Polski Merkuriusz Lekarski

POLISH MEDICAL JOURNAL

ISSN 1426-9686



VOLUME LII, ISSUE 5, SEPTEMBER-OCTOBER, 2024

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POLISH MEDICAL JOURNAL

ISSN 1426-9686



VOLUME LII, ISSUE 5, SEPTEMBER-OCTOBER 2024

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CONTENTS

ORIGINAL ARTICLES

Experience of endovenous high-frequency electric welding in the treatment of chronic diseases of the lower extremities veins
Valentyn A. Khodos, Hlib O. Melnychuk 477

Sex features of the development of oxidative stress in high and low hypoxic resistancy rats, which experienced repeated stressful episodes of immobilization
Olha V. Denefil, Viktoria A. Miroshnyk, Olena P. Venher, Ruslan S. Usynskyi, Olha O. Liuta, Larysa Ya. Fedoniuk 480

Factors influencing medication adherence among patients with idiopathic inflammatory bowel disease in Greece and Cyprus: a cross-sectional study
Anastasia N. Nicolaou, Maria Saridi, Evangelos C. Fradelos, Ioannis P. Kaimakliotis, Konstantinos Giannakou, Konstantinos H. Katsanos, Stavroula A. Apostolidou 489

Indicators of oxidative stress in the organs of the reproductive system of rats under conditions of long-term ethanol exposure
Sergiy O. Nesteruk, Yaroslav O. Bilyk, Ivan M. Klishch, Oksana M. Matolinets, Olena A. Yakymchuk, Viktor V. Tverdochlib 500

Complications in gynecological surgeries in Ukraine: results a multicenter study
Aidyn G. Salmanov, Volodymyr V. Artyomenko, Olena A. Dyndar, Oleksandra Z. Dymarska, Yuliia V. Strakhovetska, Olha D. Leshchova, Victor O. Rud, Bohdan Yu. Tofan, Taras V. Skapchuk, Anatolii V. Andriiets, Svitlana M. Korniyenko, Anna V. Kolesnyk, Oleksandr A. Voloshyn 505

Evaluation of the result of articular facet reduction and intraoperative distraction for sanders type IV calcaneal fracture in polytraumatized patients
Timur Zhanaspayev, Galiya Zhanaspayeva, Mukhtar Abilmazhinov 512

The modern view of the use of extracorporeal detoxification in the treatment of drug poisoning (overdose)
Natalia V. Kurdil, Vladislava V. Andriushchenko, Oleh V. Ivashchenko, Anton O. Volosovets, Borys S. Sheyman, Kateryna O. Bobkovych, Borys I. Palamar 522

Evaluation of the treatment effectiveness in children with coronavirus infection
Olesya M. Horlenko, Khrystyna A. Hechko, Lyubomyra B. Prylypko, Maria A. Derbak, Mykhaylo Hechko, Fedir V. Horlenko 529

Pentose phosphate pathway of glucose-6-phosphate oxidation in the liver of rats with alloxan diabetes on the background of melatonin administrations and variable photoperiod
Oleksandra Yu. Kushnir, Iryna Yaremiy, Kyrylo Pantsiuk, Oleksandra Garvasiuk, Volodymyr Vivsyannuk, Kateryna Vlasova, Olena Vlasova 536

The role of intraoperative angiography in treating acute lower limb artery occlusion
Sergii N. Didenko, Vitalii Y. Subbotin, Yurii M. Hupalo, Oleksandr M. Orlych, Andrii V. Ratushniuk, Oleksandr V. Liksunov 541

Assessment of the workload of general practitioners in outpatient clinics in Almaty
Botagoz Turdaliyeva, Muhtar Kaidaulov, Gulshara Aimbetova, Serik Meirmanov, Yelena Indershiyeva 547

Peculiarities of leadership qualities manifestation by modern managers of police organizations: psychological aspect
Ivan M. Vyhivskyi, Ivan M. Okhrimenko, Dmytro V. Shvets, Maksym V. Korniienko, Oleksandr H. Komisarov, Olga M. Smirnova 557

The severity and outcome of Covid-19 depend on the various activities of the renin-angiotensin-aldosterone system, level of the opioid growth factor, [Met5]-enkephalin and pre-existing comorbidities
Irina A. Komarevtseva, Kateryna V. Balabanova, Anna Yu. Ihnatova, Vitaliy N. Komarevtsev, Andriy I. Burachyk, Oleksandr A. Zhurba, Yuri A. Chernykh 562

