. [1] As part of the development of the etiological profile for this pathology, a fairly wide range of factors has been formed, none of which has a statistically significant advantage over others, so each particular situation requires an individual approach to diagnosis. On the other hand, according to the pathogenetic and morphological characteristics of the breast cancer group, a wide variation of neoplasms, different from genotypic and phenotypic properties, is combined [2]. According to WHO, in the epidemiological mapping there is a clear tendency to a high prevalence among the population of the Western world, which is a consequence of their cultural-traditional and socio-demographic characteristics [3]. All this explains the increased costs of maintaining and improving diagnostic and therapeutic measures by public and private insurance institutions and the fairness of growing clinical and academic interest in understanding the key aspects of breast cancer [4, 5].

A weighted approach to each individual disease dictates to consider it through an individual prism for the optimal choice of appropriate therapy. In this very perspective, in cancer practice, targeted therapy in the widest possible sense of the term looks: from vector and monoclonal bioengineering developments to direct mechanical targeting of necessary substances to the problem area by enriching the afferent vascular bed with active components of the drug. The most suitable for this method for obvious reasons are locally advanced forms of tumors, and in the context of the article, breast cancer (LA BC) [6, 7]. Despite the increasing interest of professionals and amateurs in addressing the problem of targeting this cancer, a wide range of treatments suggests that there is no statistically validated treatment for each individual case. The local problem of our country is a multicausal stagnation in the direction of conducting necessary research and accumulation of relevant information [8, 9].

The problem of finding an adequate route for delivery of chemotherapeutic agents and the composition of the drug panel itself for the selective complex treatment of LA BC is a topical issue, given the poor performance of systemic polychemotherapy (SPCTx).

Regular methods of CTx (intraarterial, intravenous, endolymphatic) are one of the modern surgical ways of solving the question of a selective approach to the treatment of malignant neoplasms. Lymphotropic therapy is based on the notion of the additivity of the lymphatic structure of a particular region with a clear direction of lymph movement from the periphery to the regional centres. The complicated and histo toxic method of intradermal injection with subsequent passive drainage on the principle of diffusion requires a combination of parallel intravenous administration and eliminates repeat CTx sessions. Therefore, the new and progressive stage of the evolution of the method was the manoeuvre of microsurgical high-precision catheterization of several major lymphatic vessels with saturation of the afferent bed of the target area for 3–5 days. The theoretical efficiency and reliability of endolymphatic infusion make the technique promising in the context of further study [10, 11]. The aim is to achieve common results for all targeting methods: increasing local exposure and reducing the systemic toxic response.

2. Aim of the research

To compare the indicators of the integrated assessment of the quality of life of patients to locally advanced forms of breast cancer (LA BC) before and after systemic intravenous polychemotherapy (SPCTx) and selective endolymphatic polychemotherapy (ELPCTx) in a neoadjuvant mode.

3. Materials and methods

The study was conducted on the basis of a random analysis of outpatient cards from 112 patients with LA BC T4A-DN0-3M0 who received a comprehensive antitumor treatment on the basis of the Donetsk regional antitumor center and the University Clinic of the Odessa National Medical University from 2000 to 2017, which was proposed a questionnaire at various stages of preoperative treatment. Before entering the patient in the study protocol, a written voluntary consent to participate in the study was obtained in accordance with the WMA Declaration of Helsinki – Ethical principles for medical research involving human subjects, 2013 form.

The sample was standardized according to age, gender, social and clinical parameters. Age range: 46.3±12.4 years. Out of all patients, 85 (76 %) belonged to the active working age group. The first (control) group consisted of 65 patients (58 %) with inoperable forms of LA BC, which was performed in neoadjuvant mode by SPCTx. The second (study group) included 47 patients (42 %) with inoperable forms of LA BC, which was performed as a neoadjuvant course ELPCTx. The number of courses spent on preoperative PCTx was at most 4. The ultimate goal was to achieve the tumour of the operable state.

The study of the quality of life of patients was conducted within the framework of the International protocol of the European organization for the study and treatment of cancer, using questionnaires for the European organization for the research and treatment of cancer (EORTC QLQ-C30) questionnaire, which have been tested in numerous foreign studies and meet the criteria for reliability, validity and effectiveness.

The questionnaire has a protocol form and includes 30 standard questions: general questions (quality of life (QL) and quality of health (QH)), functional status scale (physical, emotional, role, social and cognitive) and the scale of key symptoms. In contrast to the proposed by the authors method of the evaluation, a linear analogue scale with a range from 1 to 100 points was applied. For functional scales, the worst indicator corresponded to an estimate of 0 points, the best one was 100 points. In the symptomatic scales, the weakest manifestation was estimated at 0 points, the strongest – 100 points.

Patient questionnaires were carried out within 1 week prior to the start of PCTx and 10–14 days after each course of PCTx. The most representative changes in functional and symptomatic scales occurred at these checkpoints. The questionnaire was conducted among 100 % of patients before the start of treatment and stopped after the end of therapy for any reason or at the patient's own request.

Total course doses of chemotherapy were calculated individually for each patient according to BSA criteria (**Table 1**).

Table 1

Protocols for conducting PCTx in the ELPCTx mode according to BSA criteria

CAF protocol:	**Cyclophosphamide: from the second to the fourth day – 400 mg/m^2; Fluorouracil: from the second to the fourth day – 500 mg/m^2; Doxorubicin: on the first day IV – 50 mg/m^2.**
CAMF protocol:	Cyclophosphamide: from the second to the fourth day – 400 mg/m^2; Methotrexate: the first and fifth days – 30 mg/m^2; Fluorouracil: from the second to the fourth day – 500 mg/m^2. Doxorubicin: on the first day IV – 30 mg/m^2.
CMF protocol:	Cyclophosphamide: from the second to the fourth day – 400 mg/m^2; Methotrexate: the first and fifth days – 30 mg/m^2; Fluorouracil: from the second to the fourth day – 500 mg/m^2.

Data processing was performed using standard statistical functions of the MSExcel program. When comparing the indicators of QL in the study groups, a nonparametric index is used – the Pearson coefficient χ^2, for the study of dynamics - the indices of the study of dynamic series. Static comparison parameters: estimated value of degree of freedom=1; at p-level<0.05 χ^2=3.841; at p<0.01 χ^2=6.635).

5. Results

The general condition of patients at all stages is mainly formed due to objective (presence of tumour neoplasms, intoxication syndrome, asthenic syndrome, local and systemic manifestations of tumour lysis, the addition of secondary infection of compromised tissues) and subjective (psychological and emotional discomfort from physical condition, social disadaptation through oncological stigmatization and disability) of factors.

After analyzing the QL index (**Fig. 1**), there were no statistically significant differences in the control group: the mean value was 54±11.3 points in the control group, 57±4.1 points in the study (at p=0.67 index=0.182). After completing 1 and 2 courses of chemotherapy, the QL index had a phase-out negative dynamics of the first (7.4 % and 8.0 %, respectively, with a final result of 46±4.3 points), and in the second (5.3 % and 13.0 %, respectively, with a final result of 47±3.1 points) in groups, retaining proportional statistical closeness of results. It is worth noting that because of the expressed intoxication syndrome and the psychological discomfort of participating in the trial, 3 patients (4.6 %) of group 1 and 2 patients (4.3 %) of the second group refused to further study their quality of life and continued treatment in the usual way. Such dynamics of indicators, according to the authors, is related to insufficiently established complications with patients and insufficient explanation of the essence of treatment: the persistence of the intoxication syndrome, the dissonance of the expected and actual changes in tumour size, the panic disappointment of treatment and the lack of improvement in well-being were interpreted by most patients as a negative result . The ultimate aim was achieved in 16 (25 %) patients in the first group and in 13 (28 %) patients in the second group. After completing the third course of chemotherapy, the reference values of the QL parameter were positive, increasing by 13 % (52±2.3 points) in the control group and by 18 % (55±4.9 points) in the study groups as a consequence of improving the general condition, becoming accustomed to the systematic wave-like dynamics of the symptoms toxicity to PCTx, improvement of local tumour status and achievement of the end result in most patients. However, statistically, the indices of both groups remained indispensable (at p=0.671, the index χ^2=0.181). The regimen of the tumour was achieved in 30 (46 %) women in the first group and in 21 (45 %) women in the second group. After completion of 4 courses of PCTx, the indicators decreased by two or four points in both groups (50±4.4 and 52±2.3 points respectively), interpreted as the result of physical and moral deprivation of patients, lack of the same dynamics of clinical symptoms as in other patients, depression in the positive result and dissatisfaction with the symptoms of iatrogenic intoxication. There was no statistical difference in favour of one or another technique in the fact of holding 4 courses of PCTx (χ^2=0.08 at p=0.778). Clinical effects appeared in 17 (26 %) women in the control group and in 11 (23 %) women in the study group. Unfortunately, the resectable state of La BC did not reach 2 (3 %) patients of the first group and 2 patients (4 %) of the second group; They were offered a system of professional assistance and support for cancer patients and symptomatic therapy in an oncologic dispensary.

Another indicator of the general character – the quality of health (**Fig. 2**) – was similar dynamics. Prior to conducting PCTx in patients of the first and second groups, the following results were obtained: the average score of good health in group 1 was 32±4.1 points, and in the second – 35±3.7 points, which had no statistically significant difference (χ^2=0.202, p=0.654) According to patients, such a low estimate is due to the effect of the “depressed” state due to “incurable” disease and pessimistic predictions about the results of future treatment, formed through self-disinformation of patients when communicating with each other and studying unverified sources. Unfortunately, the conditions and format of the experiment did not allow a cleaner study to isolate patients and clarify their health and technical options for treating this pathology. Subsequently, after each course of chemotherapy, there was a stable difference of 3, 3 and 2 points, respectively,

insignificant by the Pearson coefficient (χ^2<3.841), and with the fluctuations within the group of 5±1 %, between the groups of indicators. In the phase of neoadjuvant therapy, the patient had no to evaluate the final result, however, with the help of explanatory work the doctor can correctly interpret the trends of the general state of the organism and local parameters (size and disintegration of the tumour).

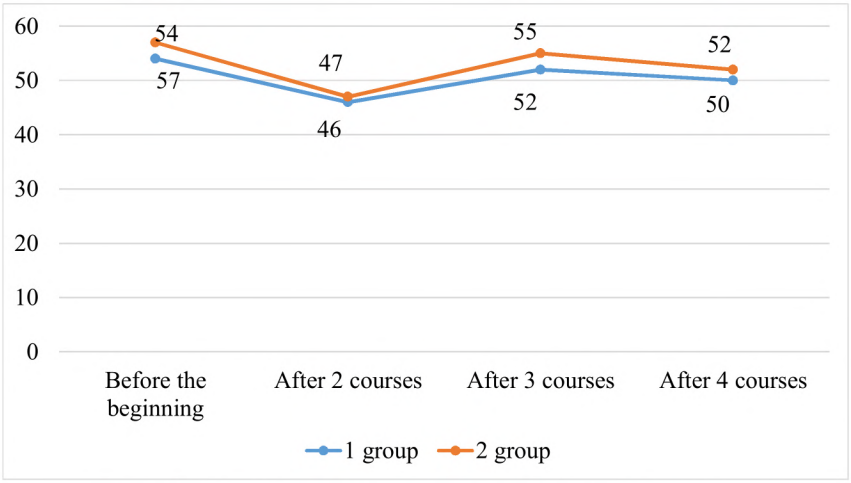

Fig. 1. QL patients before and after SPCTx and ELPCTx

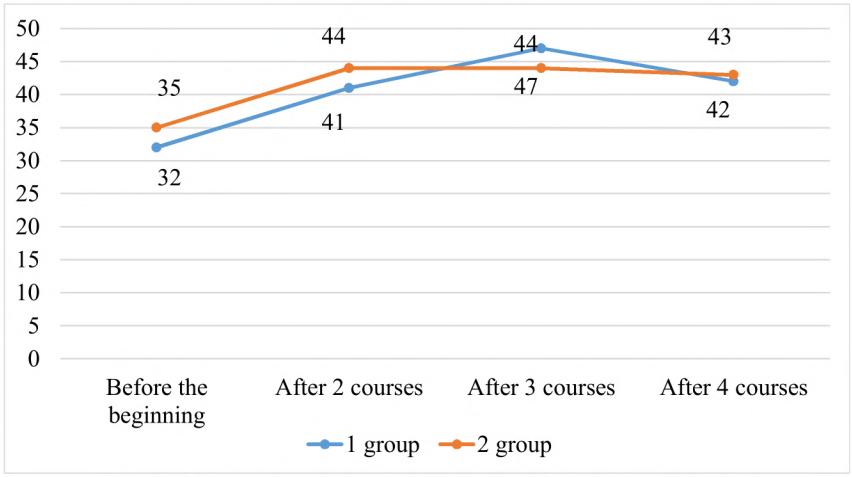

Fig. 2. QH patients before and after SPCTx and ELPCTx

In the structure of the questionnaire EORTC QLQ-C30, specific questions of the symptomatic scale are first and foremost, there are placed more general scales of functional, cognitive, emotional, psychological and social status, at the end there are two integral indicators – quality of life and quality of health, giving patients the opportunity move from solving more simple tasks to responding to global additive issues. Analyzing the questionnaires in reverse order, you can evaluate the components of these integral parameters.

The following changes were observed in the analysis of indicators on the general and physical health scales (**Fig. 3, 4**): a statistically insignificant difference before the start of chemotherapy (63±6.4 and 81±5.4 points in the first group, 65±4.3 and 83±9.6 points in the second, χ^2, respectively, 0.087 and 0.136), followed by a negative dynamics of 5 points after 2 courses of chemotherapy and almost unchanged at the time of further treatment.

The smallest changes in response to chemotherapy were observed for the indicator of cognitive status: the intergroup and intragroup incomplete differentials stood in the range of 4 points and did not have statistical differences (**Fig. 5**).

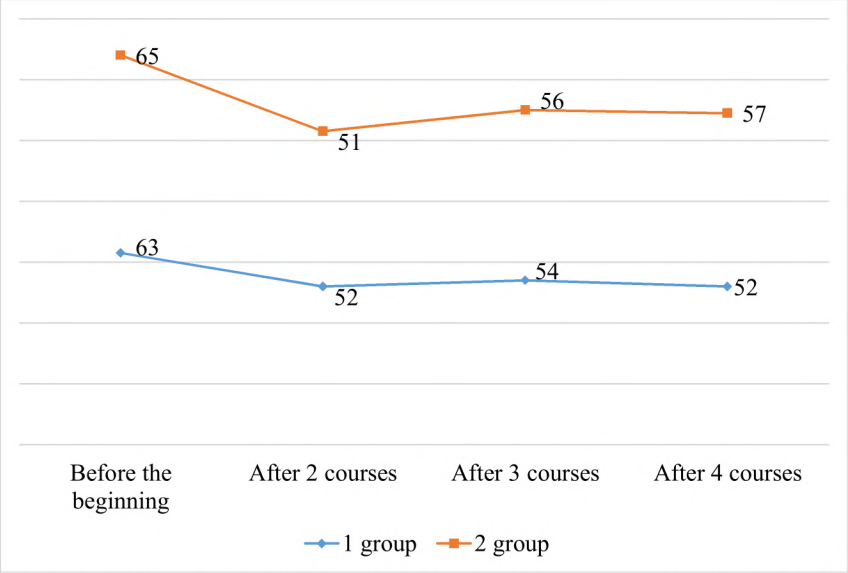

Fig. 3. The general condition of patients before and after the SPCTx and ELPCTx

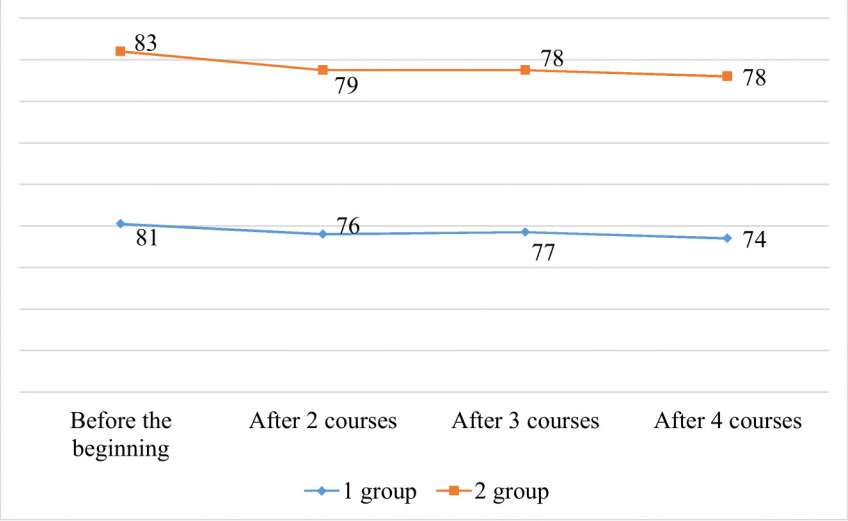

Fig. 4. Physical condition of patients before and after the SPCTx and ELPCTx

The most variability was naturally found in the results on the scales of psychological and emotional state and social adaptation. As expected, the indicators of the emotional background were extremely labile and the dynamics of the system was not traced; of course, this parameter is the most subjective and least reliable for discrete evaluation, however, as already noted, necessary for an integrated approach. During the analysis of the psychological state of women in both groups before and during the PCTx, fluctuations of wide amplitude that were not related to external factors (**Fig. 6**) were revealed, which is a serious consequence of insufficient professional psychotherapeutic assistance to patients.

On the other hand, the scale of social adaptation has shown a non-slip positive dynamics for both groups, though, again, without statistical discrepancies with intergroup differences of 5 points maximum. Yet, according to the authors, this parameter is a key component of the quality of life indicator, since it is social adaptation and self-determination that is the ultimate goal of integrated treatment and an intermediate for each of the stages.

