ЭКСТРОКОРПОРАЛЬНАЯ ТЕРАПИЯ: МЕСТО В МИРОВОЙ МЕДИЦИНЕ, РАЗВИТИЕ И РЕКОМЕНДАЦИИ ПО ПРИМЕНЕНИЮ И СОВРЕМЕННЫЕ ПОДХОДЫ К ИНСТРУКЦИЯМ (ОБЗОР ЛИТЕРАТУРЫ)

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Аннотация: В обзорной статье отражена история развития гемодиализа в мире и в нашей стране, его роль в клинической медицине, его развитие, проблемы в этой области, последствия и осложнения гемодиализа, а также взгляды современной эпохи от точки зрения инструкции по их профилактике. Поэтому в этой связи обсуждались комментарии к исследованиям и результатам мировых ученых, существующие проблемы и пути их решения.

Ключевые слова: *хроническая болезнь почек, плановый гемодиализ, экстракорпоральный, почечный, гемодиафильтрация, интрадиализ.*

EKSTROKORPORAL TERAPIYA: GLOBAL TIBBIYOTDAGI O‘RNI, RIVOJLANISHI HAMDA QO‘LLANILISHI BO‘YICHA TAVSIYA VA KO‘RSATMALARGA ZAMONAVIY QARASHLAR (ADABIYOTLAR SHARHI)

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Annotatsiya: Sharhlov maqolada gemodializ tadbirini dunyo va yurtimiz miqyosida rivojlanish tarixi, klinik tibbiyotdagi o‘rni, rivojlanishi, soxadagi muammolar, gemodializning oqibat va asoratlari hamda ularni oldini olish bo‘yicha ko‘rsatmalarga bo‘lgan zamonaviy davr nuqtai nazaridan qarashlar aks ettirilgan. Shuning, bu borada dunyo olimlarining olib borgan izlanishlari hamda natijalari bo‘yicha mulohazalar, mavjud muammolar va ularning yechimi haqida fikr yuritilgan.

Kalit so‘zlar: *surunkali buyrak kasalligi, rejali gemodializ, ekstrokorporal, buyrak, gemodiafiltratsiya, intradializ.*

EXTRACORPOREAL THERAPY: ROLE IN GLOBAL MEDICINE, ITS DEVELOPMENT, AND RECOMMENDATIONS FOR APPLICATION AND MODERN VIEWS ON THE INSTRUCTIONS (LITERATURE REVIEW)

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Annotation: The review article reflects the history of the development of hemodialysis in the world and our country, its role in clinical medicine, its development, problems in the field, the consequences and complications of hemodialysis, as well as the views of the modern era from the point of view of instructions for their prevention. Also, in this regard, comments on the research and results of world scientists, existing problems, and their solutions were discussed.

Keywords: *chronic kidney disease, scheduled hemodialysis, extracorporeal, kidney, hemodiafiltration, intradialysis.*

Relevance: Scheduled hemodialysis (SH) is the most common form of renal replacement therapy used in the treatment of end-stage renal disease [10, 12]. The problem of blood purification has occupied the thinking of mankind since ancient times. Since ancient times, people have had superstitions that some diseases are caused by the contamination of body fluids and their composition. In addition, various decoctions, plant and mineral mixtures were used to clean them. Of course, most of these attempts were ineffective and even harmful to patients. Therefore, the interest in blood purification increased at the beginning and then faded somewhat [14, 28].