Translation and preliminary psychometric evaluation of the Measurement of Midwifery Quality – MMAY postpartum in a Greek sample
Aikaterini Toska, Dimitra Souflia, Constantinos Togas, Maria Saridi, Christina Messini, Konstantinos Tsaras, Evangelos C. Fradelos 568

REVIEW ARTICLE

Development of postural-motor, coordination, and reflex functions in children in the first year of life
Mieczysław Maciak, Kamil Koszela, Anna Beniuk, Marta Woldańska-Okońska 576

The role of university clinics in advancing higher medical education
Lidiia V. Butska, Viktor A. Chernyak, Oksana O. Drevitska, Hanna B. Varina, Valentyn O. Ryzhak, Volodymyr I. Bulda, Olena A. Mialovytska 583

Perioperative acute kidney injury – cloaked and hidden – know your enemy
Przemysław Janusz Bolewski, Janusz Trzebicki 589

International standards for conducting biomedical research with human participation
Ivan Ye. Peresh, Dmytro D. Petsa, Vasyl V. Kopcha, Tetyana M. Silina 593

Selected possibilities of physical medicine *versus* cancer diseases
Dominik Dziadek, Aleksander Sieroń 598

Occupational safety of healthcare workers in the terms of the COVID-19 pandemic as the public health aspect
Denys V. Varyvonchyk, Oleksandr P. Yavorovskyi, Oksana S. Petrovska, Liudmyla A. Ustinova, Andriy A. Kalashnikov, Natalia V. Kurdil, Borys I. Palamar 604

ORIGINAL ARTICLE

The modern view of the use of extracorporeal detoxification in the treatment of drug poisoning (overdose)

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ABSTRACT

Aim: To analyze the results of the application of extracorporeal detoxification methods in the treatment of drug poisoning and their complications.

Materials and Methods: The studied data of 129 patients aged 18-46 years with severe drug poisoning treated at the Kyiv toxicological center in 2010-2020. Statistical analysis was performed using the IBM SPSS Statistics 29.0.0.0 program; Kaplan-Meier method, log-rank test, $p<0,05$.

Results: Patients who started receiving renal replacement therapy 24-36 hours after hospitalization had the highest Kaplan-Meier survival rates. The Kaplan-Meier hazard ratio for death shows that the chances of survival progressively decrease from the 48th to the 72nd hour from the moment of admission of patients to hospital, and this trend is observed in patients with both anuria and oliguria. There was a statistically significant difference in Kaplan-Meier survival in patients receiving selective hemoperfusion on the background of renal replacement therapy ($p=0,017$); ozone therapy ($p=0,051$) and plasmapheresis ($p=0,131$) did not show statistical significance.

Conclusions: The combination of various methods of extracorporeal detoxification helps to increase the effectiveness of treatment of patients with drug poisoning due to the acceleration of the elimination of toxic substances and reduces the degree of manifestation of organotoxic effects.

KEY WORDS: acute poisoning, drugs, extracorporeal detoxification

Pol Merkur Lek,2024;52(5):522-529. doi: 10.36740/Merkur202405107

INTRODUCTION

Drug poisoning is a medical and social problem of modern society which is gaining more and more significance. According to monitoring centers in the world, about 16 million people aged 15-64 are regular drug users, which causes more than 500,000 cases of drug poisoning (overdose), including those with fatal consequences [1, 2].

In Ukraine, since 2010, the number of hospitalizations in intensive care units of patients with a diagnosis of "drug poisoning" has increased significantly [3]. Patients often get admitted not only with drug overdoses, but also with combined poisonings and complications such as *compartment* syndrome, acute renal and hepatic failure, sepsis and other critical conditions. At the same time, most patients have concomitant diseases, such as hepatitis, pancreatitis, pneumonia, which complicates the course of the poisoning [4, 5].

It is important to note that despite the availability of antidotes (for example, naloxone hydrochloride), their effectiveness is often insufficient in cases of combined drug poisoning. For example, the use of naloxone hydrochloride in poisonings with synthetic opioids, in particular fentanyl, is often ineffective, and in poisonings with methadone it is a dangerous means of treatment [6, 7]. Instead, methods of extracorporeal detoxification, such as hemodialysis, plasmapheresis, and hemoperfusion are effective in the treatment of many poisonings, accelerating the elimination of toxins from the blood and preventing the development of fatal complications [8].