Before the start of chemotherapy, the patients of both groups considered themselves equally low socially adapted (47±3.7 points in the first group and 49±3.9 in the second group). After two courses of PCTx in both groups, the indicators improved: 25.5 % in control patients, making

59±7.2 points, and by 16 % in the studied cohort with 49±4.3 points. Subsequently, the positive dynamics were maintained (**Fig. 7**): in the first group +8.5 % (64±5.0 points) after 3 courses and +12.5 % (72±5.2 points) after the fourth; in the second – +11 % (65±4.7 points) in the third stage of the study +7.5 % (72±3.1 points) in the fourth. At the same time, objectively, in patients, there was a marked reduction of local symptoms in both cohorts of patients.

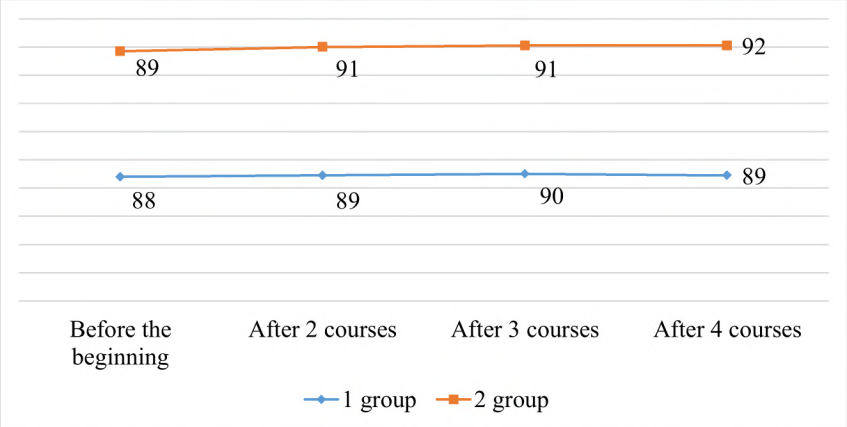

Fig. 5. Cognitive condition of patients before and after the SPCTx and ELPCTx

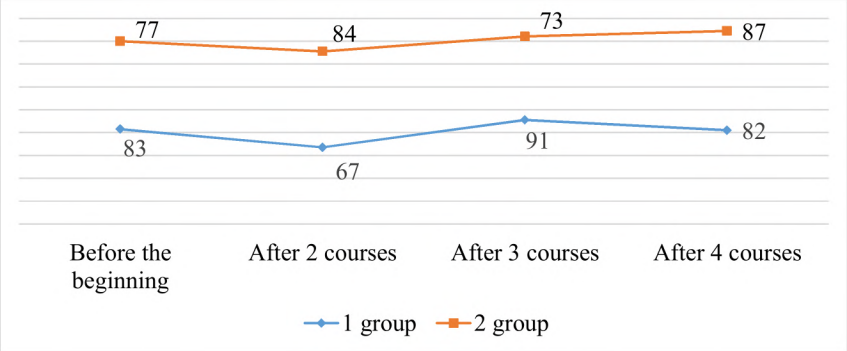

Fig. 6. Emotional condition of patients before and after the SPCTx and ELPCTx

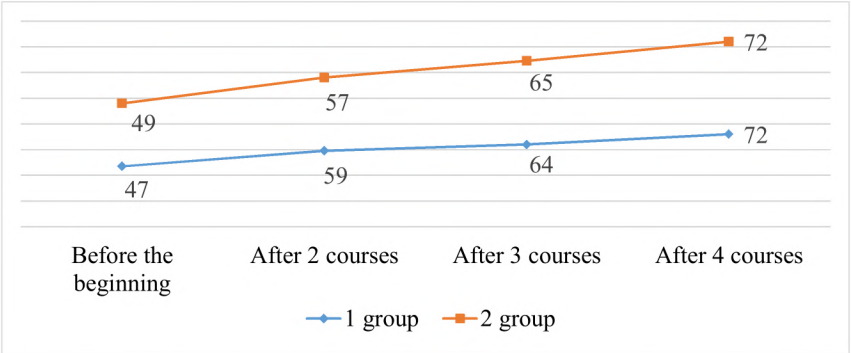

Fig. 7. Social condition of patients before and after the SPCTx and ELPCTx

During the analysis of the panel of symptomatic scales for publication only indicators with high reference values, statistically significant differences, and pathogenetic connection with the intervention: pain, nausea and loss of appetite – as parameters characterizing local and systemic changes in the body.

The intoxication syndrome is a major side effect of chemotherapeutic treatment. It is worth noting that objectively the symptoms of intoxication persist on average 5±1 day after SPCTx and

4±1 day after ELPCTx. It is also important that the intoxication syndrome is generated both by the presence of the tumour itself and by therapeutic measures. It is advisable to explain this fact in detail to patients before conducting chemotherapy and to teach them to track the dynamics of new symptoms for a proper interpretation of their own condition.

The search for new drugs and their rational combination contribute to the reduction of the symptoms of iatrogenic poisoning of the body, regardless of the route of administration of drugs, therefore, the incidence of insomnia, apathy, depression and general fatigue will not change significantly. However, as can be seen from **Fig. 8, 9**, nausea and loss of appetite are observed in many patients with lysis syndrome before the treatment, which on average gives a low score (13±1.4 and 11±0.9 points respectively in the first group, 13±1.9 and 11±1.1 – in the second). At later stages, these symptoms were noted in typical terms in general, and were evaluated respectively [64±4.3 and 62±1.3] points in the first group and [59±4.1 and 63±2.0] points in the second to the second stage, [58±5.3 i57±1.1] and [57±3.2i59±1.7], respectively, on the third; [49±5.7 i51±1.3] and [49±4.0 and 49±2.1] in the fourth. The analysis did not reveal a significant difference between the parameters at any of the stages.

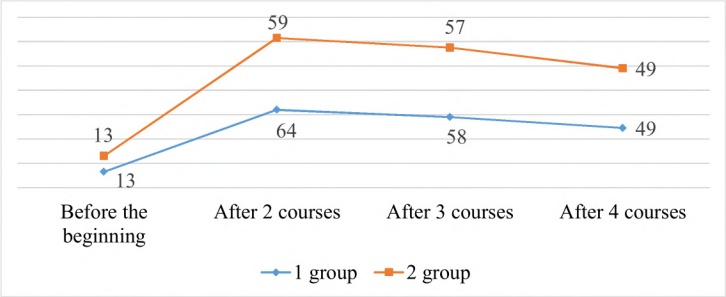

Fig. 8. Nausea of patients before and after the SPCTx and ELPCTx

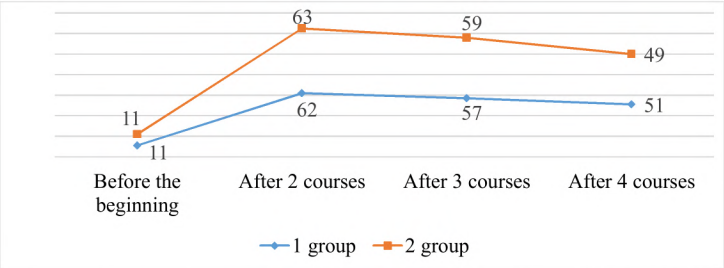

Fig. 9. Loss of appetite of patients before and after the SPCTx and ELPCTx

Separately, it is necessary to consider the parameter of pain syndrome. Unlike the others, it is an indicator of the dynamics of the local status. Interdependent control groups of reliable differences are not traced (**Fig. 10**).

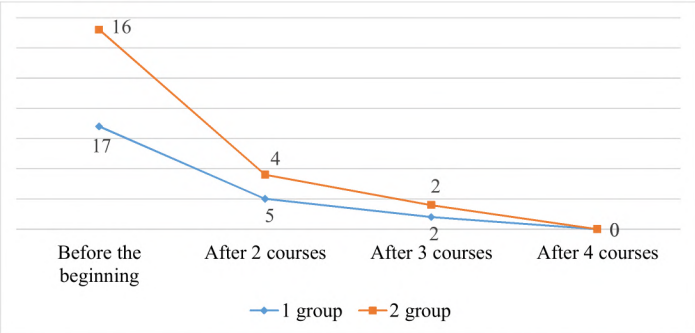

Fig. 10. Pain syndrome in patients before and after the SPCTx and ELPCTx

6. Discussion

Modern medicine is in the unbalanced conflict environment of the ideas of the past and the present. Formed at the beginning of the last century, patterns of thinking and implementation of approaches to working with patients were characterized by profound personalization and unreasonably radical actions, and now phase-by-stage processes of viewing and comparing are underway [11, 12]. With the advent of evidence-based medicine and the beginning of the formation of international information bases in the global medical community comes the conclusion about the irrationality of many classical methods of treatment, and the methods used to assess the results achieved [13]. However, despite the constant progress of medicine, new advances in the development of general and special directions, as well as the tireless and close attention of the public to the problems of medicine, statistical data on a scale of decades do not show convincing qualitative changes in the dynamics of morbidity and mortality [14, 15]. A rational approach to the organization of work posits that the achievement of the absolute result is a strategically false course, and a competent program of development envisages, first of all, the right choice of purpose and the correct statement of the problem before discipline in the person of each individual participant. Therefore, at the end of the last century, medicine completely changed the concept of its approach to the patient, turning it from the object to the subject of the medical process. The aim of achieving maximum clinical effect at the cost of limiting comfort was no longer a self-image, and the new balanced way of medicine became patient oriented, on its needs, interests and experiences [16]. The total vector of human impact in the health care system has changed the direction from quantitative intensive and extensive statistical indicators of overall survival, duration of a non-recurrent period and disability to compromise qualitative indicators of comfort and health. In this context, the question arises of the need to develop and use measures to evaluate not only the quantitative but also qualitative component of a comprehensive conclusion on the results of therapy. Therefore, an important indicator to be taken into account is the quality of life of a patient [17, 18].

In the original IndexMedicus (1977), QL is defined as the physical, emotional, financial and spiritual well-being of man [19]. According to the decision of the American Society of Clinical Oncology (ASCO), QL is more important than the level of non-recurrent survival in assessing the results of antitumor therapy [20].

The main advantage of the QL index is its integrative ability: the ideal QL index is an objective assessment of subjective data. In the future it will provide an opportunity to unite and coordinate a number of nonparametric additive characteristics such as overall health, emotional, cognitive, psychological and social aspects, i.e. implementing strategic objective to assess the condition of the patient before and after treatment in terms of the patient, then it will become possible to rationalize further therapeutic tactics more effectively. The main drawback of the QL index is idempotence its synthetic nature and lack immanence parameters, which create prerequisites for the approximability of any mathematical function for its modelling and quantitative and qualitative terms.

Modern integrated assessment questionnaire QL reflect these positive and negative aspects, but still allow you to "compare what is comparable." The widespread introduction of standardized forms surveys as a routine cancer research and regular large-scale meta-analyzes will accumulate and structure the material to further a more advanced scientific and methodological materials.

Using the EORTC QLQ-C30 questionnaire as one of the most common forms in our research is largely dictated by these considerations. In the future, the systematization of the data of each individual medical unit will create the opportunity to form the axis of academic and clinical experience in a particular direction and develop an effective system of vertical and horizontal feedback on the local, regional, state and international levels. Taking into account the difference in the structure of patterns of health care organization between the countries of Eastern and Western Europe, as well as their greater practice in the study of quality of life indicators in the framework of an expanded individual approach to patient treatment, it is promising to create national information bases on discrete issues with further versatile comparisons and definitions of the most competitive options in the context of the evolution of methods and their artificial selection.

The quality of life study as an indicator is not a competitor to classical methods for evaluating the quality of treatment and can not be considered an alternative to extensive and intensive statistical parameters. However, parallel study of objective and subjective treatment outcomes allows using the second as a tuning cart the adequate effectiveness of the patient care program and facilitates the process of understanding between the physician and the patient, allowing the latter to actively participate in their own treatment. Investigating the correlation between clinical, morphological, laboratory and instrumental effects of intervention and a comprehensive indicator of patient's quality of life will take place in the future.

7. Conclusions

1. After the study identified beyond the range of quality of life in patients with inoperable form of LA BC before and after neoadjuvant systemic chemotherapy courses (SPCTx) and endolymphatic polychemotherapy (ELPCTx).

2. Clarified value including assessment of quality of life to the complex characteristics of the final treatment results, allowing to accumulate experience and information in this area and increase the practical sense of scientific work.

3. Research the integrative quality of life and its discrete elements are ergonomic and economical means of heuristic evaluation of the health status of patients to further develop the most efficient and convenient way to address pressing issues of modern oncology by improving compliance and compromise between doctor and patient.

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THE EFFICIENCY OF GLUCOCORTICOID THERAPY IN SECONDARY-PROGRESSIVE COURSE OF MULTIPLE SCLEROSIS

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Abstract

We have investigated the efficacy of pulse-therapy with glucocorticoids (GC) at different time stages (in debuts, at the recurrent stage and at the stage of progression) of secondary progressive course (SPC) of multiple sclerosis (MS) in 70 patients (57 women and 13 men) at the ages from 28 to 67 years (mean age 45±2.5 years). The duration of the disease accounted for 7 up to 34 years (average duration was 19.8±2.3 years). We have conducted 438 courses of GC therapy: at the onsets – 11, at the recurrent stage (RS) – 178 and at the stage of secondary progression-249.

The efficacy of hormonal therapy was assessed taking into account the following criteria: the dynamics of regression of neurological symptoms under the influence of the first course of GC therapy at the stage of onsets; a comparative evaluation of remission's duration after admission and without taking GC at the onsets; duration of RS depending on the duration of remissions after the first course of GC therapy; a comparative evaluation of remissions' duration after the 1st (at the stage of onset and/or on the RS), and the period of stabilization on the SPS before the last courses of GC; the variants of secondary progression under the influence of GC courses; scores according the EDSS disability scale after the 1st and before the last course of GC therapy; the rate of progression under the influence of the repeated courses of GC therapy.

We have defined the three categories of efficacy at the repeated courses of pulse therapy with GC: the moderate efficacy, the low efficacy, the lack of efficacy. We have not observed the high efficacy in patients with SPC.

The patients with MFR <1.0, among which the pulse therapy with GC promoted the prolongation of RS, relieved the severe (less often) and moderate (more often) relapses, the outcome of which was accompanied by a moderate and stable neurologic deficit, were subsumed under the subgroup with moderate efficacy (21 individuals). The most favorable progressive variant of progression prevailed in these patients after transformation of RS into SPS.

The patients with different rate of MFR (9 – with MFR <1.0 and 12 – with MFR>1.0), with short (more often) and moderate (less often) RS, during which the accumulation of neurological deficit due to the frequent and heavy relapses had occurred, were subsumed under the subgroup with low efficiency (21 individuals). After transformation into SPS, the recurrent variant of progression prevailed in these patients.

The patients who were characterized by short RS, by predominance of severe and prolonged relapses, the MFR value greater than 1.0, the steady accumulation of a pronounced and persistent neurologic deficit, a high rate of progression and high scores on the EDSS disability scale more than 6.5 points) were subsumed under the subgroup with the lack of efficacy (28 individuals). After transformation in the SPC, the most unfavorable variant of progression prevailed (21 patients); significantly less frequent were the recurrent (5 patients) and a combination of a steady and recurrent (2 patients) progression. The persistent lack of efficacy of the hormonal therapy in this subgroup of patients was most likely associated with the genetically determined low individual sensitivity to GC.

Therefore, the results of our study showed that the efficacy of GC therapy in SPC of MS is determined by the complex interaction of clinical indicators having the prognostic value, as well as by the number of the genetic factors, which require their further observation.

Keywords: multiple sclerosis, secondary-progressive course, pulse-therapy with glucocorticoids, treatment effectiveness.

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1. Introduction

The modern algorithm for the treatment of multiple sclerosis (MS) is based on "four whales": relief of exacerbations with the help of glucocorticoids (GC); immunotherapy with drugs that change the course of MS (PITRS), symptomatic therapy, which removes various clinical manifestations of the disease and a complex of rehabilitation measures, including the development of adaptive strategies for reducing disability [1, 2].

As first-line drugs that relieve exacerbations of MS, are GC (prednisolone, methylprednisolone), the clinical effect of which is due to immunosuppressive and anti-inflammatory action. GC reduce edema in the inflammatory focus, inhibit the production of pro-inflammatory cytokines, express the main histocompatibility complex (HC) of class II and adhesion molecules, stabilize the permeability of the blood-brain barrier (BBB), induce apoptosis of activated lymphocytes [3].

Hormone therapy in MS is important not only as a factor that suppresses the autoimmune process, but also as a form of replacement therapy in connection with the development of glucocorticoid insufficiency in this disease, which changes immunological reactivity in the direction of enhancing allergic manifestations and contributes to the demyelination process [4].

As it known, the secondary progressive course (SPC), in contrast to the recurrent course (RC), is characterized by a more unfavorable course due to the progression of the process leading to accumulation of a neurological deficit and persistent disability [5, 6]. Therefore, timely and adequate appointment of GC in the early stages of the disease, i.e. in debuts and on the recurrent stage (RS), can postpone further progression of the process [7].

The revealed effects of GC allowed us to reconsider traditionally a skeptical attitude toward the appointment of GC in progressive type of flow (PTF), for which the spectrum of therapeutic measures until recently was forcedly limited by the cytostatics, that give a significant number of complications during long-term admission [8, 9].

As for the SPC, in this form it is proved that degenerative-axonal lesions are combined with autoimmune inflammatory changes of varying severity [10].

Consequently, the activity of the demyelinating process at the stage of secondary progression (SSP) is comparable with the activity of relapses in RC, despite a different time algorithm for the development of the inflammatory process and significant differences between these types of flow, manifested by clinical-immunological and clinical-morphological dissociations, named Ch. Pozer as "phenomenon of the iceberg" [11]. This provision is the evidence for the use of active immunosuppressive therapy of GC for this category of patients [12].

