

Therapeutic Apheresis in Acute Kidney Injury

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Abstract

Acute kidney injury is a serious complication of various inflammatory diseases of the abdominal and thoracic cavities, severe injuries and burns, eclampsia and sepsis, and a number of infectious diseases. Considering such a variety of etiologies there is a main pathogenesis feature, which is based on endoxemia with accumulation of a number of toxic products that cause disturbances in the vessels endothelium permeability with perivascular edema associated with decrease in the renal blood flow, glomerular filtration, tubular necrosis and oligo-anuria. The most common tactics of treatment is to perform kidney replacement therapy, mainly different methods of hemofiltration. However, not all toxic products are removed and the mortality rate remains quite high. The inclusion of hemosorption and plasmapheresis in the complex of therapeutic measures gives more favorable and stable results, showing a significant reduction of the mortality rate.

Keywords: Acute kidney injury; Endotoxiosis; Hemofiltration; Therapeutic apheresis; Plasma exchange; Hemosorbition.

Introduction

The term "Acute Kidney Injury" (AKI) means inability of the kidneys to provide their excretory function leading to retention of nitrogenous waste products in the blood [1]. Acute renal failure quite often accompanies acute inflammatory organs diseases of the chest and abdomen cavities, severe injuries and burns, eclampsia and septic shock. The AKI incidence rates were 130-150 per 10,000/year, particularly among older people [2]. It is the main reason for multiple organ insufficiency and death rate up to 80% [3,4]. All this indicates that the traditional treatment methods of acute renal failure using drugs and renal replacement therapy to be insufficient. The aim of this research is to study the possibilities of therapeutic apheresis in the treatment of AKI.

Features of AKI pathogenesis

AKI often develops on the background of acute pneumonia, which is to varying degrees accompanied by disorders of other vital organs, first of all, of the kidneys [5]. AKI is observed in one third of patients with respiratory distress syndrome [6]. It has long been observed that even in itself artificial lung ventilation, especially with a Positive End-Expiratory Pressure (PEEP) reduces renal blood flow by 32%, glomerular filtration rate by 19%, and urine output by 34% [7,8].

Often, AKI develops in the presence of sepsis or sepsis joins an already developed kidney disease [9-12]. Despite many clinical and fundamental studies giving a better understanding of the septic complications pathogenesis, the number of sepsis cases in the United States continues to increase, being the main cause of AKI and adverse outcomes [13]. Risk factors include severe burns, pancreatitis and peritonitis traumatic shock syndrome and prolonged compression ("crush syndrome"), eclampsia [14-16]. Mortality is as high as 70-80%

[7,17]. This applies to AKI, which develops on the background of severe pancreatitis when 79% of patients have to resort to renal replacement therapy [18]. AKI also often accompanies acute liver failure with high mortality [19].

Nevertheless, considering a variety of etiological factors, the AKI pathogenesis is based on the renal parenchyma toxic damage. Disturbance of the vascular endothelium permeability leads to perivascular edema with decreased renal blood flow, glomerular filtration, tubular necrosis, oligoanuria [9]. According to the consensus reached at the conference of the working group on AKI (ADQI), the criteria for inclusion of patients to the "risk" group is decreased urine output-less than 0.5 mL/kg in 6 h, to the "injury" group-less than 0.5 mL/kg in 12 h, to the "failure" group-less than 0.3 mL/kg in 24 h or anuria in 12 h [20]. In the "risk" group the risk of death is 13%, in the "disease" group -40%, and in the "failure" group-80% [3].

Possibilities of kidney replacement therapy

Such unfavorable predictions for ARE, of course, require intensive therapy. But, given the absence of any specific medication, the most common method to correct renal excretory dysfunction is to remove the accumulating fluid by hemodialysis or various methods of hemofiltration [13,21-24].

This approach is explained by the desire to eliminate only visible disorders-fluid retention during AKI. But it is actually a symptomatic therapy that does not affect the essence of the pathology-endotoxiosis, underlying these organ disorders. Indeed, the mortality rate in such patients remained high enough-up to 50-70%, regardless of the "renal replacement therapy" methods choice - dialysis, intermittent or permanent veno-venous hemofiltration [24-27].