Considering the above, the search for effective methods of extracorporeal detoxification in the complex treatment of drug poisoning and their specific organotoxic effects is an urgent issue of clinical toxicology.

AIM

The aim of the study was to analyze the results of the application of extracorporeal detoxification methods in the treatment of drug poisoning and their complications.

MATERIALS AND METHODS

Systematized medical data of 129 patients aged 18-46 years with the diagnoses of "Acute drug poisoning", "Acute

methadone poisoning" (ICD-10:T40.0-T40.3), treated in 2010-2020 in the intensive care unit and extracorporeal detoxification of the Kyiv City Clinical Emergency Medical Hospital (ICU-ED); women – 9 patients (6,98%), men – 120 patients (93,02%). Opioids were detected in all cases (100%), alcohol – in 48 cases (37,21%). Toxicological screening was carried out using: immunochromatographic analysis, liquid and gas chromatography, mass spectrometry. Along with opioids, other psychotropic substances were found in small quantities: cocaine, amphetamines, benzodiazepines, phenothiazines, barbiturates, antidepressants, nicotine, etc. All patients received treatment in accordance with the requirements approved by the Ministry of Health of Ukraine. 1069 protocols of detoxification procedures for drug poisoning were studied. Hemodialysis was performed on dialysis machines of the following brands: Gambro (model AK200 Ultra S); Fresenius (models 5003, 5008); B. Braun (Dialog model); bicarbonate and acetate buffer was used. These methods of renal replacement therapy (RRT) were used: continuous veno-venous hemodialysis (CVVHD) with ultrafiltration (UF); continuous veno-venous hemofiltration (CVVHF); continuous veno-venous hemodiafiltration (CVVHDF). The continuous plasmapheresis (PA) procedure was carried out using the following devices: Hemofenics, AS-B-02 with a membrane plasmafilter PFM 800 and a set of Fenix-AMP lines. The discrete plasmapheresis procedure was carried out on the Haemonetics PCS2 device with a set of Haemonetics PCS2 lines. Hemoperfusion (HP) was carried out using non-selective carbon and hydrogel selective sorbents and ion-exchange resins. Ozone therapy was carried out on the devices: Bozon H+ (Module "Bozon-BAGTO-LAZER" (for ozonation of autologous blood), Module "Bozon MOF" (for ozonation of physiological solution).

In cases of death of patients (7 cases), a forensic medical examination was conducted; examination of the tissues and fluids of the deceased for drug content was carried out using the liquid chromatography and mass spectrometry method (device – Aligent 6850/5973N, column - HP-5MS).

The studied materials of scientific libraries Elsevier and PubMed on the topic of research with a search depth of 20 years. Statistical analysis of the obtained data was carried out using the IBM SPSS Statistics 29.0.0.0 program.

Quantitative parameters were presented as mean ± standard deviation, and qualitative data – in the form of absolute and relative frequency (%). With the aim to assess the patients` survival, we used the Kaplan-Meier method for estimating the survival curves, and the log-rank test to compare a survival in two groups. Correlation between indicators was determined by Spearman's correlation coefficient (ρ). For all tests a p-value <0,05 was considered as statistically significant.

RESULTS

According to the Institute of Forensic Psychiatry of the Ministry of Health of Ukraine with reference to the Report on the Drug and Alcohol Situation in Ukraine for 2022 (according to 2021 data), the practice of using illegal drugs of various groups, including their simultaneous use with psychotropic substances and alcohol became more common [9].

Despite the fact that opioids do not directly possess nephrotoxicity, their combination with alcohol, amphetamines, cocaine and other psychotropic substances causes damage to organs and systems of the body, which leads to the development of multiple organ failure, in particular, acute kidney injury (AKI) [10, 11]. The acute renal syndrome is defined (Kidney Disease Improving Global Outcomes, KDIGO, 2012) as characterized by an increase in serum creatinine concentration of ≥0,3 mg/dL (26,5 mmol/L) within 48 hours or a ≥1,5-fold increase within 7 days, or diuresis <0,5 ml/kg/hour for 6 hours [12].