In recent decades, a highly effective pulse-therapy with methylprednisolone has been used to relief relapses, which has a significant advantage over prednisolone due to the presence of a methyl group that can penetrate the cell membrane and bind to intracellular receptors [13]. Due to the powerful anti-inflammatory and anti-edematous effects, the proposed scheme (intravenous drip high-dose up to 1000 mg of metipred or solu-medrol for 5–7 days) remains effective for 1.5 months after the development of exacerbations in the form of a significant reduction in brain volume, recovery affected by the demyelinating process of the functions of the central nervous system, the normalization of the permeability of the BBB. In addition, GC can prevent the development of brain atrophy, preventing early formation of persistent disability, by slowing the accumulation of residual neurological deficits [14].

2. Aim of the research

The aim is to evaluate the effectiveness of hormonal pulse therapy at different time stages of the secondary progressive course of multiple sclerosis.

3. Materials and methods

In the study, which was conducted in the Institute of Neurology of Psychiatry and Narcology of the National Academy of Medical Sciences of Ukraine (GU INPN NAMN), Department of Neuroinfections and Multiple Sclerosis, from 2008 to 2017, The patients with SPC MS were selected and monitored. GC treatment was performed at different time stages of the SPC (in the beginning, at the recurrent stage (RS) and at the stage of secondary progression (SSP)) in 70 patients (57 women and 13 men) aged from 28 to 67 years (mean age 45±2.5) years) with the duration of the disease from 7 to 34 years (mean duration – (19.8±2.3) years).

In the research next methods were used: clinical-neurological, statistical.

The following clinical indicators were taken into account in characterizing the course of the clinical course of SPC MS: the age of the manifestation of clinical symptoms, the severity of the debuts, the duration of remission after the debut and the duration of the RS, the severity and number of relapses in the RS, the mean frequency of relapses in the RS, the duration of the SSP, the progression variants, the rate of progression, the degree of disability on the EDSS scale.

The total number of courses of GC therapy in 70 patients, including all stages of the disease, was 438, including 11 at the debut stage, 178 at the RS, and 249 at the EVP.

The effectiveness of hormonal therapy was evaluated taking into account the following criteria:

– dynamics of regression of neurological symptoms under the influence of the first course of GC therapy at the stage of debuts;

– comparative evaluation of the duration of remission after admission and without taking GC in the beginning;

– the average frequency of relapses against the background of repeated courses of GC therapy in the RS;

– the duration of the RS depending on the duration of remission after the first course of GC therapy;

– comparative evaluation of the duration of remissions after the first (at the stage of debut and/or on the ER RS and the period of stabilization on the SSP before the last course of the GC;

– variants of secondary progression under the influence of GC courses;

– scores on the EDSS disability score scale after the 1st and before the last course of GC therapy;

– the rate of progression (the sum of the EDSS disability score difference between the first and before the last GC course for each patient in relation to the total number of patients in each group) under the influence of repeated courses of GC therapy.

Statistical processing of the results of the study was carried out using a package of statistical programs “Statgraph”. It was determined n - the number of patients; M is the average value of the indicator; m is the standard deviation of the indicator.

4. Results

The age of the debut at the time of evaluation of the effectiveness of treatment with GC varied significantly (from 14 to 44 years) and averaged (26.1±2.0) years.

Comparative evaluation of the severity of the debuts revealed a significant predominance of debuts of moderate severity compared with light and heavy debuts. In turn, heavy debuts were significantly less frequent than light debuts (**Table 1**).

Table 1

The frequency of debuts of varying severity with SPC MS, M±m, %

Severity of the debuts	SPC (n=70)
Light debuts	27,5±7,4[1, 2)]
Medium debuts	62,5±8,1[1)]
Heavy debuts	10,0±5,1[1,2)]

Note: n is the number of patients; [1)] – p <0.05 – between medium-heavy debuts and debuts of light and heavy severity; [2)] – p <0.05 – between light and heavy debuts

Pulse therapy of GC with the manifestation of clinical symptoms in the debuts received only 11 (15.7 %) patients who had been diagnosed with MS in a timely manner. The experience of GC in the debuts, despite the low percentage of patients, proved to be highly effective in patients with a medium severity of debuts (8 people) who had a full regress of neurologic symptoms with the release of clinical remission. In patients with heavy debuts (3 people), the output from the debuts was protracted, accompanied by a minimal regression of the neurological deficit with the outcome of incomplete clinical remission.

The average duration of remission after the debut in all patients with SPC, as well as for subgroups of patients taking and not taking GC, did not reveal significant differences. However, in patients with medium debut with GC, remission after debut was significantly longer than in patients with heavy debuts (5.3±1.4 and 3.2±0.6 years, respectively) (**Table 2**).

Table 2

The duration of remission after debut under the influence of the first course of GC therapy in patients with SPC MS, M±m, in years

Group of patients	The duration of remission after debut (n=70)
In the general group of patients	3.2±0.6
In the group after taking GC	2.8±1.2
In the group without GC	3.1±0.6

Note: n is the number of patients

Features of the course of RS, primarily its duration, frequency and severity of relapses, as well as the rate of accumulation of a neurological deficit, play a key role in starting the process of transforming RS into SSP. To implement this process, a complex selective structural reorganization of clinical indicators in the RS is necessary, the leading role among which belongs to the severity of relapses. The increase in severe relapses during the course of the RS flow accelerates the transformation of RC into the SPC [15, 16].

In terms of duration, the average duration of the RS was 10.4±3.9 years and was divided into short (from 2 to 5 years), moderate (from 5 to 8 years) and long (more than 8 years).

Neurological symptoms during exacerbations in the RS affected the leading functional systems with the predominance of pyramidal and cerebellar syndromes. As a rule, relapses of different severity (light, medium and heavy) alternated among themselves in the vast majority of patients as the RS progressed. Mild relapses were characterized by rapid rates of clinical symptomatology, short duration (no more than 3–4 weeks), mono- or oligo-syndromic symptoms with minimal signs of rapidly regressing neurological deficit. With relapses of moderate severity, oligo- or polysyndromic symptoms prevailed, predominantly developing at a gradual pace, the formation of a moderate neurological deficit with a slower rate of regression (up to 2 or more months) with an incomplete clinical remission. For severe relapses, the slow pace of formation of severe polysyndrome symptomatology with subsequent partial and differentiated for different functional systems regress and delayed output (for 3 or more months) in short and incomplete clinical remissions were characteristic.

The total number of relapses in the RS in 70 patients was 366. The mean frequency of relapses (MFR – the ratio of the number of relapses to the duration of the RS) is 0.9±0.2. However, this indicator was not sufficiently informative, since the range of fluctuations for each patient was from 0.1 to 2.8.

The analysis showed that in all patients a low MFR value (<1.0) indicated a rare recurrence and prolonged RS; an increase in MFR (> 1.0) occurred with frequent recurrences and short duration of the RS (**Table 3**).

This position is confirmed by the data obtained in the analysis of the average duration of the RS, depending on the size of the MFR, which was significantly higher in the case of an MFR <1.0 than with an MFR value> 1.0 (**Table 4**). Consequently, an increase in the MFR as an integral

measure of the relationship between the duration of the RS and the number of relapses may serve as one of the probable criteria for the nearest transformation of the RS into the SSP.

Table 3

The average frequency of recurrences in the RS with SPC MS on the background of repeated courses of GC, M±m, in years

Average meaning of MFR	SPC (n=70)
MFR of all patients. including:	0.9±0.2
MFR<1.0	0.5±0.1[1)]
MFR>1.0	1.6±0.7[1)]

Note: n – the number of patients; [1)] – p < 0.05 – differences between MFR<1.0 and MFR>1.0

Table 4

Duration of the RS, taking into account the mean frequency of relapses (MFR) in case of SPC MS, M±m, in years

Duration of the RS	SPC (n=70)
Duration of the RS at MFR<1.0	14.7±2.1[1)]
Duration of the RS at MFR>1.0	3.9±0.9[1)]

Note: n – the number of patients; [1)] – p < 0.05 – differences between MFR<1.0 and MFR>1.0

Analysis of the frequency of relapses of varying severity in all patients with SPC showed a significant predominance of relapses of moderate severity over light and severe relapses that occurred almost at the same frequency (**Tab. 5**).

Table 5

Severity of relapses in the RS with SPC MS on the background of repeated courses of GC, M±m, %

Severity of relapses in the RS	SPC (n=70)
Light	27.2±7.5[1)]
Medium	51.9±8.5[1)]
Heavy	20.9±6.7[1)]

Note: n – the number of patients; [1)] – p<0.05 – between relapses of medium severity and relapses of light and heavy severity

The first course of GC therapy was given to 59 out of 70 patients with SPC. The total number of courses was 178, including 104 for relapses of moderate severity, 74 for severe recurrences. With light relapses, GC therapy was not used, despite the fact that a significant part of patients of this subgroup had radiological activity, according to MRI. Such a violation of the protocol providing for the appointment of hormonal therapy for all relapses, regardless of their severity, led to a further increase and increase in relapse, the accumulation of a residual neurological deficit, a reduction in the duration of RS, an increased risk of transformation of RS into secondary progression.

The clinical effect under the influence of courses of GC therapy was characterized by a differentiated regression of the neurological deficit. This allowed us to distinguish conditionally "well-managed" and "poorly managed" symptoms in each functional system. In the pyramidal syndrome, reversal of the spinal tone was primarily affected by spasms, whereas the restoration of strength in the legs depended on the severity of the paresis. Within the cerebellar-atactic syndrome, a reduction in the amplitude of horizontal nystagmus and shakiness in walking, as well as an improvement in the finger-nasal test, are among the "well-controlled" symptoms. Significantly less frequent reversal was the execution of the knee-heel test and static ataxia in the Romberg sample.

The regression of sensitive disorders took place differentially and depended on their nature. The most "controlled symptoms" were violations of pain sensitivity and astereognosis, while normalization of proprioceptive and temperature sensitivity occurred slowly and, as a rule, partially. In stem disorders, vestibular syndrome, vertical nystagmus, impairment of the function of the facial musculature, as a consequence of facial nerve lesions, were more often subjected to significant regression; rarer - a variety of oculomotor disorders. Sphincter disorders, depending on the degree of their decompensation, were usually partially regressed with significant individual differences.

Thus, the analysis of the effectiveness of pulse therapy of GC indicates that the RS with relapses of varying severity formed a "dissociation syndrome" with selective and differentiated regression of clinical symptoms in individual functional systems.

Remission after the first course of GC therapy was divided into short (up to 1 year), moderate (1 to 2 years) and prolonged (more than 2 years), but their frequency did not have significant differences (short – 31.6±9.6, moderate – 38.8±9.7, long-term – 29.6±8.8).

A directly proportional relationship was established between the mean duration of remission (MDR) after the first course of GC therapy (2.3±0.7) years and the duration of the RS. Thus, with prolonged RS, MDR was significantly higher than for its short and moderate duration (**Table 6**).

Thus, prolonged remissions after the first course of GC contributed to the prolongation of the RS. Consequently, this indicator can act as a prognostic marker, indicating a reduction in the risk of transformation of RC into the SPC. This provision is of great practical importance for the timely and adequate development of a treatment strategy, including modifying agents and cytostatics, which in the RS will create real prerequisites for preventing further rapid progression of the disease.

Table 6

Dependence of the average duration of remission after the first course of GC therapy on the duration of the RS in cases of SPC MS, in years

Duration of RS	Average duration of remission
short (2 to5 years)	0.5
moderate (5 to5 8 years)	0.7
prolonged (more than 8 years)	1.8

The different sensitivity to repeated courses of hormonal therapy, obtained during the analysis of clinical indicators at the RS, led to the fact that the process of transformation in SSP proceeded at different rates in different patients.

Clinical analysis of the course of SSP made it possible to distinguish three main variants of progression, evidencing its complex structural and functional organization:

– steady variant, current without clinically outlined periods of stabilization;

– recurrent variant, proceeding in the form of abrupt deteriorations, reminiscent of relapses, at the exit from which periods of stabilization of different duration were observed;

– progressive variant, which is an alternation of periods of slow progression of neurological symptoms, alternating with periods of stabilization of different duration.

For the first two variants (steady and relapsing), usually unfavorable, the development of coarse and persistent polysyndrome neurologic symptoms, absence or relative rarity of dissociation syndromes, high rate of progression is characteristic. As a result, a deep degree of disability and persistent therapeutic resistance to GC therapy are formed. Progressive version of progression is more favorable and is characterized by the absence of a severe neurological deficit, a longer period of residual ability to work, better socio-psychological adaptation, and greater effectiveness of pathogenetic therapy. The character of the further progression was determined not only by the variants, but also by the rate of growth of the neurological symptomatology – rapid, moderate and delayed. At a rapid pace, the steady and recurrent options prevail or alternate; at moderate and especially slow rates – a progressive variant.

At the time of evaluating the results of treatment with GC, the average duration of the SSP was (7.2±1.4) years. At this stage, 249 courses of GC therapy (3.5 – the average number of courses per patient) were conducted. The need for more frequent courses on SSP, compared with the RS, indicates a steady decline in the effectiveness of hormone therapy after the formation of progressive flow.

However, against the background of repeated courses of GC, the structural characteristic of the SSP was clearly individual. A clear relationship was found between the magnitude of the MFR on the RS and the variants of secondary progression. For example, with MFR<1.0, the most favorable – a progressive variant of progression was observed in 21 patients, and a recurrent variant was observed in 14 patients. With an MFR>1.0, the most unfavorable variant prevailed, which was observed in 26 patients, while the recurrent variant was found in only 9 patients.

One of the important criteria for the effectiveness of GC treatment at the end of the study was a comparative assessment of the duration of remission in the RS after the first and the period of stabilization before the last course of GC. According to the data obtained, the duration of stabilization before the last course was significantly shorter in patients with SSP than the remission of the RS after the first course of GC (**Table 7**).

The received data confirm the position that with prolonged use of GC therapy causes oppression of the hypothalamic-pituitary-adrenal system, contributes to the formation of steroid dependence, which leads to stable hormone-dependent forms and further progression of the disease.

As one of the leading criteria for the effectiveness of hormonal therapy in the SSP, a comparative assessment of the EDSS scores on the EDSS disability score was made after the first and before the last course of pulse therapy for GC.

Table 7

The duration of remission on the SP after the first and stabilization before the last course of GC in patients with SPC MS, M±m, in years

Index	SPC (n=70)
The duration of remission on the SP after the first course of GC	2.3±0.7[1)]
The duration of stabilization before the last course of GC	1.2±0.2[1)]

Note: n – the number of patients; [1)] – p<0.05 – between the first and before the last course of the GC

The average meaning on the EDSS disability score after the first course of GC therapy were (3.2±0.5) points. Analysis of the gradual course of the disease, despite repeated courses of hormonal therapy, indicates that on the SSP before the last course of GC therapy in the vast majority of patients, the value of the mean scores on the EDSS disability scale increased to 6.1±0.9 (p<0.05).

The negative dynamics of scores on the EDSS scale corresponded to the integral index, as the rate of progression, which by the end of the study were 2.3.

5. Discussion

At the present time, according to different authors, the question of the efficacy of GC in patients with SPC MS [17, 18] remains controversial. The prognosis of the transformation of the RS in the SPC with the timely hormonal therapy of exacerbations decreases according to the data of the authors [19]. The prognosis of the course of SPC in the course of GC is unclear. However, there is no correlation between the increase in neurological deficit in patients with SPC MS in the use of GC [20].

In this study, an integrative assessment of the effect of repeated courses of pulse therapy of GC, performed at different time stages with SPC MS, made it possible to distinguish three subgroups of patients - with moderate and low efficacy, as well as lack of efficacy. High efficiency, which assumes no risk of transforming the RS into an SPC, with this type of flow absent.

Moderate efficacy was detected in 21 patients with an MFR <1.0. This category of effectiveness included patients who, under the influence of GC treatment, were able to manage severe (less often) and moderate (more often) relapses, with a moderate and stable neurological deficit. After

the transformation of RS into an SPC, the most favorable progressive variant of progression was characteristic for these patients.

Low efficacy was also obtained in 21 patients, including 9 people with MFR<1.0 and in 12 people with MFR>1.0. For this subgroup of patients, in spite of the different size of the MFR, a short (more often) and a moderate (less frequently) RS appeared to be characteristic, during which a general tendency was observed to increase and increase relapses with the accumulation of a neurological deficit. As a result, there was a transformation in SSP, in which a recurring variant of progression prevailed.

Lack of efficacy was obtained in 28 patients who had short RS, predominance of severe and prolonged relapses, greater than 1.0 MFR, a steady accumulation of a pronounced and persistent neurologic deficit, a high rate of progression and high scores on the EDSS disability score (more than 6.5) . After transformation in SSP, the most unfavorable variant of progression prevailed (21 patients); significantly less frequent recurrent (5 patients) and a combination of a steady and recurrent (2 patients) progression.

6. Conclusions

1. Under the influence of repeated courses of GC therapy with SPC MS there is a complex systemic reorganization of the clinical indices characterizing the time stages of the course of the disease. Clinical analysis of the dynamics of various indicators allowed to develop criteria for the effectiveness of treatment for patients with SPC MS.

2. Allocation of subgroups of patients with only moderate and low efficacy did not exclude the risk of transformation into the SPC. However, this process occurred at different times and was accompanied by significant individual differences.

3. Patients with moderate efficacy of hormonal therapy were characterized by an increase in the duration of remission after debut, a decrease in the mean frequency of relapses (MFR<1.0) in the vast majority of patients, closely associated with an increase in duration of RS, a decrease in the severity and frequency of relapses, longer remissions after the first course of GC, a relatively slow rate of accumulation of neurological deficits (according to the EDSS disability score scale).

4. The positive dynamics of treatment led to the formation of a progressive variant of secondary progression, which has a more favorable prognostic value.

5. Patients with lack of efficacy were the most numerous and, as a rule, characterized by severe debuts, the outcome of which was protracted, accompanied by a minimal regression of the neurological deficit and a short remission after the 1st attack. As the RS progressed, there was a tendency for weight gain and lengthening of relapses, predominance of patients with high MFR value, rapid accumulation of residual neurological deficit with an increase in the rate of progression. As a result, during SSP, the course of the disease acquired an unfavorable character with the formation of a rapid rate of a steady progression.