Hemofiltration is also ineffective when the liquid volumes accumulation is more than 20% of the body weight [28]. AKI also develops in children when using hemofiltration, the death rate reaches 50%, and in hematological patients with bone marrow transplantation

it reaches 100% [29]. Moreover, the danger is not only in high mortality, but also in long-term disability with chronic renal failure [30].

But prospectively, the survivors often show signs of chronic renal failure [22,31]. In spite of the applied methods of renal replacement therapy (continuous or intermittent hemofiltration), after discharge from hospitals the mortality rate during the first year was 23% and in the second year-7.6%, which was 65.7% in total [32]. This was also confirmed in later studies [33,34]. Using only hemofiltration we cannot remove macromolecular and other toxic products, including fibrinogen, which causes the need to use plasmapheresis [35]. This confirms our belief that purely symptomatic therapy (removal of the excess fluid) does not eliminate the problem of endotoxemia, which is the major tanatogenesis factor.

In particular, at high level of cytokines removal such as TNF- α , IL-1 β , other cytokines IL-6 and IL-8, which are more unfavorable in prognosis, were retained in the body noted that using hemodiafiltration can reduce the levels of TNF- α , IFN- α and IL-4 with correction of critical states course; however, such a procedure did not influence the course of infection. The latter responded to correction only using plasmapheresis that contributed to restoration of decreased production of INF- α and improvement of cellular and humoral immunity [36]. A combination of plasmapheresis with continuous hemofiltration is used though; it seems that it is the plasma exchange that played more essential role here [37].

Observations

We have experience in treating 164 patients who were treated in the intensive care unit of the surgical clinic at the I.P. Pavlov First St. Petersburg State Medical University. The most common types of pathology were septic inflammatory complications in abdominal and thoracic surgery (destructive pancreatitis, peritonitis, acute pneumonia and lung abscesses). The severity of the patients' condition was taken into account according to the classification of Bellomo et al. (2004) and considering the levels of medium-molecular oligopeptides [38], in the norm of 240.4 ± 14.2 Units (Table 1).

AKI severity group	AKI Criteria (diuresis)	Medium-molecular oligopeptides level (Units)
"Risk"	Less than 0.5 mL/kg in 6 h	350.0 ± 22.5
Injury	Less than 0.5 mL/kg in 12 h	644.2 ± 45.3
Failure	Less than 0.3 mL/kg in 24 h or anuria in 12 h	880.1 ± 52.6

Table 1: AKI Severity Classification.

Table 1 shows that AKI severity is clearly correlated with the level of medium-molecular oligopeptides and this indicator reflects the patient's condition dynamics during the treatment. This shows the role of endotoxemia in the genesis of acute kidney lesions.

Three groups of patients were identified depending on the AKI severity: "Risk", "Injury" and "Failure" groups, using only traditional medical therapy with artificial ventilation of the lungs (67), Extracorporeal Detoxification-Plasma Exchange or hemosorption (97) and extracorporeal membrane oxygenation (ECMO) with

hemosorption (in this analysis only 11 patients included from the "failure" group, who underwent ECMO with hemosorption) (Table 2).

AKI severity group	Traditional treatment	Hemosorption / plasma exchange	ECMO + hemosorption	Total no of patients
"Risk"	52	47	-	99
Injury	15	39	-	54
Failure	-	-	11	11
Total	67	86	11	164

Table 2: Treatment methods depending on AKI severity (number of patients).

In the "Risk" group there were no lethal outcomes, but the average duration of treatment with extracorporeal detoxification was 28.0 ± 1.5 days, while using only traditional therapy- 40.3 ± 3.3 days. In the "Injury" group, when using extracorporeal detoxification methods, the mortality rate was 31.03%, while using only traditional therapy-73.33%. Even in the "Failure" group the mortality rate was only 36.3%, while such patients are usually doomed.