In case of drug poisoning, AKI is characterized by a wide range of disorders – from a temporary increase in the concentration of certain biomarkers of kidney damage to deep and systemic metabolic disorders that require the use of other detoxification methods in addition to RRT. The structure and number of extracorporeal detoxification procedures performed at ICU-ED in the treatment of patients with drugs poisoning during the 20-year study period are shown in Fig. 1. In the period 2015-2020, there was an increase in the number of selective hemoperfusion (HP), plasmapheresis (PA) and ozone therapy (OT) procedures.

In recent years, the following detoxification methods have been used in the conditions of a specialized intensive care unit for the complex treatment of drug poisoning (overdoses) and their complications:

1) renal replacement therapy (RRT): CVVHD+UF, CVVHF, CVVHDF – used to eliminate toxins and maintain homeostasis in patients with acute renal failure of toxic origin;
2) plasmapheresis (PA), membrane and centrifugal, used for the purpose of eliminating toxins and correcting indicators of the hemostasis;
3) hemoperfusion (HP) with the use of non-selective sorbents (carbon sorbents) and selective sorbents (hydrogel sorbents with polymyxin B, Hemo-Proteazsorb and selective sorbents of the Jafron (HA230, HA130) effectively ensured the removal of inflammatory mediators at complications and accompanying diseases such as: pneumonia, sepsis, pancreatitis, hepatitis, purulent-necrotic processes of soft tissues due to rhabdomyolysis, etc.;
4) ozone therapy (ozonized autohemotransfusion, intravenous infusion of ozonated physiological solution and local application of ozone) was used in complex therapy of infectious and inflammatory processes, stimulation of healing of infected postoperative wounds, detoxification, improvement of microcirculation (pneumonia, sepsis, purulent-necrotic processes of soft tissues, vascular thrombosis).

In order to evaluate the effectiveness of the above-mentioned detoxification methods, an in-depth analysis of the results of treatment of 129 patients with AKI due to drug (opium group) poisoning was conducted. RRT was used in 40 patients with anuria (31,01%) and 49 (37,98%) with oliguria; against the background of replacement

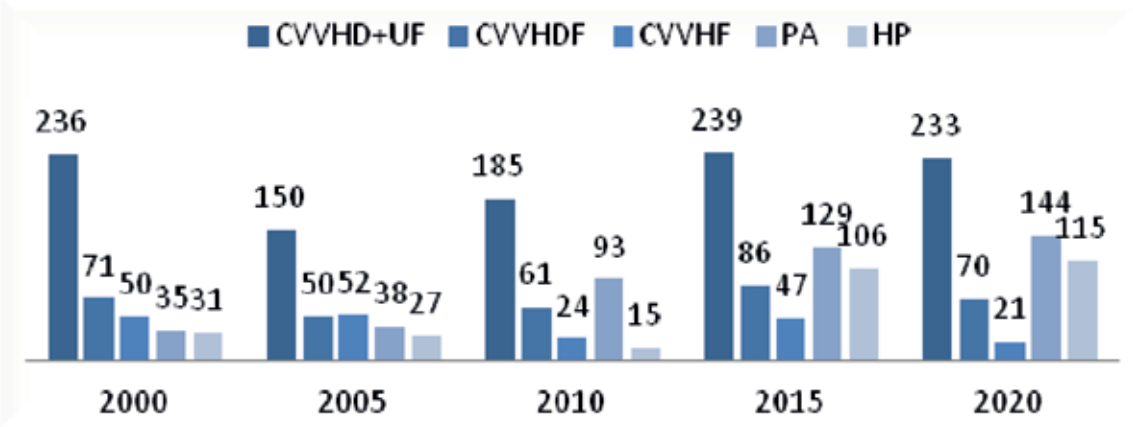


Fig. 1. Structure and number of RRT and extracorporeal detoxification procedures performed in patients with drugs poisoning during 2000-2020 (data from the Kyiv City Clinical Hospital for Emergency Medical Care, ICU-ED): CVVHD+UF – continuous veno--venous hemodialysis with ultrafiltration; CVVHF – continuous veno-venous hemofiltration; CVVHDF – continuous veno-venous hemodiafiltration; PA – plasmapheresis; HP – hemoperfusion.

therapy, the following were used: plasmapheresis – in 28 (21,71%), hemoperfusion – in 34 patients (26,36%), blood ozonation in 36 patients (27,90%).