The issues of blood purification began to rise to a qualitatively new level at the beginning of the 19th century when organic processes occurring in the human organism were determined with the development of biochemistry. The foundation stone of SH was laid in 1861 by the Scottish scientist Thomas Graham, who first published his book, Osmotic Force. In doing so, he was the first to describe a method of producing semi-permeable membranes from specially treated parchment. With the help of this method, it was possible to separate colloidal and crystalloid solutions. More than 50 years later, in 1913, John Jacob Abel created an apparatus that removes dissolved substances from the blood. The studies were conducted on dogs whose kidneys had been removed. In the course of experiments, it was proved that nitrogenous compounds not bound to proteins can be effectively removed from the blood. However, the small area of the filter membrane of the device did not allow it to be used effectively for blood purification in humans. At that time, the drug hirudin, obtained from leech, was used to reduce blood clotting. Due to the low effectiveness of the drug, thromboembolic complications were seen as a serious problem in the field [17, 28]. The first SH was performed on a patient suffering from uremia in October 1924 by Dr. Georg Haas in Germany. Purified hirudin was used as an anticoagulant; its antigenic properties did not allow dialysis for more than 30-60 minutes. In 1927, heparin was first used as an anticoagulant in SH. Thus, Haas was the first to coordinate all the elements necessary for successful hemodialysis. He used an effective and safe anticoagulant, created an apparatus with a large-area membrane, and adequately supplied the filtering membrane with blood. However, none of Dr. Haas's patients survived, and the use of SH in the clinic was delayed for a long time [26, 28]. By 1945, Dutch physician William Kolf reintroduced SH into clinical practice and improved the apparatus developed by Georg Haas. An SH procedure performed on September 11, 1945, significantly improved the patient's condition by reducing the urea and bringing him out of a coma, eliminating the threat to his life. Thus, the clinical effectiveness of this method was demonstrated for the first time in practice. In 1946, the first in the world, William Kolf, with the support of SH, published a manual on the treatment of patients suffering from uremia. The first in the former Soviet Union was A.Ya. Pytel and N.A. On March 4, 1958, the Lopatkins conducted an SH event in a patient with chronic renal failure (CRF) in the "artificial kidney" apparatus [28].

The development of this field in our country is directly related to the name of the well-known scientist and academician of the FA of Uzbekistan, Uktam Aripovich Aripov. U. A. In 1964, when Aripov was appointed to the position of the first deputy minister of health of Uzbekistan, he took steps towards the formation of highly qualified scientific-pedagogical staff to improve the specialized medical service in the republic and to train mature medical specialists in the field. In 1971-1984, U. A. During Aripov's tenure as rector of the Tashkent State Medical Institute, large-scale scientific research was carried out under his leadership on the development of kidney replacement therapy activities. Under their leadership, the first kidney transplant and hemodialysis center was established in Central Asia, and U. A. Aripov led. Based on this center, several important works have been carried out for the treatment of CRF patients. As a result of these works, for the first time in Central Asia, on September 14, 1972, a kidney transplant was successfully performed in a patient with the terminal stage of CRF [1, 6, 9].

During the years of independence, several effective works were carried out in this field, and after the President's Decision No. PQ-3846 of July 12, 2018, "On measures to increase the efficiency of providing nephrology and hemodialysis care to the population of the Republic of Uzbekistan," the SH service in our country was fundamentally reformed and improved [2, 3, 4, 8, 11].

Thus, in the world, scheduled hemodialysis has been put into clinical practice since the 1960s as the main renal replacement therapy. 80% of patients with end-stage renal failure are treated based on planned SH measures; this indicator is 72% in Russia [5]. According to the Registry of the Society of Transplantologists, 7.3 donor kidneys have been transplanted per 1 million people in Russia in recent years [7]. This figure is significantly lower than the annual increase in the number of patients requiring renal replacement therapy in the community, which is 40 per million population. Therefore, shortly, extracorporeal detoxification and planned SH treatment will remain the main methods of renal replacement therapy. In addition, in the Russian Federation, the population in need of dialysis is growing by 9%, and this requires the establishment and development of new SH centers and the training of qualified specialists in the field. In such a situation, the need to formulate clinical guidelines on the main issues of the system seems very reasonable. In addition, these issues crosswise put several economic and social problems in front of the industry [13, 22].

Currently, despite the availability of modern dialysis technologies, mortality among these patients is ten times higher than in the general population. Importantly, the main cause of death in patients with SH is cardiovascular disease (CVD). Echocardiography (echo) revealed left ventricular hypertrophy in 74% of patients who started SH. Increased pulse wave speed with decreased elasticity of the wall of large arteries and thickening of the carotid artery intima-media complex are characteristic of these patients, and this feature in them is associated with a high risk of death. Traditional risk factors of CVS cannot fully explain this situation. At the same time, according to many authors, it is recognized that causes such as uremic intoxication, increased oxidative stress, inflammation, and anemia can participate in the development of acute atherosclerosis and CV pathologies [19]. Also, factors related to the underlying disease and extracorporeal interventions, such as fluid overload, immunological reactions caused by contact of blood with foreign bodies, and contamination of the dialysis solution, play an important role. Dialysis patients who retain uremic toxins, especially "medium molecular weight" (substances with a molecular weight greater than 500 D) toxins, have a high risk of CVS [10].

Also, there are several complications of extracorporeal detoxification, which should be considered, studied, prevented, and prepared for medical measures to be taken if they occur. Complications of SH are usually divided into two groups: complications directly related to SH treatment and complications related to chronic kidney disease.