There was a notable case of a patient treated for an advanced anuria associated with eclampsia lasting for a month after the delivery. Following hemosorption procedure on the next day diuresis was already 500 mL, and after a repeated procedure it was restored completely resulting in fast recovery of the patient.

Discussion

It should be noted that the very development of acute infectious process could be due to initial immunodeficiency, developed as a result of other recent diseases (even conventional respiratory viral infections), adverse environmental or social factors, and chronic intoxication. Further develops a chain mutually aggravating events. The immune system mobilizes all its reserves to fight infectious and other agents but these reserves are not unlimited and eventually become exhausted. The increase of endotoxemia acts overwhelmingly on all cellular and humoral immunity components, leading to an even deeper immunosuppression, which can be described as "immune distress syndrome".

Thus, septic complications develop as a severe endotoxemia on the background of increasing immunosuppression, resulting in a vicious circle, which neither the body nor the most intensive drug therapy is able to break.

Sorption methods are based on such feature of many harmful products as the presence of charge of these molecules or free radicals in their structure, which in contact with the sorbent consisting of activated carbon or other surfactants (sometimes coated with enzymes or ion exchange resins), are able to be adsorbed to the latter. Hemosorption can remove not only toxic metabolites but also circulating in the blood living or already killed pathogens by antibiotics, which was confirmed by our special studies [39].

However, the immune system remains depleted. And here plasma exchange comes forward. Replacement of the removed plasma with fresh frozen donor plasma enables to quickly restore the natural defense mechanisms, without which the most powerful antibiotics of the ultra-wide spectrum are useless, and their hepatotoxicity or

nephrotoxicity can further aggravate the patient's condition. The guidelines of the American Society for Apheresis (ASFA) for 2016 also contain recommendation to use plasmapheresis in sepsis associated with multiple organ failure [40]. After massive plasma exchange a faster turning point of the disease occurs that reverses the development of the organ disorders.

Of course, the presence of concomitant acute renal failure with diuresis decrease down to anuria may justify the use of filtration methods to remove excess fluid, but this does not provide restoration of the kidneys own excretory function. It should be taken into account that hemofiltration does not remove all the pathological products, many of which have a large molecular weight.

Using hemofiltration only it is impossible to remove toxic large-molecular products, including fibrinogen, which even during hemofiltration makes us resort to plasmapheresis or hemosorption [35,41]. Severe poisoning has been observed in some countries of Western Europe in the summer of 2011, caused by serotype O104:H4 *Escherichia coli*. The secreted Shiga-toxin caused severe enterocolitis followed by development of hemolytic uremic syndrome and AKI with high level of mortality. Antibiotics in this case were useless or, on the contrary, contributed to increase of endotoxemia. It became clear only in the end of this epidemic that forced to refuse from antibiotic therapy. Use of plasma exchange in the early stages of the disease provided fast healing [42-46].

Treatment of victims in the aero-mobile hospital of EMERCOM, Russia, being in places of technogenic and natural catastrophes proves to be indicative. In cases of "crash syndrome" AKI inevitably develops. However, immediate use of plasmapheresis within two hours after the victims extracted from the rubble excluded the need to conduct renal replacement therapy [47-48].

The findings presented quite convincingly show feasibility of a more complete active detoxification therapy-hemosorption or plasmapheresis. And indeed, almost always after the "toxic burden" removal from the kidneys their excretory function was restored. The next day diuresis was not less than 500-700 mL. It was associated with improved functional status of the other vital organs such as lungs, liver, heart, and brain [49,50]. This confirms our belief that purely symptomatic therapy (removal of excess fluid) does not eradicate the problem of endotoxemia, which is the main factor of tanatogenesis.

Conclusion

The presented findings confirm the leading role of endotoxemia in the genesis of AKI, which makes it necessary to perform more complete detoxification therapy. Without diminishing the value of hemofiltration, inclusion of hemosorption and plasmapheresis in the treatment will help influence all the parts of the pathological process and achieve better and more stable results of AKI treatment.

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