The average length of stay of patients in VIT-ED ranged from 8,9±3,6 days (from 3 to 18 days); a total of 7 people died (5,42% of all observations); among the deceased: women – 3 (42,8%), men – 4 (57,1%).

Clinical parameters that had a direct positive correlation with the fact of death were: the presence of a compression zone of soft tissues and the level of creatine phosphokinase >5000 units/l (ρ=0,743, p<0,01 [n=57]); pneumonia (ρ=0,664, p<0,05 [n=51]); hypovolemia (ρ=0,611, p<0,05 [n=48]); electrolyte disturbances (ρ=0,553, p<0,01 [n=46]); female gender (ρ=0,337, p<0,05 [n=9]); the presence of alcohol in the blood (ρ=0,346, p<0,05 [n=41]); time from the moment of hospitalization to the start of renal replacement therapy > 48 hours (ρ=0,311, p<0,05 [n=35]); procalcitonin level (ρ=0,131, p<0,05 [n=21]).

According to the Kaplan-Meier method, the survival rates of all patients with AKI were studied depending on the start of RRT (Fig. 2). The survival curves of patients with anuria and oliguria were studied separately (Fig. 3). The results of the study show that the best survival rates were in patients who were started with RRT within 24-36 hours of admission to VIT-ED. After 48 hours of stay in VIT-ED in patients with oliguria-anuria who did not receive RRT, the survival rate significantly decreased (Fig. 3).

The Kaplan-Meier cumulative hazard curve of death shows that the chances of survival progressively decrease starting from the 48th hour from the moment of admission

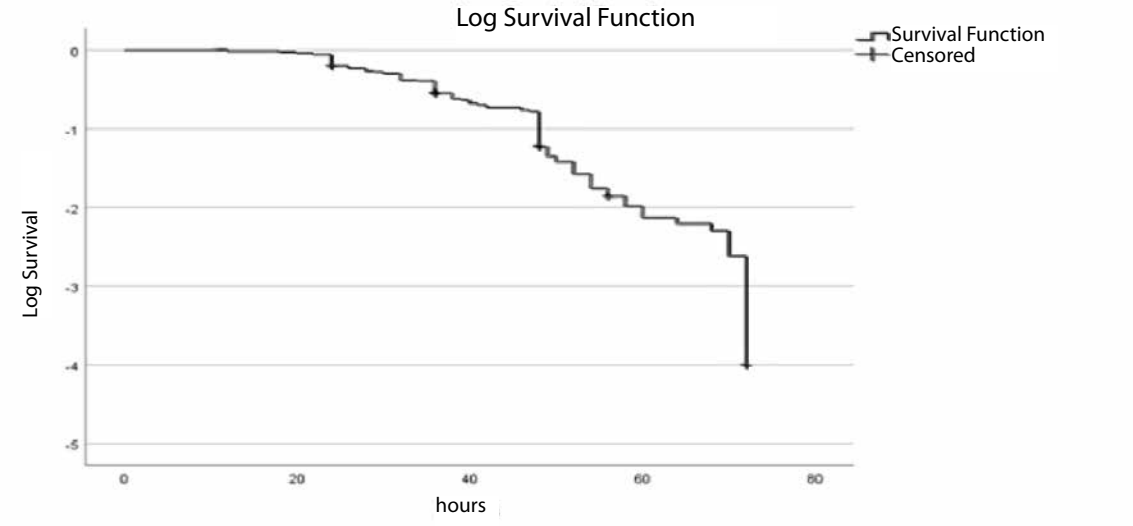


Fig.2. Kaplan-Meier (log-rank test) survival curve for all treated patients (N=129).

