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Current View on the Use of Extracorporeal Detoxification Methods for the Treatment of Rhabdomyolysis (Review)

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Современный взгляд на применение методов экстракорпоральной детоксикации при рабдомиолизе (обзор)

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Summary

Rhabdomyolysis is a syndrome caused by destruction and necrosis of muscle tissue, which is accompanied by the release of intracellular contents into the systemic circulation. The etiology of rhabdomyolysis is multifaceted, however, regardless of the etiological factor, the central element of its pathophysiology is systemic endotoxemia with multiple organ failure syndrome. Acute renal failure is one of the most common manifestations of organ dysfunction. Considering the pathogenetic model of the development of systemic endotoxemia, the timely use of extracorporeal therapy, which reduces mortality in organ failure, seems promising. All the current types of extracorporeal therapy can be divided into convection (hemofiltration), diffusion (hemodialysis), convection/diffusion (hemodiafiltration), sorption (hemoperfusion) and plasma exchange (plasmapheresis, plasma exchange, plasma sorption, etc.) methods based on physical principle.

The aim of the review was to summarize the available clinical data on extracorporeal treatments for rhabdomyolysis and to assess the feasibility and best indications for these methods based on the current pathogenetic model of rhabdomyolysis.

Material and methods. The search for information was carried out in the Web of Science, Scopus, Medline, PubMed, RSCI, E-library and other databases. Eighty-one sources were identified containing current therapeutic approaches and relevant data of clinical and scientific research on the subject of this review.

Results. In this review, the main etiological, epidemiological and pathogenetic models of acute renal injury in rhabdomyolysis have been discussed. The main methods of extracorporeal therapy have been reviewed and evaluated based on current understanding, and latest clinical data on their effectiveness have been summarized.

Conclusion. The choice of the optimal extracorporeal treatment method, the time of initiation and duration of the procedure still remain controversial. The solution to this issue can potentially help to better correct the electrolyte disturbances and could protect against organ dysfunction, which would improve the outcome in patients with rhabdomyolysis.

Keywords: rhabdomyolysis; acute kidney injury; renal replacement therapy; plasma exchange; selective hemoperfusion; review

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Introduction

The incidence of acute kidney injury (AKI) in rhabdomyolysis ranges from 10 to 55% [1–5]. Moreover, rhabdomyolysis accounts for 5–25% of all causes of AKI, and mortality among patients with rhabdomyolysis complicated by AKI is over 10% [6-9]. Myoglobin plays a specific and significant role in the pathogenesis of AKI in rhabdomyolysis, causing endogenous intoxication. For eliminating myoglobin from the bloodstream, various methods of extracorporeal detoxification (ECD) are included in the management of rhabdomyolysis [11–13]. The effectiveness of various ECD techniques at different stages of this condition remains controversial. According to current literature, the most effective methods include hemodiafiltration and hemofiltration, or hemodialysis using ultrahigh-flow membrane [11, 14–16]. Many studies report the use of ECD in rhabdomyolysis associated with plasma separation, as well as non-selective methods apheresis, such as plasmapheresis and plasma exchange. The use of these methods, however, is limited by their insufficient safety and efficiency [17–19]. Currently, selective hemoadsorption appears to be the most promising and safe among them. However, this method is most widely used in the treatment of patients with sepsis and septic shock [20].

The choice of optimal and safe method of extracorporeal treatment is an important challenge of current medicine, and the data on the effectiveness of various machines in patients with rhabdomyolysis complicated by AKI are lacking in the available literature.

Definition and Epidemiology

Rhabdomyolysis is a clinical and laboratory syndrome that develops as a result of damage and destruction of myocytes of skeletal striated muscle tissue, accompanied by the release of myolysis products into the bloodstream and toxemia of varying severity [21, 22]. The incidence of rhabdomyolysis remains unknown, but risk groups have been identified (patients with elevated body mass index of 40 kg/m^2 or more, those taking long-term hypolipidemic therapy or patients after surgery) [23].

The most life-threatening and common complication of rhabdomyolysis is acute pigmented nephropathy, often referred to as «myoglobinuric acute kidney injury».

The incidence of acute kidney injury (AKI) in rhabdomyolysis ranges from 10 to 55% [24, 25]. Moreover, rhabdomyolysis underlies 5–25% among all causes of AKI [26, 27], and mortality among patients with rhabdomyolysis complicated by AKI reaches 10% [28, 29].

According to literature data, rhabdomyolysis is caused by various exogenous intoxications (alcohol and drugs) in 60% [30, 31]. Long-term compression syndrome (crush syndrome) is also one of the frequent causes of this syndrome [32, 33]. Excessive physical activity often leads to exertional rhabdomyolysis [34–36]. Rhabdomyolysis occurring with the malignant hyperthermia during general anesthesia also was reported [37]. In general, the etiological factors of rhabdomyolysis include physical (trauma, electrical injuries, hyperthermia, burns) and non-physical (toxic substances, drugs, metabolic myopathies, electrolyte disorders, infectious diseases, endocrinological disorders) ones.

Pathogenesis of Acute Kidney Injury in Rhabdomyolysis

The most frequent and life-threatening complication of rhabdomyolysis is AKI, which largely determines the outcome of the disease [38]. In the pathogenesis of rhabdomyolysis-associated AKI three main mechanisms were identified, including renal vascular constriction, formation of renal tubular casts, and direct cytotoxic effect of heme [39, 40].

