OPTIMIZATION OF KIDNEYS' DETOXICATION FUNCTION OF SEPTIC PATIENTS IN THE PERIOD OF STABILIZATION OF TOXIC AUTOAGRESION

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Abstract:

INTRODUCTION: Kidney injuries in the endogenous intoxication syndrome of septic genesis necessitates nephroprotective therapy.

OBJECTIVES: The purpose of the work was to determine the effect of the combined use of sorbilact and L-arginine on the detoxification function of kidneys and the levels of separate indicators of endogenous intoxication syndrome.

METHODS: Detoxication function of kidneys have been studied in patients of the following groups.

The first group (I, control) consisted of 31 patients with systemic inflammatory response syndrome (SIRS, ICD-10: R-65.2).

The second group (II) consisted of 22 patients with endogenous intoxication syndrome who were treated according to Surviving Sepsis Campaign 2016 (standard therapy) [9].

The third group (III) consisted of 24 patients with endogenous intoxication syndrome, who received sorbilact in addition to standard therapy.

The fourth group (IV) consisted of 21 patients with endogenous intoxication syndrome who received sorbilact and L-arginine in addition to standard therapy.

Sorbilact infusion to patients of the III and IV groups was performed at a rate of 6-7 ml/kg body weight, intravenously dripping at a rate of 7-8 ml/min. After the end of the infusion of sorbilact, patients of the IV group were infused with 4.2% solution of L-arginine ("Tivortin" intravenous drip according to the instructions). Data was obtained and results gathered on the application of drugs in the period of stabilization (according to the state of regulation of water and ion balance by kidneys) of endogenous intoxication syndrome (fourth day of drugs' application).

As a single-celled receptor-effector system, a Paramecium caudatum culture was used. Low Molecular Weight Protein (LMWP) concentrations in blood and urine were determined using a modified method.

RESULTS: Endogenous intoxication syndrome in patients of II-IV groups was characterized by the following indicators: total blood plasma toxicity (Pt) in the II group was 151 ± 6.4 toxicity units / ml, in group II -147 ± 6.2 toxicity units / ml and 130 ± 6.6 toxicity units / ml in group IV. LMWP concentration in group II was 0.61 ± 0.03 conditional units / ml, in III group - 0.52 ± 0.029 conditional units / ml and 0.43 ± 0.037 conditional units / ml in group IV.

The following clearance detoxification function characteristics are established, which are integral indicators of its kidneys performance. Clearance of toxic substances (Ct) in the I group was 2.7 ± 0.06 ml / min, in the II group 2.1 ± 0.09 ml / min, in the III group - 2.9 ± 0.07 ml / min and 3.8 ± 0.08 ml / min in the IV group. Clearness of LMWP (C_{LMWP}) in the 1st group was 15.91 ± 0.69, ml / min, in the II group 14.65 ± 0.79 ml / min, in group III - 25.61 ± 0.71 ml / min and 37.31 ± 0.7 ml / min in group IV.

CONCLUSION: Under conditions of septic endotoxemia in the period of stabilization of endogenous intoxication syndrome optimization of standard therapy with the use of sorbilact and L-arginine is accompanied by the activation of the kidneys'detoxication function according to their clearance characteristics.

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Introduction

Mayr et al. (2014) writes, that sepsis remains an urgent problem of clinical medicine. According to Pavliak (2011), sepsis is accompanied by the formation of an endogenous intoxication syndrome (EIS). As Yurieva et al. (2015) writes, kidneys are the main homeostatic organ whose functions undergo intensive strain of various circumstances of multiple organ failure, especially in the event of an initiated toxic aggression.

According to Ferguson & Waikar (2012), the implementation of nephroprotective therapy necessitates the use of renal function markers to assess impressions and control the effectiveness. In obedience to Neirynck et al. (2012) for the study of the functional state of the kidneys, in particular in the case of EIS, it is advisable to use generalizing markers of intoxication, for example Low Molecular Weight Proteins (LMWP). The complex toxicity assessment methods, including in biological fluids, Ershov et al. (1999) include the Paramecium caudatum mobility test. On the other hand, the influence on the flow of EIS remains an important component of the complex of therapeutic effects. Despite the use of extracorporeal

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methods of detoxification, according to Zarbock et al. (2014) infusion therapy remains the basis of the program of complex intensive care of acute EIS of septic genesis. Nichitaĭlo (2011) writes, among infusion solutions there are enough promising preparations of polyhydric alcohols, in particular on the basis of sorbitol. Senbel et al. (2014), expands the prospects for using infusion solutions adjuvant therapy, in particular, the combination of solutions of polyhydric alcohols with L-arginine. However, the effect of combined use of sorbilact with L-arginine on renal function remains unknown.

The purpose of the work was to determine the effect of combined use of sorbilact and L-arginine on the detoxication function of kidneys and the levels of separate indicators of the endogenous intoxication syndrome (EIS).

Methods.

The study included patients with surgical infections from the Chernivtsi Regional Clinical Hospital. Patients were randomized into groups:

The first group (I, control) consisted of 31 patients with systemic inflammatory response syndrome (SIRS, ICD-10: R-65.2).