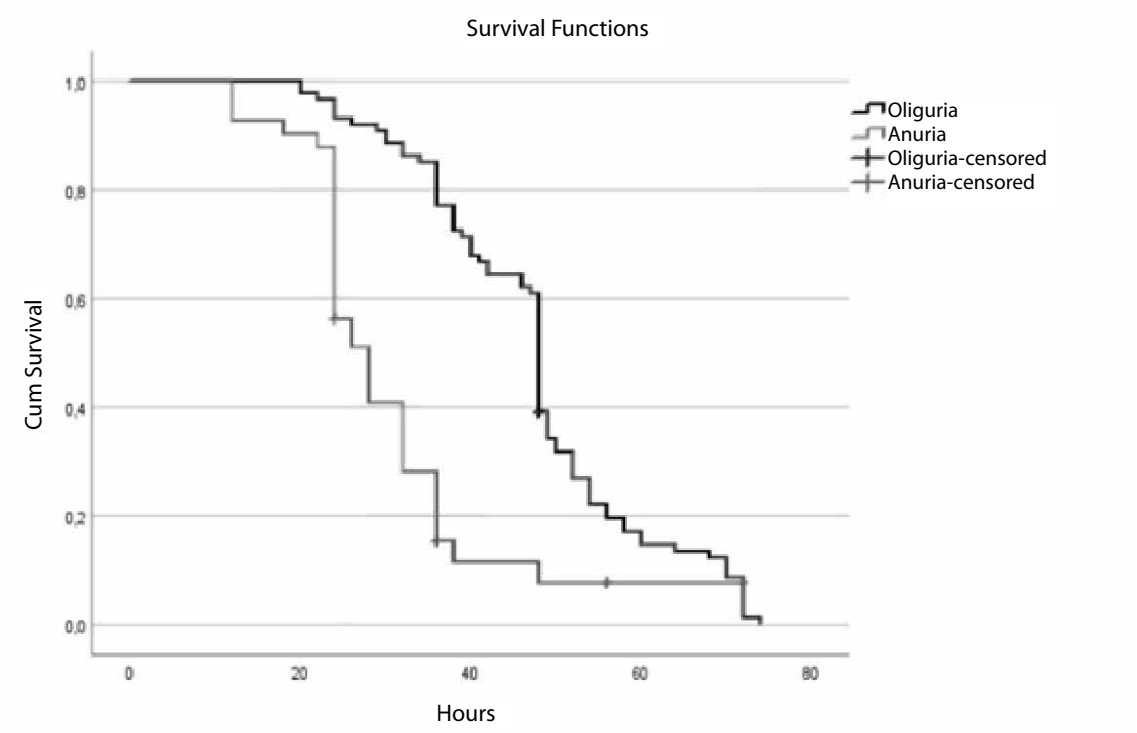


Fig. 3. Kaplan-Meier cumulative survival curve for patients with drug poisoning complicated by oliguria and anuria (N=129), depending on the time of initiation of RRT (p=0,039).