6. As a result of the study, it was possible to prove that the effectiveness of GC therapy in the case of SPC MS is determined by the complex interaction of clinical indicators characterizing different time stages of the course of the disease, as well as a number of genetic factors that require further study.

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PROGNOSTIC VALUE OF KIDNEY FUNCTION PARAMETERS IN PATIENTS WITH CHRONIC HEART FAILURE AND LEFT VENTRICULAR REDUCED EJECTION FRACTION

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Abstract

Chronic heart failure (CHF) is a complex clinical syndrome characterized by progressive course, unsatisfactory quality of life, poor prognosis and high incidence of concomitant renal dysfunction (RD).

The aim of our work was to study the prognostic value of a number of renal function indicators in patients with CHF and a reduced left ventricular ejection fraction (LVEF).

Materials and methods. 134 patients with stable CHF and reduced (<40 %) LVEF, II-IVNYHA class were examined. Patients were divided into two groups according to the level of GFR: the first group of GFR<60 ml/min./1.73 m², the second – GFR≥60 ml/min./1.73 m². The average follow-up period was 13.4 months, the maximum was 27.5 months.

Results. In 53 patients RD was detected (glomerular filtration rate was <60 ml/min/1.73 m²), which was 39.5 %. Patients of both groups did not differ in their main hemodynamic parameters, left ventricular ejection fraction, and pharmacotherapy structure, but were older in age and heavier clinically. After the analysis of survival curves of patients depending on GFR, a group of patients with RD had a significantly worse survival prognosis compared to a group without RD. After adjusting the groups by age and NYHA class, the indicated difference was maintained. The subjects were divided according to median levels: blood urea nitrogen, blood urea nitrogen/creatinine ratio, microalbuminuria, albumin / creatinine ratio in urine.

The long-term survival of the formed groups was analyzed. The level of blood urea nitrogen did not significantly influence the prognosis of patients with CHF and reduced LVEF. At the same time, when the groups were divided, depending on the median value of the blood urea nitrogen/creatinine ratio, there was a significantly higher risk of fatal outcome in the group with lower indices. The level of MAU did not significantly affect the survival of patients. In addition, a comparison of the survival of patients with higher and lower values of the albumin/creatinine ratio in the urine revealed a significantly higher risk of death in patients with higher values.

Conclusions:

1. The presence of RD (GFR<60 ml/min/1.73 m²) is observed in 39.5 % of patients with CHF and reduced LVEF and is associated with their worst long-term survival.

2. The BUN and MAU do not have sufficient predictive information about the forecast of long-term survival of the above category of patients.

3. At the same time, the values of the BUN/ Creatinine ratio <24.5 and the ACR>12.7 indicate patients with CHF who have a higher long-term risk of death.

Keywords: chronic heart failure, reduced left ventricular ejection fraction, glomerular filtration rate, blood urea nitrogen, microalbuminuria.

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1. Introduction

Chronic heart failure (CHF) is a complex clinical syndrome, characterized by a progressive course, unsatisfactory quality of life and a worse prognosis [1, 2]. The risk of death within one year in patients with CHF, even with modern methods of their treatment, is from 6.9 to 15.6 % according to different data [3]. CHF is characterized by a high incidence of concomitant pathology, among which renal dysfunction (RD) occupies one of the leading positions.

According to the results of various studies, the number of patients with CHF and RD varies from 32 to 66 % [4, 5]. The combination of cardiac and renal pathology is considered within the cardio-renal syndrome [6] and is discussed in the context of common factors of pathogenesis and mutual influence on the course of CHF, drug therapy, and a prognosis [7]. The glomerular filtration rate (GFR) is a universal marker for assessing renal function, with a decrease of GFR below 60 ml/min/1.73 m^2 being considered as the presence of RD [8]. It is known that a decrease of GFR in patients with CHF has a greater prognostic value than of the left ventricle ejection fraction (LVEF) [9]. One of the most important parameters of the renal function is blood urea nitrogen (BUN), which, according to a number of researchers, can serve as an indirect marker of neurohumoral activation [10]. Non-ligand diagnostic markers of kidney condition include microalbuminuria (MAU), and albumin/creatinine ratio (ACR), which makes it possible to level the variability of albumin excretion fluctuations due to drinking regimen and hydration [11]. MAU is a proven independent predictor of cardiovascular complications in patients with hypertension [12], but data on its prognostic value with stable CHF are almost absent.

2. Aim of the research

Taking into account the above, and taking into account the expediency of searching for new markers that can help improve the quality of dispensary observation of such patients, the aim of our work was to study the prognostic value of a number of renal function indicators in patients with CHF and reduced left ventricular ejection fraction (LVEF).

3. Materials and methods

Patients were observed on the basis of the heart failure department in National Scientific Center "M.D. Strazhesko Institute of Cardiology" from 2016 to 2018.

134 patients with stable CHF and <40 % LVEF, NYHA class II–IV, whose median age was 59.5 (54; 68) years were examined. The criteria for inclusion in the study were:

1) the age of patients from 18 to 75 years;

2) CHF caused by ischemic heart disease (including in combination with AH) or dilated cardiomyopathy;

3) LVEF <40 %;

4) II–IV functional class according to the criteria of the New York Heart Association (NYHA).

The criteria for exclusion were:

1) age over 75 years;

2) LVEF>40 %;

3) GFR≤30 ml/min./1.73 m^2;

4) acute forms of ischemic heart disease;

5) signs of congestion;

6) acute infectious diseases;

7) acute and chronic diseases of the urinary tract and chronic organic kidney damage (glomerulonephritis, pyelonephritis), nephrotic syndrome;

8) unsatisfactory adherence to treatment;

9) diabetes mellitus type I;

10) acquired valvular heart disease;

11) inflammatory and restrictive lesions of the myocardium;

12) oncology;

13) acute disorders of cerebral circulation;

14) availability of artificial pacemakers, cardio-resynchronizing therapy;
15) severe anemia (Hb<80 g/l).

All patients underwent general clinical examination, routine 12-lead ECG and ultrasound examination of the heart by a standard procedure. The creatinine concentration was determined by the kinetic method of Jaffe without deproteinization, the level of GFR was estimated using the CKD-EPI equation [8]. Determination of the urea concentration was carried out by the urease method, the appropriate recalculation factor was used to determine urea nitrogen: urea (mmol/l)× ×0.467=blood urea nitrogen (mmol/l) [13]. The determination of MAU was carried out using the turbidimetric method [14]. The MAU criteria is 29–300 mg of protein in urine per day.

The patients were treated with standard inhibitors of the renin-aldosterone system (RAS), diuretics, beta-blockers and antagonists of mineralocorticoid receptors (AMR) in accordance with the current standards of the Association of Cardiologists of Ukraine for the diagnosis and treatment of chronic heart failure [15]. Statistical processing of information was carried out using the "STATISTICA" software package v. 6.0. Absolute and relative frequencies (n, %) were used to describe the qualitative characteristics, for the quantitative indices – the median, upper and lower quartiles. The reliability of the differences in the parameters was verified using the Mann-Whitney test, for qualitative ones, using the Pearson χ^2 criterion, with the construction of conjugacy tables. The difference was considered reliable at a value of $p<0.05$. To find the connection between the phenomena, the Spearman rank correlation coefficient was used. To evaluate the survival rate, a log rank test was used to construct the Kaplan-Meier curves.

5. Results

Patients included in the study in stable CHF with a reduced LVEF were divided into two groups according to the level of GFR: the first group of GFR<60 ml/min/1.73 m², the second – GFR≥60 ml/min/1.73 m². In 53 patients RD was detected, which consisted 39.5 %. At the first stage, patients were compared by age, NYHA class and hemodynamic parameters, and the structure of pharmacotherapy, depending on the presence of RD (**Table 1**). Patients of both groups did not differ in hemodynamic parameters such as heart rate (HR), systolic blood pressure (SBP), LVEF and were comparable in the structure of the prescribed treatment. At the same time, patients with RD were older and characterized, in contrast to patients without RD, by a predominance of higher (III–IV) classes according to NYHA (**Table 1**).

Table 1

Comparability of groups of patients with RD and without RD according to age, indicators of hemodynamics, NYHA class and the structure of pharmacotherapy

Indicators	GFR<60 ml/min/1.73 m² (n=53)	GFR≥60 ml/min/1.73 m² (n=81)	P
Age, (Me (LQ;UQ)	67 (63; 70)	58 (45;76.4)	<0.001
HR, bpm (Me (LQ;UQ)	76 (70; 82)	72 (66; 80)	0.357
SBP, mm Hg (Me (LQ;UQ)	110 (100; 120)	110 (110; 120)	0.286
LVEF, % (Me (LQ;UQ)	26 (21; 33)	29 (22; 35)	0.443
NYHA II (n, %)	9 20 %	36 80 %	<0.010
NYHA III–IV (n, %)	44 83 %	45 56 %	0.009
Diuretics (and) (n, %)	51 96 %	76 93 %	0.541
ACE inhibitors or ARB II (n, %)	26 49 %	51 63 %	0.111
BB (n, %)	45 85 %	72 90 %	0.376
AMR (n, %)	42 79 %	70 87 %	0.272

Notes: HR – heart rate; SBP – systolic blood pressure; LVEF – left ventricular ejection fraction; NYHA – New York Heart Association; ACE inhibitors – angiotensin-converting-enzyme inhibitor; ARB – angiotensin receptor blocker; BB – beta-blockers; AMR – antagonists of mineralocorticoid receptors

We compared and analyzed the survival curves of patients depending on the above-mentioned indicators of kidney function. The average follow-up period was 13.4 months, the maximum was 27.5 months.

It turned out that a group of patients with RD had a significantly worse survival prognosis compared to a group without RD (**Fig. 1**). After adjusting the groups by age and the NYHA class, the difference was maintained (**Fig. 2**).

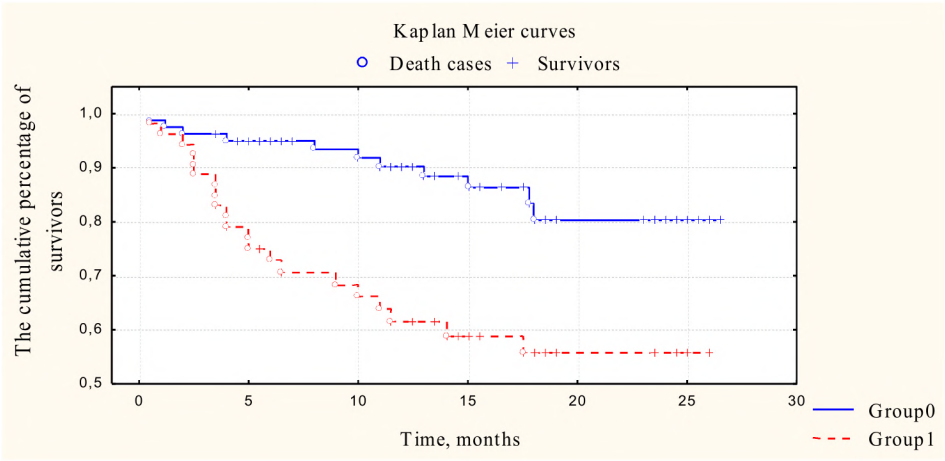

Fig. 1. Survival curves of patients with CHF and reduced LVEF depending on the level of GFR, n=134; p=0.00065; group 0 – GFR<60 ml/min/1.73 m²; group 1 – GFR≥60 ml/min/1.73 m²

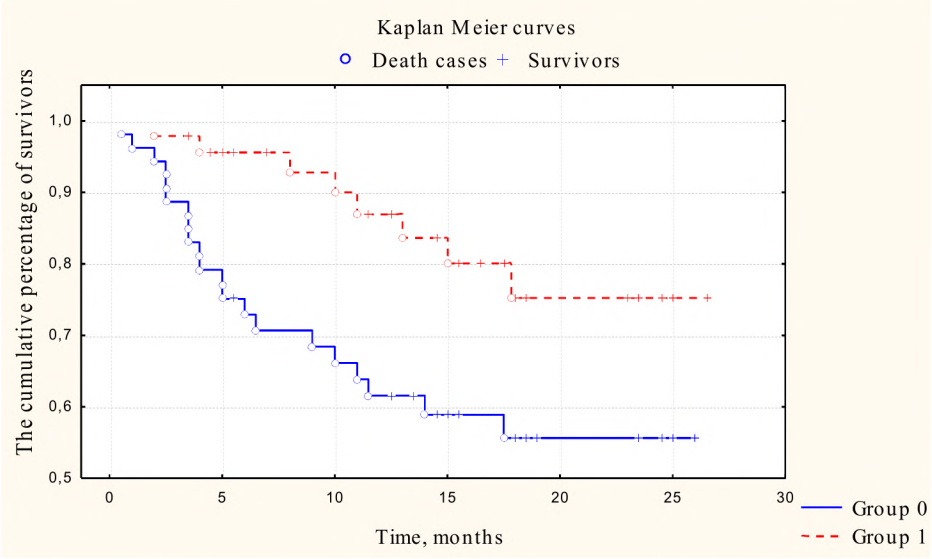

Fig. 2. Survival curves of groups of patients with CHF and reduced LVEF with and without RD, age-adjusted and NYHA class, n=99, p=0.014, adjusted; group 0 – GFR<60 ml/min/1.73 m², group 1 – GFR≥60 ml/min/1.73 m²

The groups of patients were formed depending on the median of BUN, the BUN/creatinine ratio, MAU, the albumin to creatinine ratio (ACR) to assess the prognostic value these indicators. It was found that the level of BUN did not significantly affect the prognosis of patients with CHF and reduced LVEF (**Fig. 3**).

At the same time, when the groups were divided, depending on the median value of the BUN/creatinine ratio, a significantly higher risk of fatal outcome was observed in the group with lower indices (**Fig. 4**).

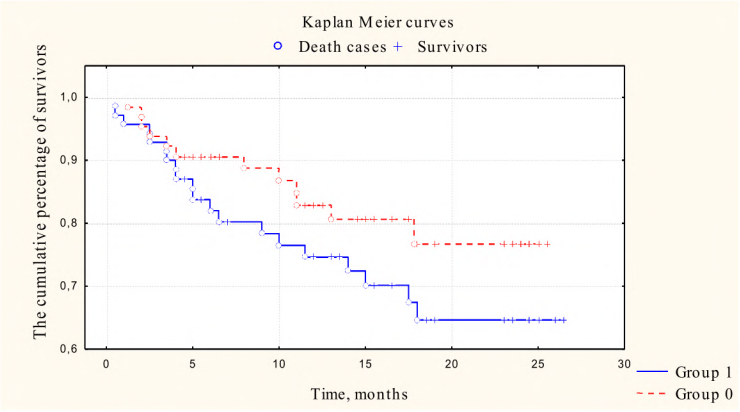

Fig. 3. Survival curves of patients with CHF and reduced LVEF, depending on the median plasma level of BUN, n=134, p=0.176; group 1 – BUN level 2.5 mmol/l; group 0 – BUN level <2.5 mmol/l

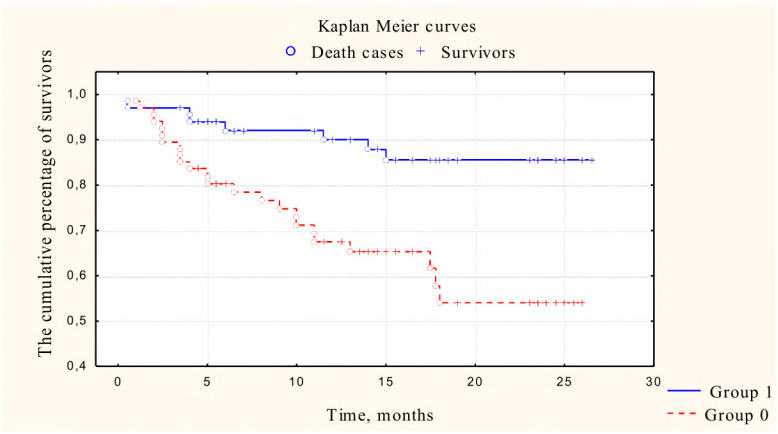

Fig. 4. Survival curves of patients with CHF and reduced LVEF, depending on the median of BUN/creatinine ratio in plasma, n=134, p=0.0009, group 1 – ratio of BUN/creatinine ratio in plasma ≥24.5; group 0 – ratio of BUN/creatinine ratio in plasma <24.5

Among the examined MAU patients (29-300 mg/day) occurred in 94 % of cases. The level of MAU did not significantly affect their survival (**Fig. 5**).

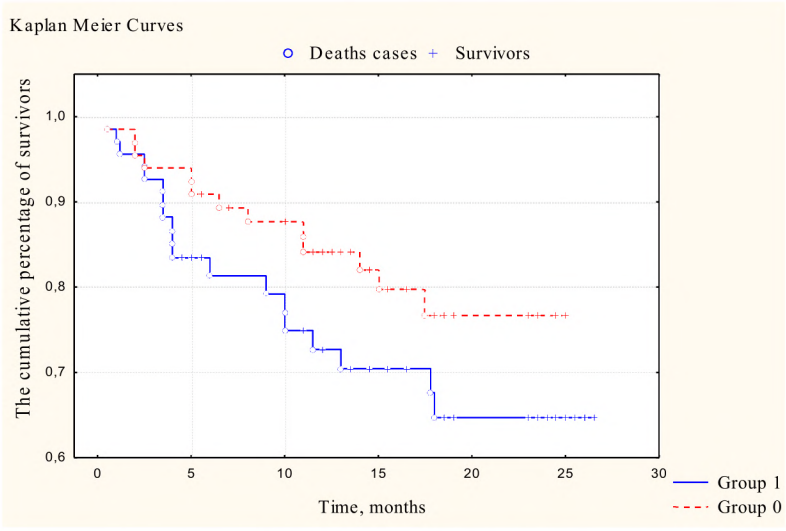

Fig. 5. Survival curves of patients with CHF and reduced LVEF, depending on the median of the MAU level, n=127; p=0.147; group 1 – level of MAU>104 mg/day; group 0 – level of MAU<104 mg/day

In addition, a comparison of the survival of patients with higher and lower ACR revealed a significantly higher risk of death in patients with higher values (**Fig. 6**).