The second group (II) consisted of 22 patients with EIS of septic genesis and were sorted by level of cell-mediated and humoral intoxication index according to Konovchuk et al. (2016) with 20-60 points, who were treated according to Surviving Sepsis Campaign 2016 (standard therapy).

The third group (III) were 24 patients with EIS of septic genesis with 20-60 CHII points, who received sorbilact in addition to standard therapy.

The fourth group (IV) consisted of 21 patients with SEI of septic genesis with 20-60 CHII points, who received standard therapy as well as Sorbilact and L-arginine.

Sorbilact infusion to patients of III and IV groups was performed at a rate of 6-7 ml/kg body weight, intravenously dripping at a rate of 7-8 ml/min. After the end of the infusion of sorbilact, patients of the IV group were infused with 4.2% solution of L-arginine (“Tivortin” intravenous drip according to the instructions).

Inclusion criteria to groups II-IV: acute surgical infection of different localization due to the association of aerobic gram-positive and gram-negative microorganisms with the subsequent development of secondary toxic autoaggression on the scale of CHII more than 40 points; more than 2 points on the SOFA scale with stable hemodynamics; 1 stage of acute kidney damage by the classification of KDIGO (2014); no signs of artificial ventilation.

During the entire treatment period (from the first to the fourth day of observation), patients received standard complex therapy according to the Surviving Sepsis Campaign (2016) (surgical sanitation of the source of infection, antibiotic therapy, infusion therapy, rheological, metabolic and inotropic support, etc.), with what the scheme of the therapy was coordinated with the practical recommendations of KDIGO (2014). Medications with a diuretic effect were not used in the period of the study.

The circumstances of the termination of the study were regulated by the inclusion criteria (a decrease of CHII below 20 points).

The exclusion criteria were the emergence of one or more circumstances that were not included in the inclusion criteria, in particular: supplementing the intensive therapy with hemodialysis, plasmapheresis, artificial ventilation, hyperbaric oxygenation; a significant deterioration of the general condition due to the activation of comorbid diseases or the progression of complications, which required the use of intensive care measures that were not subject to the inclusion criteria.

Blood and urine collection were performed 4 hours (±10 min) from the beginning of infusion of sorbilact on the fourth day of observation (in the period of stabilization of the volume-regulatory function).

CHII was determined by the scale described by Konovchuk et al. (2016). The total concentration of toxic substances was determined using cellular receptor-effector systems (Paramecium caudstum) according to Ershov (1999). LMWP were determined by a modified technique from Kamyshnikov (2009). For statistical data processing, a Student's t-criterion for independent samples was used (IBM SPSS Statistics 8).

The state of detoxification function of the kidneys' and the level of toxemia by the state of single-cell receptor-effector systems and LMWP in the period of stabilization of endogenous intoxication syndrome

The complex of indexes of the detoxication function of kidneys on the fourth day of observation was investigated (Table 1).

Table 1: Indicators of EIS and kidneys' detoxification function

Indicator, units of measure	Group I, SIRS (31 patients)	Group I, EIS+s.t. (22 patients)	Group I, EIS+s.t.+ sorbilact (24 patients)	Group I, EIS+s.t.+ sorbilact+L-arginine (21 patients)
P_t, toxicity units / ml	103±4.1	151±6.4*	147±6.2	130±6.6***
U_t, toxicity units / ml	290±8.9	330±9.7*	341±8.3	359±9.5***
U_tV, toxicity units / min	275±5.1	303±5.9*	417±5.7*	495±6.1***
EF_t, %	2.3±0.05	3.6±0.08*	3.9±0.07*	4.1±0.09**
C_t, ml / min	2.7±0.06	2.1±0.09*	2.9±0.07*	3.8±0.08***
U_tV/GFR*100, toxicity units / min	234±4.2	416±4.8*	480±4.5*	486±4.9**
P_{LMWP}, cond. units / ml	0.27±0.011	0.61±0.03*	0.52±0.029*	0.43±0.037**
P_{LMWP} GFR, cond. units / min	31.47±0.71	44.58±0.79*	45.27±0.75	42.91±0.81*
U_{LMWP}, cond. units / ml	4.5±0.13	9.8±0.21	10.3±0.19*	11.6±0.20*
U_{LMWP} V, conditional units / min	4.22±0.18	8.92±0.26*	13.36±0.23*	16.02±0.27***
RF_{LMWP}%, %	85.21±0.37	80.11±0.59*	70.28±0.60*	62.75±0.02***
EF_{LMWP} %, %	14.41±0.35	19.85±0.37*	29.70±0.38*	37.21±0.41***
C_{LMWP}, ml / min	15.91±0.69	14.65±0.79	25.61±0.71*	37.31±0.7***
U_{LMWP} V/GFR* 100, conditional units / min	3.60±0.16	12.23±0.22*	15.31±0.23*	15.75±0.25**

Source: Natalia Maksymchuk, Victor Konovchuk (2017)