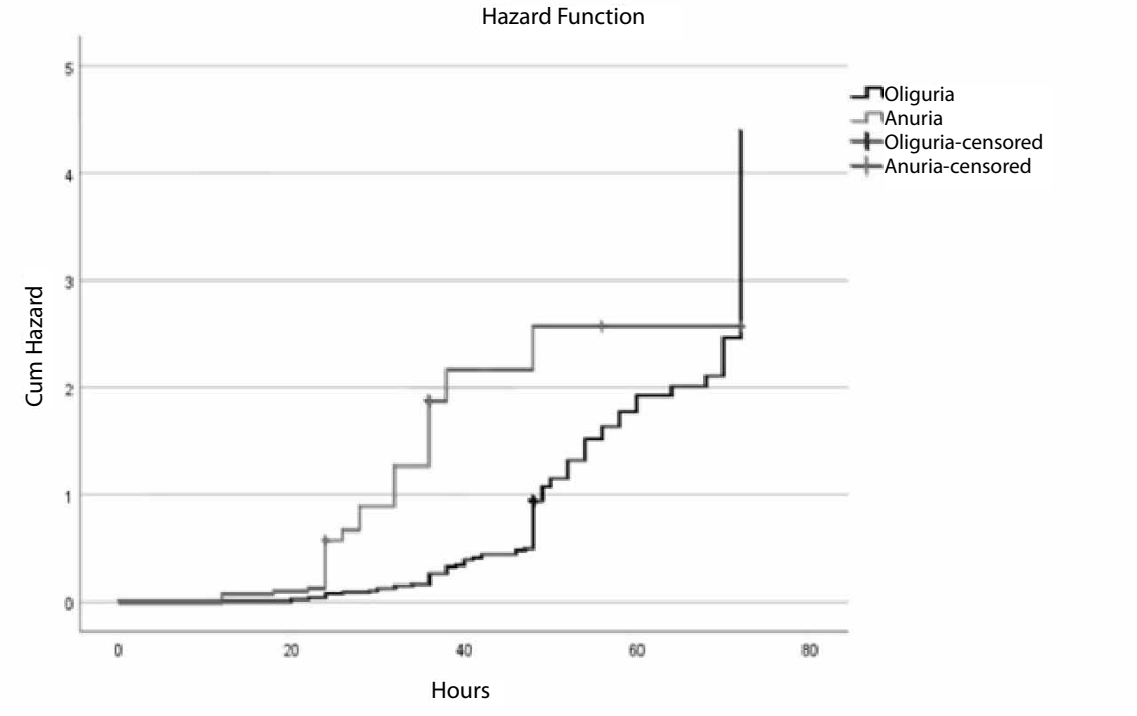


Fig. 4. Kaplan-Meier cumulative hazard curves for patients (N=129) with drug poisoning complicated by oliguria and anuria, depending on the initiation of RRT (p=0,025).

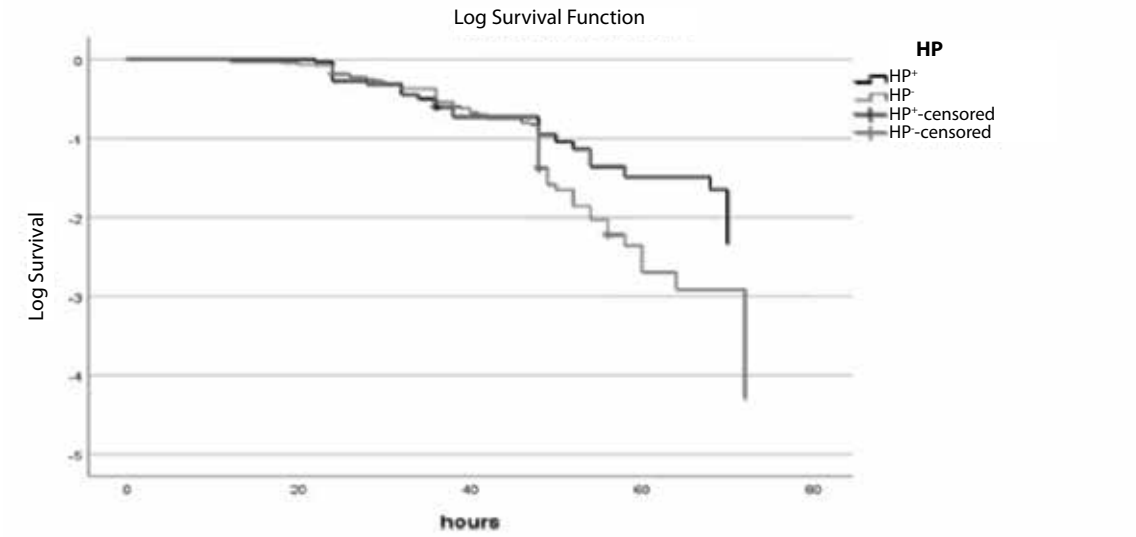


Fig. 5. Kaplan-Meier (log-rank test) survival curve of patients on the background of RRT depending on the use of hemoperfusion (HP) (p=0,017).

of patients to VIT-ED, and such a trend is observed in patients with both anuria and oliguria (Fig. 4).

Investigating the effectiveness of various methods of extracorporeal detoxification (hemoperfusion, plasmapheresis, ozone therapy) on the background of RRT, it was established that a statistically significant difference in Kaplan-Meier survival rates was demonstrated by patients who received selective hemoperfusion on the background of RRT (p=0,017) (Fig. 5), however, ozone therapy (p=0,051) and plasmapheresis (p=0,131) did not show statistical significance.

Our practical experience proves that the use of several methods of extracorporeal detoxification in the treatment of poisoning is appropriate and justified due to their mutually reinforcing effects. Each of the methods – be it hemodialysis, hemofiltration, plasmapheresis, hemoperfusion, or ozone therapy – has its own unique mechanisms of action that allow not only to effectively remove toxic substances, but also to maintain homeostasis, reduce the level of inflammatory mediators, and correct impaired functions of organs and systems.

DISCUSSION

Today, the mechanisms of toxicokinetics and toxicodynamics of most toxic substances are known, which made it possible to develop recommendations for the use of extracorporeal detoxification methods. It has been proven that the indications for the use of extracorporeal elimination of toxins depend on the dose and concentration of the toxin, the clinical course of poisoning, the individual characteristics of the patient, etc. [13, 14].