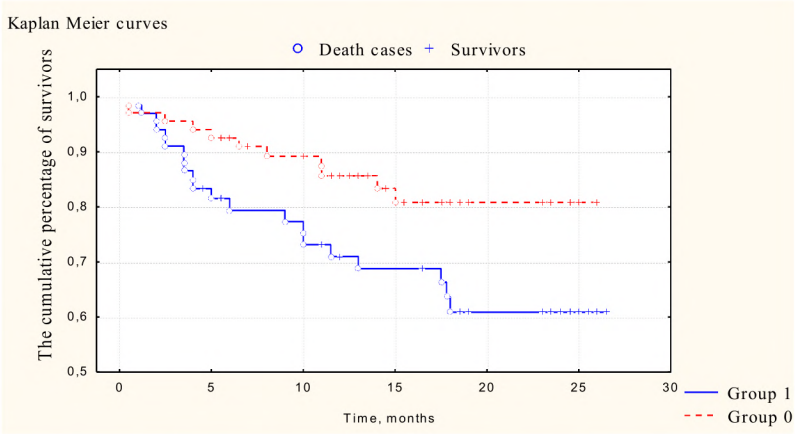

Fig. 6. Survival curves of patients with CHF and reduced LVEF, depending on the median of ACR, n=134; p=0.028; group 1 – ACR≥12.72 mg/mmol, group 0 – ACR <12.72 mg/mmol

5. Discussion

The study confirmed, on the one hand, the high prevalence (almost 40 %) among patients with CHF and reduced LVEF, and on the other hand, the high prognostic significance of low GFR<60 ml/min/1.73 m² in this category of patients [4, 16].

At the same time, we were not able to confirm the prognostic significance of BUN for long-term survival of such patients [17]. Nevertheless, the analysis of the BUN / creatinine ratio demonstrated its corresponding high informative value [18]. It is known that both BUN and creatinine are freely filtered in the glomerulus of the kidneys, while a part of BUN is reabsorbed under the action of vasopressin through the V2 receptors in the proximal tubules [10]. Thus, BUN reflects not only the function of glomeruls and tubules, but indirectly indicates the severity of neurohumoral activation, which in patients with CHF is most pronounced in a state of decompensation [19, 20]. Our patients had standard therapy with neurohumoral antagonists and were in the euvolemic state, which may explain the insufficient prognostic information level of BUN as such. An increase in the predictive informative value of the last indicator of such a component, which reflects the filtration status of the kidneys in the form of BUN / creatinine ratio, allowed to statistically reliably separate patients with the worst and best prognosis, which indicates the expediency of further study of this marker with stable CHF.

The study showed an almost total (94 %) prevalence of MAU in the surveyed, which is higher than that found in a similar category of patients by other authors [21, 22]. The explanation for the discrepancy may be the high prevalence of hypertension and diabetes mellitus (83 % and 42 %, respectively) among our patients. It is known that the presence of MAU displays an increase in the permeability of the glomerular membrane due to its damage by increased hemodynamic load and endothelial dysfunction [23]. Nevertheless, the trend toward a higher risk of death in a group of patients with large MAU values has not been statistically confirmed. However, the approach that allows to compare the levels of albumin and creatinine excreted in the urine was more informative about the stratification of the long-term risk of death, which requires confirmation by further studies.

7. Conclusions

1. The presence of RD (GFR<60 ml/min/1.73 m²) is observed in 39.5 % of patients with CHF and reduced LVEF and is associated with their worst long-term survival.

2. Levels of BUN and MAU do not have sufficient predictive information about the forecast of long-term survival of the above category of patients.

3. At the same time, the values of the BUN/Creatinine ratio <24.5 and the ACR>12.7 indicate patients with CHF who have a higher long-term risk of death.

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ROLE OF THE PERICARDIOSCOPY IN THE TREATMENT OF PERICARDIAL EFFUSION

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Abstract

In recent years surgical treatment of pericardial effusion has been favoured by mini-invasive interventions. Pericardioscopy supplements it. In the literature actively discusses its expediency, efficiency and informativeness.

Aim of the study. Analyze our experience of using pericardioscopy during surgical treatment of pericardial effusion using mini-invasive interventions.

Materials and methods. From 2000 to 2017, 92 patients with pericardial effusion were operated in our clinic using mini-invasive interventions. Pericardioscopy was used in 72 (78.26 %) cases. In 32 (44.44 %) pericardioscopy was performed with subxiphoid pericardiotomy, in 40 (55.56 %) – with thoracoscopy on the right or left side.

Results and discussion. The use of pericardioscopy has allowed to significantly reduce the number of idiopathic pericarditis from 20.0 % to 5.56 % and increase the informativeness of the minimally invasive interventions by 14.44 % (χ^2=4.11, with v=1, α=5 %). There is no reliable difference in the number of relapses of the disease.

Conclusions. The use of pericardioscopy during mini-invasive interventions is safe and effective. The method of choice in most cases is subxiphoid non-pleural pericardiotomy with pericardioscopy.

Keywords: pericarditis, pericardioscopy, surgical treatment, minimally invasive.

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1. Introduction

In recent years, the incidence of pericarditis has been rising steadily. The reason for this, according to many authors, is the development of diagnostic and therapeutic technologies and the deterioration of the quality of life of the population [1, 2]. The most common pericardial pathology is exudative pericarditis of different etiologies. Cases of the initial occurrence of effusion in the pericardium cavity are singular [3, 4]. Their cause in the vast majority are various infectious (viral and bacterial), systemic, autoimmune, neoplasm diseases, injuries, heart disease and pericardium, etc. [5, 6]. At the same time, to find out the cause of the disease can not always be possible and then they speak about the idiopathic nature of the disease [7, 8]. A large number of idiomatic exudative pericarditis is an urgent and debatable problem, because without identifying and eliminating the root cause, the risk of chronic and recurrent pericardial inflammation is significantly increased [1, 9]. The level of mortality from exudative pericarditis depends on many factors, including the etiology, the prescription of the process, the severity of the underlying disease and related disorders,

the timeliness and completeness of diagnosis and treatment, and ranges from 1.1 % for uncomplicated viral to 85–90 % with purulent inflammation of the pericardium [3, 5].

Despite the long history of the study of pericardium, the methods for diagnosis and treatment, the choice of method and the extent of surgical intervention remain discursive. Today actively discusses the use of mini-invasive interventions for the treatment of exudative pericarditis [10, 11]. They are attributed to the pleural fenestration of the pericardium through mini-thoracotomy or with thoracoscopy, outside of the pleural subxiphoid pericardiotomy and their variations. They are less traumatic, but not always allow to provide a complete revision, sanitation of the pericardial cavity, to find out the cause of pericarditis [12, 13]. The use of pericardioscopy is aimed at increasing the informativeness, improving the effectiveness and results of mini-invasive interventions [14, 15].

2. Aim of the research

To analyze own experience of use of pericardioscopy during surgical treatment of exudative pericarditis of different etiology with the help of mini-invasive interventions.

3. Materials and methods

For the period from 2000 to 2017 in the clinic of the State University "Institute of General and Emergency Surgery named after V. T. Zaitsev of the National Academy of Medical Sciences of Ukraine" 92 patients were operated using mini-invasive interventions for exudative pericarditis of different etiologies. Pericardioscopy was performed in 72 (78.26 %) patients. Subxiphoid non-pleural pericardiotomy with pericardioscopy was performed in 32 (44.44 %) cases, thoracoscopic left-sided pericardiotomy with pericardioscopy – in 36 (50.0 %) cases, thoracoscopic right-sided thoracotomy with pericardioscopy – in 4 (5.56 %) cases.

To evaluate the informativeness and effectiveness of using pericardioscopy during mini-invasive interventions, 2 groups of comparison were formed. The first (main) group was made up of 72 patients who had undergone pericardioscopy during the surgical procedure. The comparison group consisted of 20 patients operated using mini-invasive interventions but without pericardioscopy. Both groups are representative of the gender and age of patients, the degree of heart failure. With the number of degrees of freedom equal to unity ($\nu=1$), the probability of differences between the main and the control group is not more than 5 % ($\alpha=5$ %), i. e. both groups are random samples of one general population (**Table 1**).

Table 1

Representation of comparison groups

The analyzed indicator		Main group (n=72)	Control group (n=20)	χ^2
Gender	Men	40	12	0.13*
	Women	32	8	
Age (years)	Before 40	28	7	0.10*
	After 40	44	13	

*Note: * – groups represented at $\nu=1$, $\alpha=5$ %*

All surgical interventions were performed under conditions of general anesthesia and artificial ventilation of the lungs. In all cases, the cytological and bacteriological examination of the pericardial effusion, histological examination of the pericardium was performed. In cases where pericardioscopy was used, it was performed using a rigid thoracoscope.

As the evaluation criteria, the possibility and amount of visualization of the heart and pericardium surface, the number of idiopathic cases and the number of relapses of the disease during 6–18 months after the end of treatment in both groups of comparison were used.

4. Results

The volume of surgical intervention in all 92 (100 %) cases of exudative pericarditis, regardless of etiology, consists in the disclosure, revision, rehabilitation and drainage of the pericardial cavity from the subxiphoid or oral thoracoscopic access.

Regardless of access, pericardioscopy was performed by rigid thoracoscope after pericardiotomy, partial pericardiotomy and evacuation of most of the exudate. Exudate was removed partly and gradually to prevent the development of acute right ventricular failure. The biopsy of the pericardium was performed as follows: if pericardioscopy was not performed, then the study sent a pericardial region removed during partial pericardiotomy; pericardioscopy allows you to perform a sighting multiple (from 1 to 5 biopsies) biopsy of the inner surface of the pericardium/epicardium under visual inspection. This made it possible to perform a biopsy, first of all, visually altered areas of the pericardium/epicardium.

The pericardial efficacy information of the effectiveness of the surgical intervention itself depends on the possibility of visualization of the heart organs, the disclosure and review of vascular processes, the discovery of altered sections of the pericardium or epicardium and the implementation of their biopsy. Possibility with pericardioscopy to visualize different areas of the pericardial cavity with various available at mini-invasive interventions is different (**Table 2**).

Table 2

Visualization of anatomical regions of the heart with a pleural and subxiphoid non-pleural pericardioscopy

Anatomic region of the heart	Left-sided through pleural pericardioscopy		Right-sided through pleural pericardioscopy		Subxiphoid non-pleural pericardioscopy	
	N	%	N	%	N	%
The front surface of the right ventricle	–	–	–	–	30	93.75
Diaphragmatic surface of the right ventricle	–	–	–	–	32	100
Right atrial appendage	–	–	3	75	28	87.50
The lateral surface of the right atrium	–	–	4	100	30	93.75
The lateral surface of the left ventricle	36	100	–	–	5	15.62
Diaphragmatic surface of the left ventricle	11	30.56	–	–	12	37.5
Left atrial appendage	5	13.89	–	–	16	50
Aortic root and pulmonary trunk	–	–	–	–	10	31.25

Thus, through pleural thoracoscopic access, one can only visualize a small area of the heart and pericardium around the fenestration from the corresponding side. So, right-sided thoracoscopic pericardioscopy allows you to perform a revision of the surface of the heart and pericardium only in the region of the right atrium. Left-side thoracoscopic pericardioscopy is more informative and allows visualization of the left heart, lateral, and diaphragmatic surfaces of the pericardium. Subxiphoid non-pleural pericardioscopy allows visualization of almost the whole surface of the heart, pericardium, and even major vessels (**Fig. 1**). It also allows you to revise and split the encoded processes into the pericardial cavity.

In the course of research, subxiphoid non-pleural pericardiotomy with pericardioscopy has proven itself as a priority intervention in the treatment of purulent pericarditis. It provides an opportunity to perform revision, sanitation and drainage of purulent cells under visual control and with a minimal probability of proliferation and generalization of the septic process. This can be done even in patients who are in a difficult condition.

The use of pericardioscopy for revision and sight biopsy allowed, in one case, to diagnose the malignant neoplasm of the pericardium – liposarcoma that sprouted into the cavity of the heart and was not diagnosed during preoperative echocardiography. Sight biopsy of the changed sections of the pericardium and the epicardium under the control of pericardioscopy allowed in 4 cases to

diagnose wounding of the pericardium, in 3 cases it was metastatic, in one case it was to detect, open and revise the pericarditis encrusted at the back of the heart.

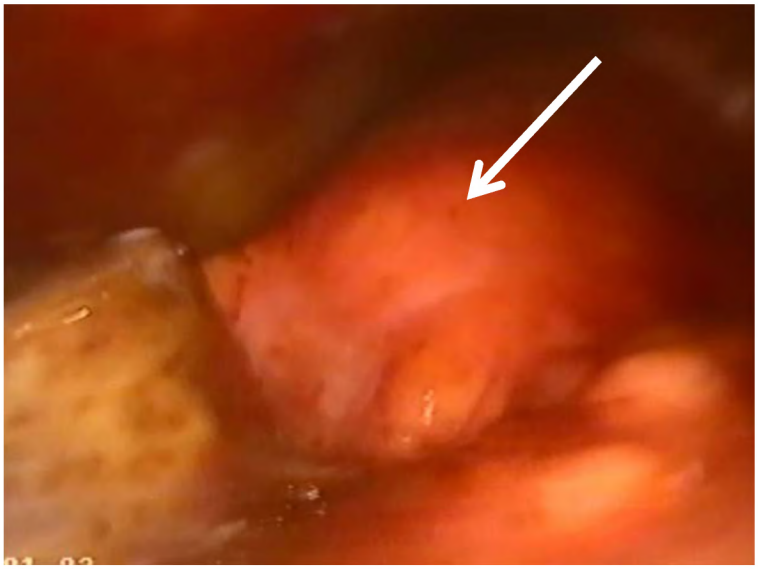

Fig. 1. Visualization of the aortic root (indicated by an arrow) during subxiphoid non-pleural pericardioscopy

The analysis of the results of diagnosis and treatment of patients with exudative pericarditis of different etiologies suggests that the difference in the number of idiopathic cases of this disease is statistically significant (**Table 3**).

Table 3

The reliability of the difference in the comparison groups by the number of idiopathic and recurrent pericarditis

The analyzed indicator		Main group (n=72)	Control group (n=20)	χ^2
Idiopathic pericarditis	Yes	4	4	4.11
	No	68	16	
Recurrence of pericarditis	Yes	0	1	3.64*
	No	72	19	

*Note: * – at v=1, α=5 %*

The use of pericardioscopy significantly increases the informativeness of less invasive interventions by 14.44 % (χ^2=4.11, with v=1, α=5 %) due to the reduction of the number of idiopathic pericarditis from 20.0 % to 5.56 %, that is, more than 3 times. The difference in the number of relapses in the two groups is not statistically significant (χ^2=3.64, with v=1, α=5 %, so, p<0.05). There were no complications associated with the use of pericardioscopy among patients. There were no fatalities in both groups for the entire period of the study.

5. Discussion

The use of mini-invasive interventions in combination with pericardioscopy is becoming increasingly popular due to the greater specificity and sensitivity of other interventions [5, 12]. In this case, a large amount of intervention with minimal access with less effect on hemodynamics and general condition of the patient. With the development of technical equipment, virology and molecular biology, the diagnostic value of the epicardium and pericardium is gradually increasing [16, 17]. Sight biopsy of the altered sections of the pericardium is justifiable in cases of tuberculosis, purulent, neoplasm pericarditis and pericarditis, which are not subject to standard treatment methods [18, 19].

Despite the great popularity of mini-invasive interventions and pericardioscopy among researchers, there are currently no large randomized trials and clear, proven recommendations for their use [17, 20].

Our studies have shown that mini-invasive interventions, especially non-pleural subxiphoid pericardiotomy, using pericardioscopy are more effective and informative, but in our opinion, the study needs further development involving more patients and expanding the criteria for evaluating the efficacy of pericardioscopy and comparing it with other interventions.

6. Conclusions

1. Pericardioscopy allows to perform sanitation, revision, biopsy and drainage of the pericardial cavity under visual control, which significantly expands the volume of surgery while maintaining the minimally invasive access.

2. Use of pericardioscopy during mini-invasive interventions is safe and reliably increases their informativeness by 14.44 % (χ^2=4.11, with ν=1, α=5 %).

3. The most safe and informative interference with exudative pericarditis, especially purulent, is subxiphoid non-pleural pericardiotomy with pericardioscopy.

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INDICATORS OF RESPIRATORY SYSTEM IN CONDITIONS OF CHRONIC ACTION OF HARMFUL ENVIRONMENTAL FACTORS WITH TYPE OF BODY CONSTITUTION

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Abstract

The article presents the results of the study of the peculiarities of the respiratory system functioning in unfavorable environmental conditions in workers involved in industrial production and agrarian sector, taking into account the type of constitution of their bodies. Investigation of the influence of the complex of anthropogenic factors associated with production on the parameters of the respiratory system revealed a significant level of interconnection of the investigated parameters with anthropometric indicators.

During the experiment, a significant decrease in the functional lung capacity in the studied subjects involved in industrial production was shown, compared with the control group and workers of argo-industrial production. Such a trend may be evidence of functional violations of tracheobronchial conduction, which is indirectly confirmed by the values of the Tifno index, which is the main method of an objective assessment of respiratory tract imperfections, and which is characterized by significantly lower values in the group of workers involved in industrial production compared with residents relative to environmentally friendly areas.

The analysis of the pneumatachographic survey performed on the basis of the Pignier index revealed some differences in the functional parameters of the respiratory system in the groups of hyposthenics (capacity of the lungs) and hypersthenics (maximum volume velocity of 75 %). In the group of normosthenics, intergroup differences were found for the values of functional lung capacity in comparison with all groups, and for the Tifno index, the reliable difference between the indicators was noted only between the group of industrial workers and the control group.