Complications directly related to SH treatment:
Low blood pressure (hypotension) is a common complication of SH, occurring in 15-40% of cases, especially in the first year of SH treatment, in one out of every three patients. Its main reason is due to the sudden decrease in the volume of circulating blood due to the removal of fluid from the blood. Also, lack of vasoconstriction causes hypotonia (higher than necessary temperature of heated dialysate solution, fullness of internal organs due to food, overdose of hypotensive drugs, tissue ischemia, neuropathies). At the same time, the decrease in blood pressure is caused by hypertrophy of the left ventricle, its diastolic dysfunction, ischemic heart disease, and low heart rate. In rare cases, cardiac tamponade, myocardial infarction, occult bleeding, septicemia, arrhythmia, reaction to the dialyzer, hemolysis, air embolism, etc., can also be the cause [30].

Contraction of the muscles of the limbs – it occurs due to the release of a large amount of microelements (sodium, calcium, magnesium) from the body, added to the extra fluid being excreted, and is treated with preparations containing calcium and magnesium ions [30].

Individual sensitivity to hemodialysis components and allergic reactions that occur due to its high concentration is mainly related to dialyzer solution and heparin, characterized by skin itching, rashes, difficulty breathing in severe cases, and severe hypotonia [30].

Disequilibrium syndrome is a loss of orientation with the external environment and the inability to keep the body in a vertical position. This syndrome is observed at the beginning of the first dialysis measures and in obvious uremia. It is caused by the difference in osmolarity between cerebrospinal fluid and blood. In the beginning, it is accompanied by nausea, vomiting, fainting, and convulsions [29].

Fever and chills occur in dialysis patients due to the addition of bacterial infection and are characterized by a higher incidence, rapid onset, and slow resolution than in the general population. Bacterial infections are more likely to enter the bloodstream. In 50-80% of cases, the temporal vein becomes a source of bacteria (when the catheter is used in this place is important). At the same time, infection can also occur through permanent vascular routes (the frequency of infection of AV-fistula is lower than that of AV-prosthesis). It is also possible that fever is associated with pyrogenic reactions [29].

An increase in arterial blood pressure occurs in 80% of patients at the beginning of dialysis treatment, in 60% during long-term SH, and in 30% during peritoneal dialysis. It is caused by excessive consumption of liquid and table salt, incorrect calculation of "net weight," treatment with erythropoietin, hyper circulation in the patient due to existing arteriovenous fistulas, lack of effect of hypotensive drugs, as well as the removal of these drugs from the body during dialysis [29, 30].

Neurological disorders are manifested by disturbances of balance, dizziness, headache, nausea, and vomiting, which are caused by unstable changes in arterial blood pressure [30].

Complications related to chronic kidney disease:

Anemia is caused by deficiency of erythropoietin, a special protein produced in the kidney parenchyma, mechanical damage of erythrocytes during dialysis, reduction of erythrocyte life span against the background of uremic intoxication, and deterioration of iron absorption. Optimal hemoglobin levels in SH patients should be 100–120 g/dL [30].

Uremic skin itching is observed in 50-90% of hemodialysis and peritoneal dialysis patients. Uremic pruritus can be observed in 25-33% of patients before the start of dialysis and in the rest 6 months after the start of SH. Skin itching is several times less common in patients undergoing peritoneal dialysis. Uremic skin itching can be periodic and permanent, local and generalized. In some patients (25%), itching starts immediately during SH or after the session. It is caused by the following factors:

•Hyperphosphatemia
• Reaction to dialyzer
•Uremic (mixed) polyneuropathy
•Secondary hyperparathyroidism
•Allergy to medicines (heparin).
•Chronic hepatitis with cholestatic components
• Skin diseases.

The main treatment of uremic pruritus consists of modeled adequate scheduled dialysis, strict adherence to hypophosphatemic paresis, recommendations to coordinate medication of calcium-phosphorus imbalance disorders and withdrawal of these drugs in cases associated with drug allergies [29].

Secondary hyperparathyroidism is caused by the overproduction of parathyroid hormone from the parathyroid gland. It is usually associated with long-term excess of phosphorus. Therefore, it is recommended to measure parathyroid hormone levels in hemodialysis patients every three months. Also, it is necessary to strictly follow the time and frequency of the recommended dialysis procedure for the prevention of hyperphosphatemia. If the parathyroid hormone exceeds the normal values for a long time by more than 9 units, additional examinations (ultrasound and scintigraphy of the thyroid gland) are required, and it is necessary to think about the practice of removing a certain part of the gland if deemed necessary with the advice of a surgeon [30].