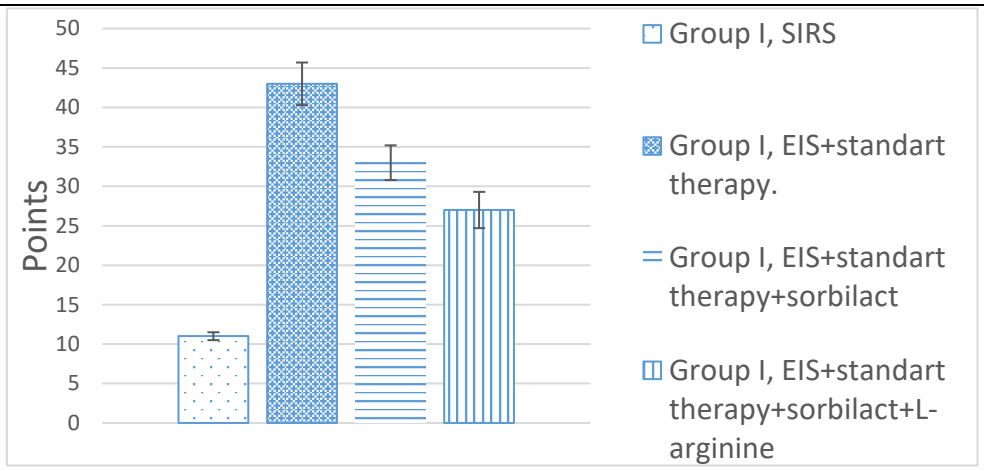
In patients with EIS, who were treated by standard treatment, the levels of total toxicity of blood plasma (P_t) and urine (U_t) remain elevated in relation to patients with SIRS ($p<0.05$). Accordingly, there is an increase of excretion of toxic substances (U_tV) and their excreted fraction (EF_t) in comparison with the first group ($p<0.05$). It is important that the clearance of toxic substances (C_t) remains lower compared to the control group ($p<0.05$). An increase of the excretion of toxic substances to 100 ml GFR (U_tV/GFR*100) demonstrates an increase of functional load on active nephrons ($p<0.05$). So, patients of group II have been found to have inadequate processes aimed at toxic substances elimination (according to the levels of indicators of total toxicity, which is confirmed by Ut / Pt index calculations). The release index (Ut / Pt) is a punch which indicates the correlation between production and the elimination of toxic substances, which in patients with the second group was reduced (2.2 ± 0.04) in relation to group I (2.9±0,02) ($p<0.05$). On the fourth day of observation, the EIS manifests by a significant increase in the concentration of LMWP in the blood plasma (P_{LMWP}) and urine (U_{LMWP}). Despite the lower GFR, the LMWP filtration fraction (P_{LMWP} GFR) increases substantially (by 41%, $p<0.05$), and consequently there is a rapid increase in the LMWP excretion (U_{LMWP} V) (by 82%, $p<0.05$) compared to patients with SIRS. In general, the performance of the detoxification function of kidneys was aimed to eliminate LMWP, and also testifies to this, an increase in LMWP excreted (EF_{LMWP}) fraction (by 38%, $p<0.05$) and a decrease in LMWP reabsorbed (RF_{LMWP}) fraction (by 6%, $p<0.05$). EIS continued to exert a significant load on each active nephron, which was confirmed by an increase of the intensity of LMWP excretion by 100 ml GFR (U_{LMWP} V/GFR 100 mL) (239%, $p<0.05$) in relation to patients with SIRS. It is important that in the period of stabilization of toxic autoaggression, the recovery of LMWP clearance (C_{LMWP}) is observed (in comparison with the control of SIRS, $p<0.05$).

It has been established that sorbilact did not change the level of total toxicity of blood plasma and urine (in comparison with patients who did not receive it), and therefore did not affect the release index (Ut / Pt). But an increase of U_tV, U_tV/100ml GFR and EF_t suggests that sorbilactone activates the intake of toxic substances from cells and the interstitial to the vasculature, where they are excreted by the kidneys. Incorporation of sorbilact on the background of standard therapy caused a decrease (by 17%, $p<0.05$)

of plasma LMWP concentration. Although $P_{LMWP}GFR$ did not change under the influence of sorbilact, C_{LMWP} was more significant than in the control group by reducing reabsorption, including proximal metabolism and transport ($U_{LMWP}V\uparrow$, $R_{LMWP}\downarrow$, $EF_{LMWP}\%\uparrow$).

Analysis of indicators characterizing the detoxication function of kidneys shows that L-arginine enhances the influence of sorbilact on this function. Despite the increase of C_t and C_{LMWP} in the case of L-arginine treatment, P_t and CHII remained high (Figure 1).

Figure 1: Cell-mediated and humoral intoxication index.



Source: Natalia Maksymchuk, Victor Konovchuk (2017)

Conclusion

Standard therapy causes recovery of the detoxication function of kidneys according to the LMWP clearance.

With the use of sorbilact and sorbilact with L-arginine on the background of standard treatment, the activation of the detoxication function of kidneys is observed by clearance characteristics.

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