Keywords: pneumotachography, production conditions, industrial production, agro-industrial production, respiratory system.

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1. Introduction

The study of adaptive-compensatory landslides in the organism, caused by the influence of environmental factors, acquires a qualitatively new scale and transforms into one of the fundamental medical-biological problems. Over the past ten years there has been a steady increase in the frequency and severity of respiratory diseases [1, 2]. According to many scientists, the assessment of the impact of adverse factors on the human body associated with environmental pollution, is the most important task of biological science at the present stage [3].

At the present stage, the influence of environmental factors on the development of respiratory diseases in the population of urbanized areas is generally recognized, while factors of the production environment and their effects on the organism are rarely analyzed taking into account the peculiarities of the body structure of workers. The main manufacturing factors affecting the airways: agricultural and industrial dust with particle sizes from 0.25 nm to 30 nm, steam and heavy metals, adverse weather conditions (excessive dryness or humidity, sharp temperature fluctuations, drafts, etc.). Harmful effects on the body carry out general toxic, sensitizing, carcinogenic, mutagenic effects, and the increase in the effect of the influence, scientists associated with the common complex impact of allergens and chemical pollutants of the environment. It is proved that the intensive environmental load negatively affects the metabolic resistance of the organism, suppresses the system of local protection [4, 5], especially with prolonged action [6]. These changes lead a certain part of the population to stable respiratory hyperresponsiveness, obstruction of small bronchi, morphological rearrangement of the mucous membrane of the airways and, in the future, the formation of acute and chronic inflammation [4, 7], as well as the development of a number of nonspecific pathological processes among which the leading place oxidative stress [10]. In addition, the analysis of modern literature suggests that industrial toxic substances affect not only people engaged in production [11, 12], but also on the population of so-called rural areas by pollution of the environment [13].

2. Aim of research

Determination of the peculiarities of physiological changes in the respiratory system of the workers of the agrarian sector and industrial production, depending on the type of their body structure.

3. Methods of research

Investigation of the indicants of external respiration was carried out on the basis of the Laboratory of environmental physiology at the East European National University named after Lesya

Ukrainka in the 90-hour period of 21–35 years (average age 26.40±3.66) during the spring-autumn 2016–2017 years. The study of complex spectrum was included in our research and included measurements of anthropometric indices, on the basis of which the Piene index is calculated and definition of the state of indicators of external respiration. Registration of indicators of the respiratory system was carried out with the help of pneumotachography technique on the complex of hardware and prognostic methods of inspection «Askold» (Kyiv, 1997). Referred to the purpose of the study all of the investigated patients were divided into 3 groups:

1) the control group (30 people) – inhabitants that resides in a relatively «pure» ecological zone (the population of the Kivertsi district);

2) agrarian sector (30 people) – inhabitants of agrarian districts, who work in the agricultural sector and consistently in contact with fertilizers and chemical products (the settlements who live in Ivanichivsky and Lokachinsky district);

3) industry (30 people) – inhabitants who work at the industrial enterprises of the chemical industry at least 10 years in the Lutsk.

Based on the results of measurements of height, body weight and chest circumference, physical indices were calculated [14].

The Pignet index (PI) characterizes the proportionality of the development and composition of the body structure. Applicable only to those who do not have signs of obesity. Formula for calculating the Pignet index (PI): PI=L–(M+O), where L – height in centimeters, M – mass in kilograms, O – chest girth in centimeters.

In our researches for the establishment of the type of constitution, the subjects examined the classification by V. M. Chernorutsky (1927): hyposthenic (asthenic type of body structure, the value of the Pignet index >30 c. u.), normosthenic (athletic type of body structure, the value of the Pignet index from 10 to 30 c. u.), hypersthenic (picnic type of the body structure, the value of the Pignet index <10 c. u.). [15].

Pneumotachography was used to record the rapid movement of the light during the periodic breathing and the removal of certain respiratory maneuvers. The method is oriented on the diagnostics of the type and degree of ventilation of the lungs at the base of the analysis of quantitative and qualitative changes of pneumotachographic pathways [16]. The study took place in the first half of the day, irrespective of meal.

The obtained data was processed by the method of variation statistics with the use of parametric and nonparametric criteria for the comparison of averages. To compare the studied groups, depending on the type of distribution of the values, the criterion of reliability of the Student (t) was used for the comparison of the mean values and the Mann-Whitney (W) with the median and the degree of validity (p). The difference was reliable at $W>2.1$; $t>2.1$; $p<0.05$. Correlation analysis of data was carried out using the Pearson correlation coefficient (r). Under the statistic analysis of the obtained results, the standart software packages and Statistica 6.0 were used.

4. Results of research

The analysis of the obtained data showed that the indicators of life capacity of the lungs of people working in agricultural production are significantly higher (5.24±1.53 liters) for those in the group involved in industry (4.58±1.24 liters) and inhabitants relatively environmentally friendly regions (4,37±1,43 l), but do not show statistically significant differences in values. However, all values are within the age range.

The value of the indicator of functional lung capacity, which is used to diagnose tracheobronchial conduction disorders, unlike the previous one, is characterized by statistically significantly lower values in the group of people involved in the industrial sector than in the other two groups (**Fig. 1**).

The Tifno index, which is the main method for an objective assessment of airway patency violations, is characterized by a statistically significant decrease in the values of persons involved in industrial production compared with the control group (**Fig. 2**). Such a decrease in the index from industrial production may indicate the initial obstructive changes in the bronchial tree, while the indicators of the workers of the agro-industrial complex and the control group are within the age limit.

It is worth noting that the Tifno index in the control group of the subjects showed a high correlation with the growth indices (r=–0.46), chest circumference (r=–0.30), age (r=–0.43), and the nature of interdependence is inversely proportional.

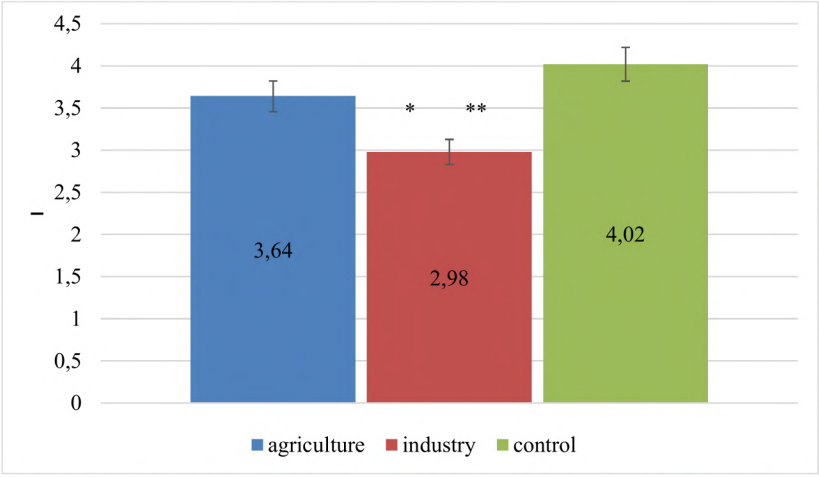

Fig. 1. Indicators of functional life capacity of lungs in the subjects undergoing chronic effects of various environmental factors: * – statistically significant difference of the indicators compared with the control group; ** – statistically significant difference between the indicators among groups of people engaged in agricultural production and industry

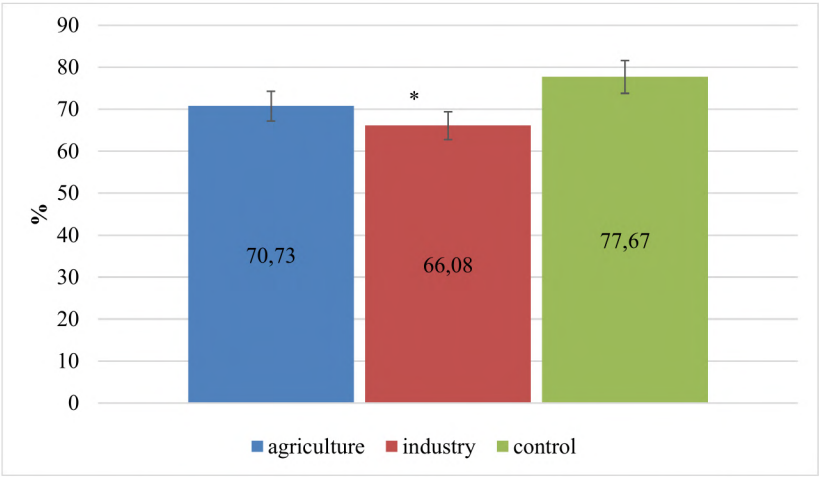

Fig. 2. Indicators of the Tifno index in the subjects undergoing chronic effects of various environmental factors: * – statistically significant difference of the indicators compared with the control group

Indicators of maximum volumetric rate of 25 %, 50 % and 75 % of forced exhalation, which indicate, respectively, the patency of large and small bronchuses in all subjects did not reveal significant intergroup differences, except for the indicator MOS 50, which was significantly higher in the group of persons involved in the agricultural industry, in comparison with the control group (**Fig. 3**).

Correlation analysis of functional parameters of the respiratory system of the subjects showed a high level of dependence between the anthropometric data and the indicators MOS25 and MOS50. So the relationship between the MOS25 score and the height (r=0.48), weight (r=0.49), chest circumference (r=0.33), age (r=0.42) is directly proportional, whereas in the subjects undergoing chronic negative the influence of the factors of the production environment, this dependence is practically absent. Thus, the group of workers in the agro-industrial complex maintains a mod-

erate correlation between the indicator MOS25 and growth (r=0.33), and in the group of industrial production, it completely disappears. This tendency can be evidence of the effect of more intense environmental influences on the respiratory system than the genetically determined dependence.

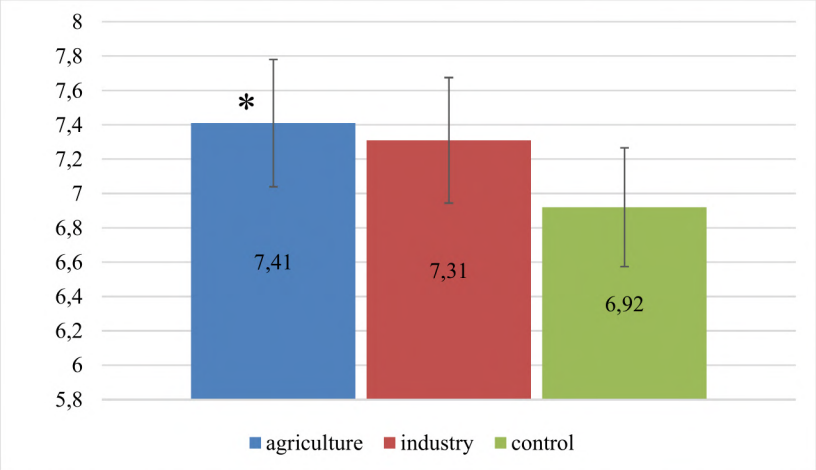

Fig. 3. The indicators of maximum volume velocity at the level of 50 % of forced volume vital capacity in the subjects undergoing chronic effects of various environmental factors:
* – statistically significant difference of the indicators compared with the control group

At the next stage of the study, we analyzed the parameters of the respiratory system in workers of various industries, exposed to long-term influence of negative factors depending on the characteristics of physical development of man. The distribution of the studied subjects according to the values of the Pignet index in the study groups, selected according to the ratio of harmful environmental factors of the production environment, showed that all surveyed predominates the normosthenic type of body structure: in the group of workers in agriculture – 71 %, in industrial production – 48 %, and in the control group residents of environmentally friendly areas – 50 %.

It is interesting to note that individuals involved in agro-industrial enterprises do not have a hypersthenical type of body structure, whereas in the industrial workers and in the control group their percentage is 26 % and 30 %, respectively.

The significance of forced volume vital capacity in a group of persons with a hyposthenic type of body constitution does not reveal a significant difference between the investigated people who work in industry or agriculture and residents of relatively clean areas (**Fig. 4**).

In the subjects with normosthenic type of constitution the presence of reliable ($p<0.05$) differences of the forced vital capacity as between the comparison groups, distinguished by the peculiarities of harmful factors of the environment (workers of the agricultural and industrial complex) and their comparison with the control group of the subjects (rice 4). At the same time, residents of relatively environmentally friendly areas are characterized by higher values of the indicator.

In the group of hypersthenics, the absolute values of the indicator show a decrease in the industry, but the difference does not reach the level of statistically significant (**Fig. 4**).

Taking into account the previous indicator and previously described features, it is interesting to note the characteristics of the indicator of the volume vital capacity, taking into account the index of physical development. Thus, in the group of hyposthenic body building, statistically significant ($p<0.05$) is higher than the value of the indicator in the groups of agricultural workers, compared to the control group (4.72±0.81 l against 3.85±0.62 liters).

In the subjects with normal and hypersthenic type of constitution, there were no significant differences in the values of volume vital capacity.

The Tifno index in the subjects undergoing chronic effects of harmful ecological factors in the production is characterized by lower rates in all groups, compared to the control group (**Fig. 5**). The level of reliably reaching differences in the hyposthenic group between the workers

of the agroindustrial complex and control, among normosthenics – between persons involved in industrial production and control, as well as subjects with a hypersthenic type body constitution.

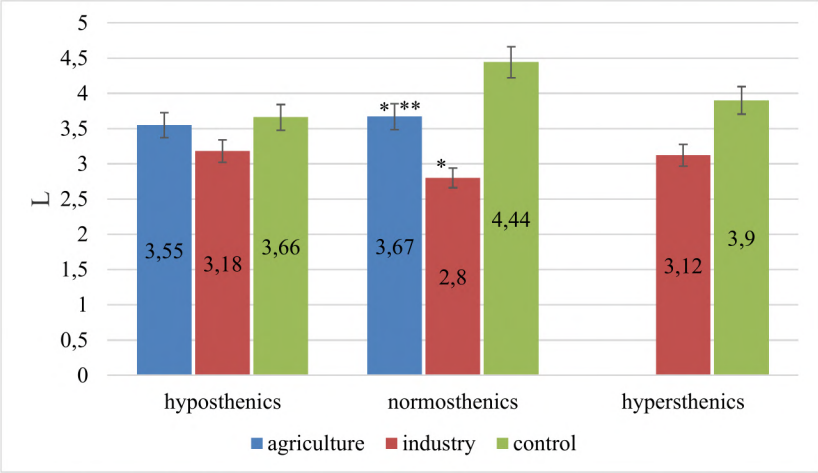

Fig. 4. Indicators of forced vital capacity of the lungs in the subjects undergoing chronic effects of various environmental factors depending on the type of constitution: * – statistically significant difference of the indicators compared with the control group; ** – statistically significant difference between the indicators among groups of people engaged in agricultural production and industry

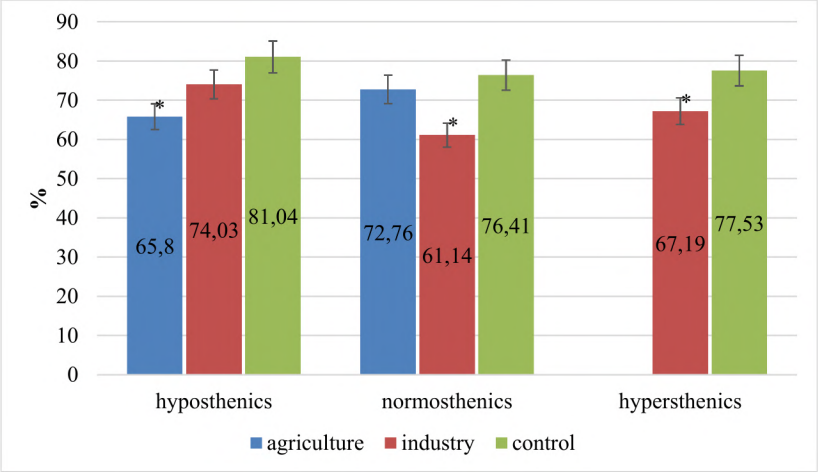

Fig. 5. Indicators of the Tifno index in the subjects undergoing chronic effects of various environmental factors depending on the type of constitution: * – statistically significant difference of the indicators compared with the control group

Indicators of maximum volumetric rate of 25 %, 50 % and 75 % of volume vital capacity in subjects who were exposed to harmful production factors, do not statistically significantly differ between comparison groups, except for subjects with hypersthenic type body constitution. They showed statistically significant ($p < 0.05$) higher values of MOSH75 in the subjects involved in the industry (6.05±0.86), compared with the control group (3.59±1.07).

6. Discussion

Investigation of the influence of the complex of anthropogenic factors associated with production on the parameters of the respiratory system revealed a significant level of interconnection of the investigated parameters with anthropometric indicators. At the same time, as already indicated above, the closest relationship between these indicators is noted in the group of persons

living in a relatively environmentally clean area [17, 18]. The lowest level of statistically significant correlations was found in the group of workers in the agro-industrial complex.

Concerning the intergroup features of the respiratory system, here the attention is paid to the significant decline in the indicators of functional lung capacity in the subjects involved in industrial production, compared with the other two groups of comparison [18, 19]. Such a trend may be evidence of functional violations of tracheobronchial conduction, which is indirectly confirmed by the values of the Tifno index, which is the main method of an objective assessment of respiratory tract imperfections, and which is characterized by significantly lower values in the group of workers involved in industrial production compared with residents relative to ecologically clean areas [20].

The validity of the division of the subjects studied into groups, taking into account the index of their constitution (Pignet index), was manifested in the fact that most of the studied parameters were characterized by a significant number of statistically significant correlation relations with this indicator. Such a feature of the obtained results made it possible to analyze the parameters of the respiratory system of persons who have been exposed to harmful factors in production for a long time, taking into account the groups allocated on graduations, which are based on the value of the Pignet index.