"Restless legs" syndrome is a subjective complaint that is observed in uremia, iron deficiency, and pregnant women. In this case, the patient is characterized by involuntary movements of the legs, which is worse at rest and night. This syndrome is observed in 6.6 - 62% of patients, mainly in those with long-term SH, and a high frequency of lethality is characteristic of this group of patients. The pathogenesis of development includes dysfunction of the subcortical branch of the brain and disturbance of iron and dopamine metabolism. Also, anemia, hyperphosphatemia, and psychological factors play an important role. Restless legs syndrome episodes are divided into two groups according to the cause of origin [29].

primary (idiopathic) "restless legs" syndrome;
secondary (symptomatic) "restless legs" syndrome.

Secondary (symptomatic) "restless legs" syndrome appears due to several somatic and neurological diseases, and if these diseases are eliminated, this symptom disappears. Scores up to 50% in CRF patients with the following conditions: anemia, diabetes, vitamin (B1, B12, folic acid) and micronutrient (magnesium) deficiency, amyloidosis, rheumatoid arthritis, cryoglobulinemia, alcoholism, radiculopathy, multiple sclerosis, spinal cord tumors or injuries occur [29].

Thus, there is evidence that there is work to be done in the field to reduce the incidence of the aforementioned complications in patients receiving elective SH sessions.

Several studies evaluating the outcomes of early initiation of renal replacement therapy have failed to find benefits for such a strategy [13]. Therefore, when deciding to start an SH event, that is, for extracorporeal detoxification, if the patient has abnormalities according to the instructions, it is necessary to take into account the possibility of a certain decrease in the quality of life of this person [13].

However, it is not appropriate to delay the SH event by ignoring these abstractions and other mental and social problems. Because the necessary or necessary extracorporeal detoxification event is not started in time, the occurrence of irreversible dystrophic changes in other organs important for life (heart, brain, liver, lungs, etc.) in the body will reduce the effectiveness of SH therapy, which will be carried out later anyway. Therefore, several authors recommend the CKD-EPI formula for the assessment of kidney function, that is, the calculation of KFT in patients with SBK stage 5, to clearly define the indication. The results obtained by calculating the KFT according to the MDRD formula are much less correlated with the parameters checked by the laboratory method [20,21].

There are different scheduled hemodialysis programs, all of which are recommended three times a week or every other day. This is the minimum frequency indication of extracorporeal detoxification [13]. This continuity criterion ensures the quality of planned SH. It has been recognized by mature authors that the survival of patients is significantly higher in the program of SH treatment three times a week, each session lasting 240 minutes [15, 16, 24]. Therefore, dialysis time is an independent, factor-independent dialysis dose that affects treatment results and cannot be changed even if other goals are achieved!!! This rule must be accepted as a basic recommendation [13,16,17]. At the same time, the difference between the concepts of "dialysis time" and "effective dialysis time" should be distinguished: the first defines the beginning and end of the event, and the second - the period of active treatment, the period of low blood flow at the beginning and end, the interruption of the treatment in case of complications, etc. removed from dialysis time. Currently, modern dialysis equipment can extract "effective dialysis time" [13].

A reliable, functional vascular system remains a fundamental and fundamental component of adequate SH. Ideal vascular access should provide safe and effective therapy, adequate blood flow, be simple and reliable to use, and pose minimal risk to dialysis patients. A high-quality native arteriovenous fistula (AVF) is considered the gold standard and is present in most patients in modern SH clinical practice. AVF is a durable, low-complication, minimally invasive, and cost-effective vascular route [13].

Central venous catheters (CVCs) are another example of vascular access for SH, and catheters are not recommended for elective SH procedures. However, they are used when SH is necessary according to important vital indications (when urgent SH is necessary due to acute kidney injury, anuria, hyperkalemia, when it is not possible to place AVF due to vascular problems, before the formation of AVK) and in very old dialysis patients [13].