For example, it was proven that extracorporeal elimination is appropriate if it significantly (by 30% or more) increases the total detoxification effect, on the basis of which the modality of extracorporeal detoxification methods for various poisonings and pathological conditions was determined [15].

Today, the scientifically proven effectiveness of extracorporeal detoxification is studied by the international and interdisciplinary project EXTRIP (extracorporeal treatment of poisoning). Clinical recommendations for the use of certain methods of extracorporeal elimination of toxins and their toxic metabolites are provided by the authors of the project in the form of detailed tables and guidelines. For each of the common poisonings, a toxidrome, the mechanism of toxicokinetics of the poison, a clinical picture, a treatment plan, as well as the role and indications for the use of the extracorporeal detoxification method are provided [16]. However, methods of artificial detoxification have certain limitations for use in the treatment of poisoning. Limitations are mainly associated with the risk of such complications as: hypotension; loss of blood components due to residual blood in the circuit and partial hemolysis; bleeding against the background of the use of heparin or other anticoagulants; metabolic and electrolyte disorders; air embolism; sensitization, etc. [17-19].

Antidotes are an important component of drug poisoning therapy. Over the past decade, new approaches have emerged to create antidotes against powerful synthetic opioids, such as fentanyl and its analogs. Today, pharmacological antagonists and specific antibodies have been synthesized that allow effective treatment of opioid poisoning [20-22].

However, their clinical effectiveness in combined poisoning is quite limited and requires additional research. In recent years, information has been appearing regarding the use of artificial intelligence (AI) in the selection of a detoxification method. According to some scientists, the creation of prognostic models based on "machine learning" (ML) will make it possible to predict the survival of patients receiving, for example, hemodialysis with high efficiency. Based on vast amounts of data and evidence, newly developed ML models have great potential to become a practical tool for decision-making in the treatment of patients requiring artificial detoxification. Further large-scale multicenter

studies will confirm the effectiveness of these models AI for further implementation in practice [23].

In the conditions of constant changes in the spectrum of toxic substances, in particular, the rapid spread of highly toxic drugs, psychotropic substances and their precursors, the constant improvement of traditional technologies of extracorporeal blood purification remains relevant. An actual direction of research is the study of the effectiveness of the combination of various methods of efferent therapy, including extracorporeal detoxification in complex intensive therapy of poisoning.

CONCLUSIONS

1. The increase in the number of combined drug poisonings and the limited effectiveness of naloxone hydrochloride led to the need to improve methods of artificial detoxification (hemodialysis, plasmapheresis, hemoperfusion, ozone therapy) by developing methods of their combined use.
2. It was found that patients who received selective hemoperfusion against the background of renal replacement therapy (CVVHD+UF, CVVHF, CVVHDF) had better survival rates (p=0,017) according to the Kaplan-Meier method.
3. The combination of different methods of artificial detoxification, taking into account their modality, can contribute to the detoxification process and minimize organotoxic effects.

PROSPECTS FOR FURTHER RESEARCH

The specific toxicity of synthetic opioids, new psychotropic substances and their precursors remains an area that requires additional research. In particular, a promising direction of scientific research is the development of techniques for the combined use of extracorporeal detoxification methods (for example, hemodialysis, hemoperfusion, plasmapheresis, ozone therapy, etc.) to accelerate the process of eliminating toxins and correcting homeostasis.

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Research was carried out within the framework of research work (No. 0112U001133; 2012-2022); "Scientific substantiation of measures of toxicological safety of the human environment in the health care system." The study did not require additional funding.

In this study, the authors adhered to the Ethical principles of medical research involving human subjects, set forth in the Helsinki Declaration of the World Medical Association (VMA, 1964 p.) and current Ukrainian regulatory documents. The research protocol was approved by the Commission on the Ethics of Medical and Biological Research of the "L.I. Medved's Research Center of Preventive Toxicology, Food and Chemical Safety of the Ministry of Health of Ukraine" (SE). The research was not conducted on animals.

CONFLICT OF INTEREST
The Authors declare no conflict of interest

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A – Work concept and design, B – Data collection and analysis, C – Responsibility for statistical analysis, D – Writing the article, E – Critical review, F – Final approval of the article

RECEIVED: 11.06.2024
ACCEPTED: 02.09.2024

CREATIVE COMMONS 4.0