The analysis of the pneumotachographic survey performed on the basis of the Pignet index revealed some differences in the functional parameters of the respiratory system in the groups of hyposthenics (capacity of the lungs) and hypersthenics (maximum volume velocity of 75 %). In the group of normosthenics, intergroup differences are detected for the values of functional lung capacity when comparing all groups and the Tifno index when comparing workers of industrial enterprises and control groups.

7. Conclusions

1. The Pignet index made it possible to identify the predominance of normosthenic body type in all subjects (values ranged from 48 % in the group of people involved in industrial production, up to 71 % - in agricultural enterprises).

2. The value of functional lung capacity in the study subjects involved in industrial production is reduced in comparison with the workers of agricultural enterprises and with the control group, which may be evidence of functional disorders of tracheobronchial conduction, which is indirectly confirmed by the values of the Tifno index.

3. Analysis of the data of the pneumotachographic survey, based on the Pignet index, revealed some differences in the functional parameters of the respiratory system in the groups of hyposthenics (life capacity of the lungs) and hypersthenics (maximum volume velocity of 75 %). In the group of normosthenics, intergroup differences are detected for the values of functional lung capacity when comparing all groups and the Tifno index when comparing workers of industrial enterprises and control groups.

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THE ROLE OF GROUP EDUCATIONAL PROGRAMS IN MODIFICATION OF THE CARDIOVASCULAR RISK MAIN FACTORS

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Abstract

Aim – to study the influence of Healthy Schools "Healthy Lifestyle Basis" education on modifying of cardiovascular risk main factors.

Materials and methods. 57 patients with cardiovascular diseases were examined. General clinical examination, anthropometric examinations (body weight, height, body mass index, and body composition), blood pressure measurement, and cholesterol determination, as well as its fractions in blood, were carried out before and after training course. The educational cycle included 9 lessons.

Results. It was found that Healthy Schools education contributes to better both systolic and diastolic blood pressure monitoring. Thus, initially target blood pressure levels (<140/90 mmHg for patients without diabetes mellitus and <140/85 mmHg in case of diabetes) were observed in 49 % of patients, at the end of the training cycle – in 67 %. At the same time, the patients' anthropometric parameters (BMI, fat and muscle tissue content, visceral fat) as well as cholesterol and its atherogenic serum fractions, did not change significantly. The patients' education did not affect motivation level for their lifestyle improvement. So the number of patients consuming less than 5 grams of table salt per day and over 400 grams of vegetables and fruit did not change significantly. The level of physical activity between the examined patients did not change.

Conclusion. The training course "Healthy Schools: Healthy Lifestyle Basis" contributes to improvement of blood pressure level monitoring, but does not significantly affect behavioral risk factors and does not lead to improvement of lipid metabolism monitoring in patients with cardiovascular disease. It is necessary to search for new more effective preventive care models for patients with high cardiovascular risk.

Keywords: cardiovascular prophylaxis, group educational programs, group preventive counseling.

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1. Introduction

Measures for active cardiovascular prevention are the most important condition for morbidity and mortality reducing [1]. In most developed countries, specialized prevention programs for people with high cardiovascular risk and patients with cardiovascular diseases, based on learning of medical knowledge basics, practical development of measuring blood pressure techniques, development of individual diet plan, increase physical activity, etc. , have been introduced into public health practice [2]. At the same time it was determined that the patients education aimed at explaining the role of a particular risk factor in cardiovascular diseases development or their complications improves the patients adherence to healthy lifestyles principles [3, 4]. The efficiency and economic feasibility of educational programs are confirmed by numerous studies [5, 6]. In 2016, a program of cardio rehabilitation for countries with low socioeconomic level, including Ukraine, was proposed [7].

In the context of limited resources, efficiency evaluation of the presented preventive care model, such as group educational cycles – Schools of Patients – is of a particular interest [8]. It is shown that education in the Schools helps to effectively correct the main behavioral risk factors, improves emotional state and quality of life of patients, and increases their adherence to long-term drug therapy. The development of an effective training program for patients aimed at monitoring of cardiovascular risk main factors would reduce the financial burden on the existing health care system.

2. Aim of research

To estimate the influence of Healthy Schools "Healthy Lifestyle Basis" education on modifying of cardiovascular risk main factors in patients with high and very high cardiovascular risk.

3. Materials and methods

The study was carried out on the basis of Department of chronic non-infectious diseases comprehensive risk reduction of the State Institution "National Institute of Therapy named after L. T. Malaya of NAMS of Ukraine", Kharkiv, during 2016–2018.

Study Limit:

57 patients with cardiovascular diseases were examined. The mean age of the patients was (63.3±2.2) years. The patients' descriptions, depending on the nosological forms are presented in **Table 1.**

Table 1

The patients' descriptions, depending on the nosological forms

Nosological forms			Number of patients (n (%))
CHD	Hypertensive heart disease	Stage II	32 (56 %)
		Stage III	25 (44 %)
	Stable exertional angina	II function. cl.	40 (70 %)
		III function. cl.	7 (12 %)
	Myocardial infarction in anamnesis		21 (37 %)
	Revascularization (PCI)		8 (14 %)
	Heart failure II, III function. cl. (NYHA)		50 (88 %)
	Diabetes mellitus type 2		13 (23 %)

The lectures cycle was developed for patients with high and very high cardiovascular risk; it includes 9 lessons, each lesson included the lecture material, as well as practical work with the patient, dietician and exercise therapist. The practical part included detailed analysis of the individual nutrition features and the necessary physical exercises, the individual patient's diary data

were estimated, and a practical task for the next month was given. The patients were trained to calculate their individual caloric needs, and to estimate food products composition. As a part of these lessons, information concerning the most common chronic non-infectious diseases: coronary heart disease, hypertensive heart disease, diabetes mellitus, musculoskeletal disorders, thyroid gland disorders, and the central nervous system age-associated lesions was given to the patients. A particular attention was paid to highlight of the role of known risk factors in the development and progression of the mentioned diseases, the importance of these risk factors modification, as well as the most effective methods for their correction. Also dietary recommendations and instructions for physical activity were analyzed in detail. At the beginning of the cycle, the patient receives methodical materials, and individual diary. The use of the diary allows the patient to estimate individual risk factors (body mass index, fat and muscle tissues content, visceral fat, blood glucose and lipid levels) with a doctor.

All patients were examined before and after the the educational program cycle. The questionnaire assessed behavioral risk factors: the amount of table salt per day (less or more than 5 grams per day), fruit and vegetables (less or more than 400 grams), smoking (in the past and now), and alcohol consumption. Physical activity of the patients was calculated by the number of steps within 24 hours. General clinical examination, blood pressure measurement (BP), anthropometric examinations (body weight, height, body mass index, fat and muscle tissue, and visceral fat), determination of cholesterol and its fractions was carried out. The amount of fat and muscle tissue, and visceral fat was determined by bioelectrical impedance method using Omron Body Composition Monitor BF511. Muscle strength was determined using electronic car dynamometer Camry EH 101.

The achievement of target blood pressure levels (BP) was assessed in accordance with the European Society of Cardiology (2013) recommendations [9]. The target office blood pressure level was <140/90 mmHg and 140/85 mmHg in case of diabetes. It was considered that the patient achieves the target blood pressure level, if in case of a double measurement with an interval of 1 month the office BP did not exceed the above levels.

Achievement of lipid metabolism target levels was assessed in accordance with the European Society of Cardiology recommendations (2016). Target level of low-density lipoprotein cholesterol (LDL-C) was <2.6 mmol/l or its decrease at least for 50 %, if the initial level was 2.6–5.1 mmol/l, for patients with high cardiovascular risk; and <1.8 mmol/l or at least 50 % decrease if the initial level was 2.6–5.1 mmol/L, for patients with very high cardiovascular risk [10].

The lipid blood spectrum was determined by the enzymatic method using "Humalyzer 2000" biochemical analyzer, №18300-5397.

The study protocol was approved by the local ethical commission of the State Institution "National Institute of Therapy named after L. T. Malaya of NAMS of Ukraine". The study was carried out in accordance with the principles of the Helsinki Declaration. All patients signed an agreement to participate in the study.

The statistical data processing was carried out using the statistical software package "SPSS 21" (IBM), Microsoft Office Excel-2003.

4. Results

The survey results analysis shows that the majority of patients – 51 (89.5 %) – did not smoke in the past and do not smoke now; 4 smoked in the past, and 2 still smoke at the moment of the study. The questionnaire data show that 2 patients (3.5 %) used alcohol in moderate amounts (1–2 servings per day) in the past, the other – very rarely or in such small amounts that it can be neglected. Despite Health Schools training, 1 person continues smoking.

There were no significant changes in other behavioral risk factors. For example, 13 (22.8 %) patients actively ate vegetables and fruit before the beginning of education, and 14 of them (24.5 %, $p > 0.05$) after the training finishing, as well as the number of patients consuming less than 5 g of table salt per day – (28.1 % before and 22.8 % after, $p>0.05$). Also, the patients' physical activity was not significantly increased, as it was determined by the number of steps during the day – 2108 [524÷5099] steps initially and 1988 [440÷41289] steps after the education, $p>0.05$.

After the educational programs, the main anthropometric features of the patients, as well as the indexes characterizing body composition, did not change significantly (**Table 2**).

Table 2
The patients' anthropometric features before and after training in Healthy Schools

Index	Before training (n=57) Me [25÷75 %]	After training (n=57) Me [25÷75 %]	P
Body weight, kg	86.1 [75.6÷100.7]	87.9 [76.6÷97.7]	0.7987
Body mass index, kg/m^2	31.6 [27.6÷38.2]	34.4 [28.9÷37.6]	0.4322
Fat tissue, %	42.0 [341÷50.0]	43.9 [35.3÷49.1]	0.6953
Visceral fat, %	12.0 [10.0÷14.0]	12.0 [10.0÷15.0]	0.6223
Muscle tissue, %	25.5 [22.3÷28.8]	24.6 [22.5÷28.4]	0.7332

Muscle contraction strength also did not change significantly – 27.9 [23.2÷40.2] kg before the beginning and 27.4 [21.9÷32.4] kg after the end of the educational cycle, p=0.0925.

Initially, target blood pressure levels were noted in 49 % of patients. Lessons in Health Schools contribute to the improvement of this indicator – by the end of the educational cycle, target BP levels were observed in 67 % of patients (**Table 3**).

Table 3
Blood pressure levels in the patients before and after Healthy Schools education

Index	Before training (n=57) M±m	After training (n=57) M±m	P
SBP, mmHg	141.8±16.2	123.4±9.3	p=0.001
DBP, mmHg	88.1±9.8	76.0±8.8	p=0.001

Before the training start, the total cholesterol target levels (TC) and low-density lipoprotein cholesterol (LDL cholesterol) were observed in 49 % of patients, in 9 months of training – in 35 % of patients (**Table 4**).

Table 4
Lipid metabolism indexes before and after Healthy Schools education

Index	Before training (n=57) Me [25÷75 %]	After training (n=57) Me [25÷75 %]	P
Total cholesterol, mmol/l	5.17 [4.25÷6.18]	5.82 [4.59÷6.42]	p=0.1505
Cholesterol HDL, mmol/l	1.40 [1.16÷1.63]	1.34 [1.07÷1.64]	p=0.0769
Triglycerides, mmol/l	1.34 [1.14÷1.92]	1.52 [1.22÷2.44]	p=0.4050
Cholesterol LDL, mmol/l	2.69 [1.95÷3.89]	2.78 [2.38÷3.56]	p=0.594

5. Discussion

A number of different studies point to the efficiency of group training programs devoted to improvement of blood pressure monitoring. Thus, it was shown that the number of patients with improved target blood pressure levels (for 14.3 %) among the ones attending Healthy Schools has increased. According to Shemetova G.N. et al. data, Healthy Schools education allowed to increase the proportion of patients with a target blood pressure level from 32 % to 42 % [12]. Results of the

study with 239 patients having hypertensive heart disease, indicate that education at the Healthy Schools improves blood pressure monitoring (initially the number of people with a target blood pressure level was 12.6 %, after the end of the training cycle – 50.6 %, $p < 0.05$). Thus, the number of smokers decreased from (52.9±3.2) % to (37.0±3.1) % ($p < 0.05$), the number of obese patients – from (38.2±3.2) % to (22.7±2.7) % ($p < 0.05$), patients with hypercholesterolemia – from (58.4±3.2) % to (41,2±3.2) % ($p < 0.05$), patients with hypodynamia – from (71.4±2.9) % to (42.4±3.2) % ($p < 0.05$) [13].

According to Kontsevaya, A.V. and co-authors (2011) data, among the CHD patients, who attended Healthy School in addition to their standard therapy, the total cholesterol level decreased by 23.9 %; and in the group of patients who had only standard therapy – by 14.3 %. Also among the patients educated in Healthy School, target BP levels were 42.5 %, and in the standard therapy group – 6.7 %.

In the European Recommendations concerning cardiovascular diseases prevention (2016), advantages of individual forms of patient education have shown. In this case, a key role in preventive counselling is assigned to general practitioners. There is a data showing that both nurses and general practitioners can be equally effective in providing individual counselling to correct major cardiovascular risk factors [15, 16].

Recently, there is no developed optimal model of preventative care [17]. Its structure, type and duration should be adapted to individual countries, regarding their national standards, legislation, economic opportunities and cultural features. The most efficiency was shown by comprehensive programs, which include such mandatory components like dosed physical activity, risk factors correction, education and psychological support [18, 19]. Also, predictive factor is the intervention duration. Thus, the GOSPEL study results (3.441 participants with recent myocardial infarction) indicate that long (up to 3 years) training programs contribute to improving control of behavioural risk factors (physical activity, diet, body weight control, stress level), and also contribute to drug therapy adherence increase [20].

Development and widespread implementation of specialized prevention programs should be health care priority in countries with a high risk of cardiovascular mortality, including Ukraine. However, the data concerning description of such programs have not been found in the available national literature.

6. Conclusion

1. Educational cycle “Healthy Schools: Healthy Lifestyle Basis contributes to BP monitoring improvement.

2. Training in the Healthy Schools does not lead to behavioral risk factors modification.

3. Patients who graduated from the Healthy Schools training did not show lipid metabolism indexes improvement.

4. It is necessary to search for new more effective preventive care models for patients with high cardiovascular risk.

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«NovuMedical» DEVICES ARE THE VECTOR OF REALIZATION OF P4 MEDICINE COURSE

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Abstract

The issues of modern personified preventive medicine, the development of modern methods, courses, technologies of healthy active longevity are in the focus of attention and these issues are relevant. The purpose of the article is to study the influence on prevention of diseases, improving the quality of life by massage and thermal device «NovuMedical» intended for home use.

In the research the analysis of results of the equipment use in 140 patients aged from 61 to 78 years is conducted by the method of comparison and grouping. A significant improvement in the quality of life, stabilization of the psycho-emotional state and blood pressure is noted among 93.5 % of patients. Reduction of pain syndrome is noted among 85 % of patients, reduction in serum cholesterol is noted among 30 %, glucose normalization is noted among 25 % of patients, and 46 % has a tendency to reduce it. A tendency to normalize blood coagulation function is noted among 40 % of patients, that makes prevention and correction of diseases legitimate and necessary, timely with the help of «NovuMedical» devices at home. «NovuMedical» devices allows both to improve well-being, normalize homeostasis, and to form in patients a system of knowledge and skills to improve the quality of life, and include them in active actions for health self-improvement, mental and physical self-improvement. This participatory approach leads to a fundamentally new paradigm of caring and managing health, when not only the social institutions of the state, but also patients themselves are direct and active participants in the process of preserving and strengthening their own health.

Keywords: device for home use, quality of life, preventive medicine, health promotion, participatory medicine.

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1. Introduction

It is well-known that it is easier to prevent any disease than to heal it. The prophylaxis of diseases, age pathology, increase of the active longevity and life quality of humans are ones of most important problems of health protection and is especially urgent in the context of the coming pension reform [1, 2]. Preventive medicine plays a leading role in saving health of a modern human, just that is why the great attention is paid to it, innovation technologies are improved and developed [3, 4], and also molecular physiological processes of ageing are studied for correcting them that inevitably results in diseases prophylaxis and ageing speed decrease [5]. A risk of any pathology is conditioned by not only genetic but also epigenetic factors. Main epigenetic factors include – the food quality, life style, ecological environment [6, 7]. All these factors influence appearance and progress of many acquired diseases, which genetic predisposition is inherent to each human. Modern preventive medicine proposes a complex of arrangements, oriented on decreasing a risk of appearance and development of acquired diseases and their consequences. It is in first turn, an individual or personalized approach that distinguishes preventive medicine from other ones [8, 9]. It is well-known that a sustainable remission is possible only at understanding of the importance of healthy life style and personal responsibility for own health by each human.

The most famous American inventor of XX century Tomas Alva Edison, who registered 1093 patents in the USA and 3000 ones in other world countries, said words which meaning is undoubted for all medical scientists even now, after a century: A future doctor will not give drugs to a patient, he/she will try to interest a patient in observing own organism condition, diet, and prevention of diseases".

Main strategic directions of developing the system of health protection in the RF for the period till 2035, included in roadmap are: "Health and longevity", "Preventive medicine", "Biomedicine" and other [10]. And this is just not occasionally. According to most Russian and foreign experts, main trends of developing national strategies of health protection for the nearest 20 years will be: personalization of medicine, mass approach to preventive medicine, mass transfer to it,

course for active longevity, stable growth of popularity of naturopathic and preventive methods of prophylaxis and healing of diseases [11, 12].

In 2002 in Paris there was created the European association of anti-age medicine (ESAAM), named today the "European association of preventive, regenerating and anti-age medicine". It created a new interdisciplinary direction in medical science and practice – Medicine - "4P"; predictive, preventive and personalized, participative – partner with patients that, from our point of view, may be a base for the future development of prophylactic medicine.