Even though urea is a uremic toxin in determining the effectiveness of SH, the method of evaluating the dialysis dose based on its excretion has not lost its value in the practice of nephrology. This is because urea is the main residual product of nitrogen metabolism; it accumulates in large quantities in the body, its concentration can be easily, cheaply, and repeatedly measured, and it easily penetrates all membranes used for dialysis. In addition, using urea kinetics in dialysis patients, a large amount of statistical material has been collected so far, and they allow us to draw reliable conclusions in this regard. Because the effectiveness of extracorporeal detoxification can vary from procedure to procedure due to vascular recirculation, blood flow limitation, and intradialysis complications, there is the potential for inadequate individualized dialysis dosing. Therefore, if the available hemodialysis equipment allows, it is desirable to determine Kt/V online during each session [13].

Another form of extracorporeal detoxification is hemodiafiltration (GDF) - continuous dialysis with a special semi-selective membrane method. It is based on the principle of diffusion, filtration, and convection of water and its dissolved substances through a highly permeable high-flow biocompatible membrane due to the pressure and concentration gradient. This ensures the effective removal of water and low and medium molecular components of blood serum. Its distinctive features: low blood flow rate (100-200 ml/min), dialysate flow (16-34 ml/min), massive ultrafiltration (24-48 l/day), simultaneous replacement with a balanced solution, consists of the use of high-purity dialysate during the procedure directly through the equipment (online), requiring bolus or regular anticoagulation. Also, the process lasts 8-12 hours a day in the long-term dialysis method and requires highly qualified personnel and infrastructure. Their effectiveness has been proven in many randomized epidemiological studies that determine the relationship between the use of high-flow synthetic membrane dialyzers and better patient survival [18, 25, 23].

However, the superiority of GDF over SH has not yet been fully proven. It should be noted that the ESHOL study showed that online hemodiafiltration statistically significantly improved survival with a convection volume of more than 23.1 liters per procedure. At the same time, providing such a high convective volume requires intensive extracorporeal blood flow, and in some cases, especially in patients with a high hemoglobin level, it is impossible to achieve this indicator without involving modern automatic devices for convection optimization or without changing the duration of the procedure [13, 27].

According to the results of many comprehensive studies, correction of hydration is less important than adequate correction of uremia in the practice of scheduled hemodialysis. The state of hyperhydration has a significant adverse effect on the main outcomes of treatment - morbidity, and mortality. In this case, the degree of hyperhydration consists of two components. The first is intradialytic weight gain, which is largely dependent on fluid intake—intermittent hyperhydration. The second is the possible "core," persistent hyperhydration in patients with an incorrectly estimated net weight, that is, cases where excess volume remains even after ultrafiltration treatment sessions [13].

Studies using bioimpedance testing show that one-third of scheduled SH patients do not achieve their optimal post-dialysis weight, the so-called net weight, which describes a state of normal hydration or even mild dehydration. In such cases, even subtle interdialysis weight gain consistent with clinical recommendations can lead to excessive hyperhydration, which is associated with increased mortality [13]. Taking this information into account, we must conclude that we should always pay strict attention to the concept of net weight in the planned SH practice. Achieving net weight gain in the majority of scheduled SH patients is complicated by intradialytic symptoms related to intravascular volume depletion on the background of ultrafiltration, primarily intradialytic hypotension. Intradialysis hypotension not only reduces the effectiveness of treatment sessions but also leads to the development of heart failure. This, in turn, leads to a decrease in the survival of patients [13]. Therefore, to achieve the prevention of intradialysis hypotension in the field, it is necessary to follow several guidelines.

Thus, hemodialysis, which is a renal replacement therapy that is inevitable (it can be planned, urgent) in stage V of SBK, is not only a mechanical process but also has its complex infrastructure and system, forms, possible consequences, and characterized by complications. Also, its direct connection not only with the kidney and excretory system but also with several factors such as ENT pathologies, neuro-endocrine, water-electrolyte, and homeostasis makes the matter more serious. Therefore, it is necessary to carry out research on alternative hemodialysis programs with the evaluation of the clinical significance of episodes of hypotension during hemodialysis and the evaluation of the clinical significance of episodes of hypotension during hemodialysis.

Conclusions

1. Hemodialysis measures have different effects in different methods, forms, and duration, and the patient's age, comorbidity, and nutritional status affect the viability of patients.
2. There is an interaction between hemodialysis, hemodiafiltration, ultrafiltration, and intradialysis arterial blood pressure variability, and it depends on many extra and intracorporeal factors.
3. The clinical importance of hypotensive episodes during extracorporeal detoxification is reflected in hemodynamic disturbances in hemodialysis.
4. It is necessary to replace hemodialysis programs with a comprehensive assessment of medical indicators, quality of life, and survival of patients undergoing scheduled hemodialysis.

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