The decrease of the level of morbidity, tenderness, invalidism and also saving, strengthening and restoration of health, increase of life duration can be attained only using innovative preventive methods of diagnostics, healing and prophylaxis. The early diagnostics of diseases is extremely important, but without means influencing correction of found pathological disorders it is incorrect to say about predictive medicine [13, 14]. The use of preformed physical factors for correcting pathological disorders in prophylactic and restorative healing usually stimulates sanogenetic mechanisms of the organism and organ level, improving the tissue and cellular methods that inevitably results in the reverse development of a pathological process and its stabilization [15].

Direction of healing in home conditions, which bright representative is a company «NovuMedical», results in a principally new paradigm of caring about health, when not only all social institutes of a state, but country dwellers themselves, first of all the most conscious and educated part of the population, become direct active participants of the process of saving health.

2. Aim of the article

To study the influence of «NovuMedical» equipment on the prophylaxis of diseases, patients' life quality increase.

3. Research materials and methods

The research included studying patients' healing processes in 50 free demonstration centers (FDC) «NovuMedical» of Russia, Ukraine, Kazakhstan. FDC «NovuMedical» provides studying and demonstration of possibilities of the massage-thermal equipment for removing fatigue and stress, full-value rest, improving mood and state of health, everyday care for health of eyes, legs and spine, primary and secondary prophylaxis of diseases. Having convinced him/herself in the personal efficiency of the equipment, a patient buys a device for further using it in home conditions. FDC specialists realize the dynamic observation over patients in the healing process under home conditions. For the period of 2014–2017 142000 patients were treated in centers, more than 5000 patients a day visit centers, their average age is 65±3.6 years.

For correcting acquired diseases and their prophylaxis, there were used «TopRelax», «NovuHeat», «NovuEye» «BodyHealth» devices.

«TopRelax» (Corea) – it is a vibro-massage device that makes diverse rhythmic, vibration percussions with a possibility of including infrared heat to 770nm. Magnets, inserted in the device, create a constant magnetic field in the working process – 72 mT, and tourmalin inserts enrich impact zones by negative air ions – 1000 ions for cm^3±200. Obtained energy radiates heat, the local heating is realized. Infrared energy can penetrate tissues of the organism by waves, also heating them. At the expanse of vibratory massage there is realized the purposeful system of transmitting mechanical vibrations on the human body for affecting its different organs and systems at the expanse of irritating receptors of the skin, muscles and tendons surfaces. Such impacts result in creating electric moving systems, transformation of energy of acting factors in energy of cells of the organism, widening vessels and accelerating the movement of blood flows and other liquids inside the organism.

«NovuEye» (Corea) – a massage device for eyes, it realizes acupressure of points of eyes, vibratory massage, infrared heat to 770nm, constant magnetic field – 85 mT, ionization – 1000 ions for cm^3±200.

«NovuHeat» (Corea) - a thermal carpet, enriched with magnets and tourmaline, for heating the body to 70 degrees, impact by infrared heat to 770 nm, ionization of impact zones – 1000 ions for cm^3±200, constant magnetic field – 30 mT.

«BodyHealth» (Corea) – a miostumulator with a changing configuration of electric impulses, allowing to activate the blood circulation effectively, completely painlessly and safely. The impulse duration – 0.5–300 m/s. Impulse frequency – 10–150 Hz. Form of impulses – neuron-like. A device is designed for the restoring healing of vessels of low extremities, active factors are miostimulation, stimulation of reflectory points of feet and infrared heat.

Thus, active preformed physical factors, used in these devices, are: constant magnetic field, infrared heat, ionization, mineral therapy, miostimulation, apparatus massage techniques. They all are studied well, and their use for treating and preventing purposes is scientifically grounded [16, 17]. The function mechanism of physical factors is based on their energy transformation in one of biological processes, as a result therapeutic effects develop – anti-inflammatory, analgesic, tropic and so on [11, 18].

A series of works on studying «NovuMedical» equipment demonstrates that these devices are rather effective in primary and secondary prophylaxis of diseases of the vertebral-neurologic profile [19, 20], eyes, peripheral vessels of legs [21], normalize homeostasis, activate sanogenetic mechanisms of the organism, have immune-modeling, stress-limiting, geroprotective effects [22].

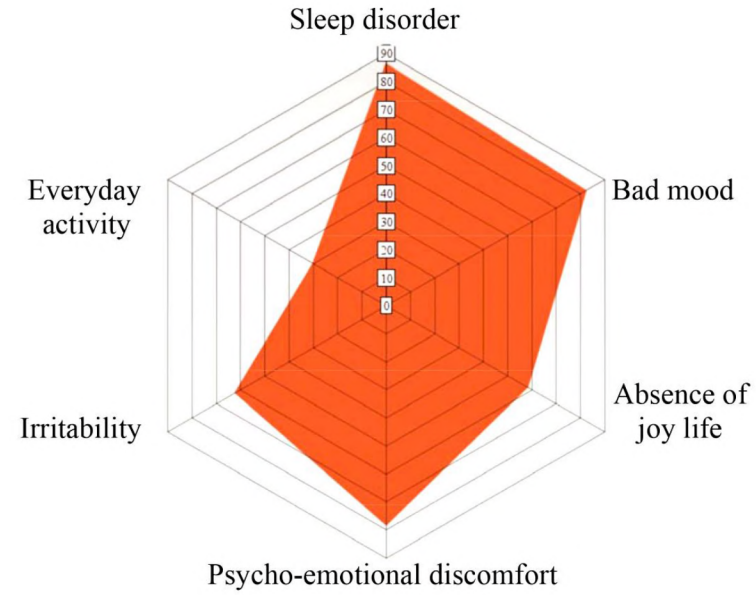
The study included 140 patients. The analysis of the effectiveness of using «NovuMedical» devices for for prophylactic of diseases and healing patients in home conditions was realized by the method of grouping and comparison. Examined persons were 99 women and 41 men, 61–78 years old. All them underwent out-patient and stationary examination and treatment and had a fixed disease. Among the examined patients, 100 % had a certain "bouquet" of so-called age diseases. Thus, 85 % had diseases of the cardio-vascular system, 70 % – diseases of the locomotor system, 50 % – diseases of peripheral vessels, 55 % – diseases of internal organs, 80 % – of eyes, 30 % – of respiratory organs. 89 % had lipid metabolism disorders, 56 % – carbohydrate metabolism, 72 % – disorders of the coagulating system. As far as patients had different combinations of diseases, each one had own "bouquet" of diseases, we separated them conventionally in groups, depending on the level of deviations of biochemical indices of blood from the norm. Thus, glucose level less 7 mmol/l was fixed in 20 persons, from 7 to 10 mmol/l – in 35 persons, more than 10 mmol/l – in 22 persons. Patients with lipid metabolism disorders were grouped analogously, because the cholesterol level in blood serum less7 mmol/l was revealed in 38 persons, higher 7 mmol/l – in 87 persons. The prothrombin index less than 100 % was revealed in 40 persons, more 100 % – in 61 persons.

Patients underwent the examination of biochemical blood parameters in 'Synevo" laboratory, certified by the international standard of managing a quality 9001:2000. The statistical processing of research results was made using STATISTICA v.6.0 professional course.

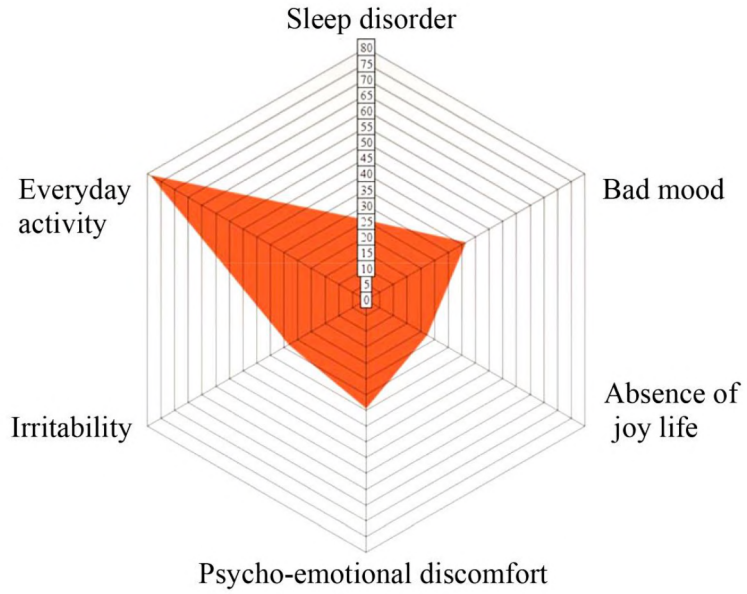
5. Research results

According to the data of the interrogation, questionnaire, interviewing, 93.5 % of patients noted the essential increase of the general health state, life quality improvement. Patients noted the sleep improvement (92 %), mood improvement (98 %), interest and pleasure of life (87 %), state of psycho-emotional comfort (96 %), stress-resistance increase (86 %), everyday activity (94 %) **Fig. 1**.

It was established, that the systematic use of the equipment results in 85 % of patients in decreasing the pain syndrome. According to Oswestry's pain scale, the index of pain expressiveness decreased from 4.3±1.25 before starting healing to 1.4±1.45 points ($p<0.05$). In 20 % there was observed the decrease of the arterial pressure to normal values, thus SAP decreased from 158.7±2.5 to 125±7.2 mmHg. ($p<0.05$). DAP from 97.3±3.2 to 85±0.5mmHg, respectively ($p<0.05$). 43 % of patients demonstrated the dynamics to the arterial normalization, thus at initial SAP 175.3±3.5, it decreased to 156.6±2.5 ($p<0.05$), and DAP from 109.8±3.2 to 96.2±0.5 mmHg, respectively ($p<0.05$), that resulted in correcting a dose of taken hypotensive preparations. The dynamics of biochemical parameters in blood of the examined patients in the healing process in home conditions using «NovuMedical» equipment is presented in **Table 1**.



a



b

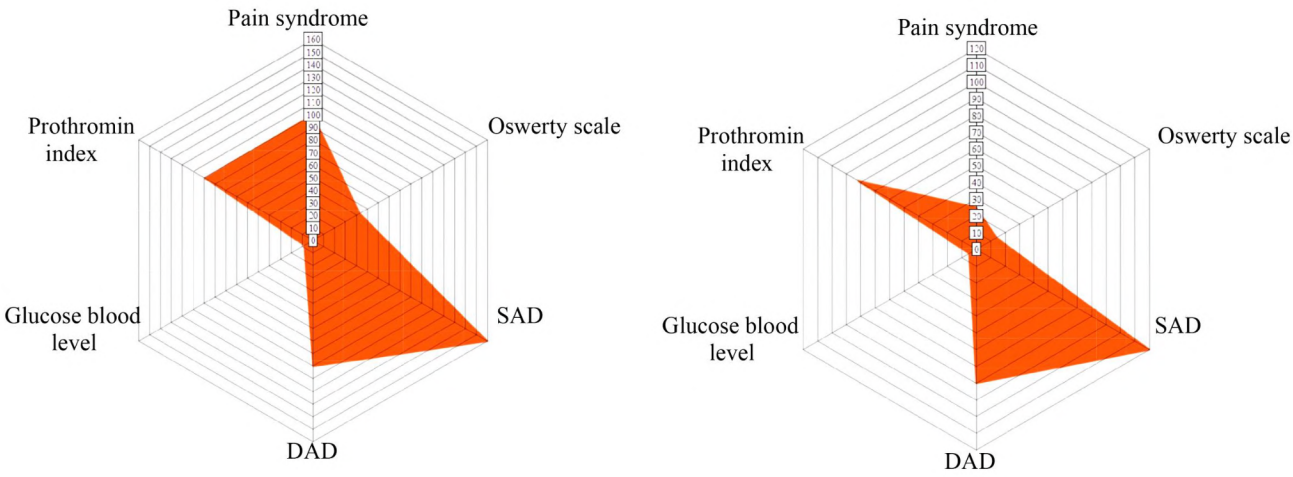
Fig. 1. Dynamics of subjective data: *a* – before treatment; *b* – after 3 months

In 30 % of patients there was revealed the decrease of cholesterol content in blood serum, thus it decreased from 6.6±0.2 to 5.8±0.1 mmol/l ($p<0.05$), and triglycerides of blood in these patients decreased from 1.750±0.072 to 1.556±0.069 mmol/l ($p<0.05$). In 25 % of patients there was observed normalization of the glucose level in blood from 6.3±0.4 mmol/l to 5.5±0.2 mmol/l ($p<0.05$), and in 46 % - there was fixed the positive dynamics to its decrease, thus at the initial glucose level in blood 9.4±0.2 mmol/l it decreased to 7.6±0.4 mmol/l ($p<0.05$). In 40 % of patients there was revealed the positive dynamics to normalizing the blood coagulating system, thus the prothrombin index (%) changed from 98.3±0.6 to 90.2±0.5 ($p<0.05$). The decrease of indices is not statistically reliable in patients with the high glucose blood level. Probably for reaching reliable results in this group of patients, the longer period of healing is needed (**Fig. 2**).

Table 1

The dynamics of biochemical parameters in blood of the examined patients in the healing process in home conditions using «NovuMedical» equipment n=140

No.	Parameters	Fixed pathology (persons)	Initial data	Data after three months of treatment	Reliability of results
1	Carbohydrate metabolism	78			
1.1	Glucose level in blood less 7 mmol/l	20	6.3±0.4 mmol/l	5.5±0.2 mmol/l	p<0.05
1.2	Glucose level in blood 7–10 mmol/l	35	9.4±0.2 mmol/l	7.6±0.4 mmol/l	p<0.05
1.3	Glucose level in blood more 10 mmol/l	23	10.3±0.2 mmol/l	9.8±0.2 mmol/l	Not reliable
2.	Lipid metabolism	125			
2.1	Cholesterol level in blood serum less 7 mmol/l	38	6.6±0.2 mmol/l	5.8±0.1 mmol/l	p<0.05
2.2	Cholesterol level in blood serum more 7 mmol/l	87	7.9±0.4 mmol/l	7.4±0.2 mmol/l	Not reliable
3.	Coagulating system of blood	101			
3.1	Prothrombin index less 100 (%)	40	98.3±0.6	90.2±0.5	p<0.05
3.2	Prothrombin index 100 (%)	61	107±0.5	103±0.4	Not reliable



a *b*

Fig. 2. Dynamics of objective data: *a* – before treatment; *b* – after 3 months

The use of «NovuMedical» equipment causes the general adaptive transformation of the organism, including a psychic status, thus the anxiety degree by Spielberger, high in all patients before healing, both reactive and personal had a tendency to decrease. After using the equipment, the mean degree of anxiety stayed in 18 % of patients, but indices were reliably lower than initial values (<0.05).

6. Discussion

Physiotherapeutic and preformed healing methods are widely used in the treatment, prophylaxis and rehabilitation of patients with different diseases of the cardio-vascular, lo-

comotor, nervous, respiratory and other systems, that is scientifically grounded [15, 17]. The studies demonstrate that physiotherapeutic methods are widely used at stationary and out-patient treatment stages. For preventing exacerbation of diseases, patients at remission may underwent the prophylactic treatment also in sanatoria institutions, where leading healing factors are climatic and physiotherapeutic ones that are very effective methods at preventing diseases [14, 18]. But they are available for patients only one, in the best case, two times a year, the rest of the time patients usually stay face to face with their disease. But it is necessary to make prophylaxis and restoration of injured organs continuously [6, 12]. Practical health protection cannot deal with these questions continuously because of a series of causes, and patient, having undergone a treatment in a hospital or finished a course one in a clinic, after eliminating acute manifestations of a disease and having returned home, needs continuation of healing for restoring disordered functions of the organism. In the study we demonstrated that at this contradiction, when a patient needs restorative treatment, but health protecting institutions are not able to deal with restoration of disordered functions of the organism at remission, the treatment in home conditions may be recommended by offering a patient to use individually chosen devices for home. Stable remission is possible only at understanding a necessity of healthy life style, personal responsibility for own health and everyday care for the organism, changed by a disease by each person.

The positive dynamics in the patients' state as a result of using a constant magnetic field, infrared heat, ionization, mineratotherapy, miostimulation, apparatus massage technique corresponds to data, presented in scientific works about this question [11, 16]. The novelty of our study is the use of preformed factors in home conditions for everyday care for the injured spine, joints, muscles, eyes, feet, hands, vessels of low extremities.

Patients, who used preformed factors for prophylaxis in home conditions, demonstrated the increase of life quality, stabilization of psychoemotional state, arterial pressure. The everyday use of devices in home conditions results in normalization of hemodynamics, lipid, carbohydrate metabolism, blood coagulation system that confirms prophylaxis of diseases and their correction using home devices and makes it necessary.

During the study it was established, that the use of devices results in decreasing a pain syndrome, and just pain syndrome is an important esodic link that testifies to the incorrect or inaccurate attitude to the own body. That is why stopping a pain syndrome by pharmacological means in most cases doesn't favor patient's rehabilitation, but often decelerates or inhibits mechanisms of sanogenesis. Adequate parameters of physical factors, used in devices, stimulate the development of a cascade of reactions of sanogenesis in the patient's organism that allows to improve the health state and to normalize homeostasis, and everyday use of devices includes a patient in active steps for self-healing, physical and psychic self-improvement.

Scientific studies of preventive medicine more and more often talk about a necessity of the personified approach and correction of disease syndromes [8]. Healing of patients in home conditions by individually chosen preformed physical factors is a component of personified, preventing and participating medicine.

7. Conclusions

1. The obtained results testified to the effectiveness and prospects of using home devices for preventing diseases, because their use results in normalization of homeostasis, expressed in the positive dynamics of carbohydrate, lipid metabolism and improvement of blood rheology.

2. The use of home devices results in stabilizing the psychoemotional state, normalization of sleep and arterial pressure, improvement of patients' life quality.

3. The use of the equipment in home conditions is a prospective direction that opens possibilities of improving healing results, not realized yet. It allows to include each patient in active steps for self-healing.

4. The use of «NovuMedical» home devices in everyday life and healing patients by them is a vector of realizing the course Medicine – "4P" in practice.

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