Myoglobin plays a specific and significant role in the pathogenesis of AKI in rhabdomyolysis. During filtration, myoglobin freely passes through the basal glomerular membrane and accumulates in the renal tubules. In the tubules, due to water reabsorption, myoglobin concentration increases, which leads to its precipitation and formation of casts which obstruct the tubular lumen [41, 42]. In addition, myoglobin potentiates smooth muscle spasm, leading to renal vasoconstriction, which along with dehydration increases water reabsorption and reduces fluid flow in the renal tubules [43–45].

Massive damage of muscle tissue results in a significant increase in urinary production and excretion of uric acid with the formation of crystals, which further obstruct the tubular lumen. Myoglobin and uric acid precipitation is also promoted by intravesical acidosis [46].

Free iron released as a result of myoglobin breakdown has a damaging effect on the kidneys. Free iron can activate lipid peroxidation with the production of free radicals that have a cytotoxic effect on the renal tubules [47, 48].

Moreover, dehydration underlying early rhabdomyolysis can lead to systemic hypoperfusion with associated organ ischemia, including intestines. Intestinal ischemia leads to translocation of microflora into the bloodstream with the development of endotoxinemia, cytokinemia and, later, sepsis and septic shock. These conditions worsen renal hypoperfusion and promote progression of AKI [49, 50].

The Use of Extracorporeal Detoxification Methods in the Treatment of Rhabdomyolysis

After skeletal muscle injury, various substances enter the systemic circulation, causing endogenous intoxication. Given the developing failure of detoxification systems, the use of methods eliminating these substances from the bloodstream is considered a necessary component of pathogenetic therapy. To achieve this goal in the management of rhabdomyolysis, various methods of extracorporeal detoxification (ECD) are used. In the current literature, the effectiveness of ECD at different stages of rhabdomyolysis remains controversial.

Various modifications of renal replacement therapy (RRT) are most commonly used in the treatment of rhabdomyolysis [51, 52]. As a rule, they are employed when AKI has already occurred in order to replace the lost renal function and prevent further kidney damage by circulating endogenous toxins. The concept of proactive use of RRT recommending its initiation before the development of clinically significant AKI in rhabdomyolysis, has not been recognized to date due to the lack of evidence of effectiveness. Recent publications report the results of treatment of patients with rhabdomyolysis complicated by AKI receiving ECT based on diffusion or convection mass transfer and techniques combining both types of mass transfer. Myoglobin has been considered the major pathogenetic factor of kidney damage in rhabdomyolysis, thus the prevention of further progression of AKI lies in the use of RRT techniques capable of myoglobin elimination. With myoglobin molecular weight being 17.8 kDa, the use of RRT in hemodialysis mode with standard dialyzers removing low molecular weight substances is ineffective [53, 54].

Given the pathogenesis of rhabdomyolysis and mechanisms of kidney damage, the so-called cut-off point of the hemofilter membrane and its pore diameter is the crucial factor of choosing the technique of RRT. According to current opinion, the preferred techniques to correct the water, electrolyte and acid-base disorders and azotemia, as well as to effectively eliminate myoglobin in patients with rhabdomyolysis complicated by AKI, are hemofiltration with dialysis or hemodialysis using ultrahigh-flow membrane [55]. The use of continuous hemofiltration using ultrahigh permeability membrane (cut-off point 100 kDa) is characterized by higher values of sieving ratio, clearance and degree of reduction of serum myoglobin compared with the continuous hemofiltration using standard polysulfone hemofilter with cut-off point of 20 kDa [56] in the treatment of AKI-associated rhabdomyolysis.

High efficacy of myoglobin elimination during RRT in hemofiltration mode during treatment of rhabdomyolysis with AKI has been shown [57]. According to the results of this study, myoglobin clearance after 2, 6, 12, and 24 hours after starting the prolonged hemofiltration was 14.3±3.1, 11.5±3.2, 7.5±0.9, 5.6±1.0 ml/min, respectively.

Also, according to many authors, the most effective in terms of myoglobin elimination from the systemic blood flow is the hemodiafiltration technique, which combines diffusion and convection mechanisms of mass transfer. The use of hemodiafiltration is associated with better clearance of myoglobin and larger reduction of its blood level compared with hemofiltration using similar hemofilters. The obtained result is attributed to the implementation of double type mass transfer during hemodiafiltration [58].

A case observation comparing the efficacy of hemodiafiltration and hemofiltration in pre- and post-dilution modes in treating a patient with exertional rhabdomyolysis complicated by AKI has been published. Efficacy of different modes of RRT was assessed by myoglobin clearance and elimination (relative clearance). Clearance and elimination of myoglobin during hemodiafiltration in pre- and post-dilution modes was 10.8 ml/min and 4.3%, 69 ml/min and 23.1%, while during hemofiltration in pre- and post-dilution modes it was 13.3 ml/min and 5.3%, 17.5 ml/min and 5.8%, respectively. The findings indicate greater efficacy of hemodiafiltration in post-dilution mode compared with other studied modes of RRT [59].

A prospective clinical trial also showed the efficacy of hemodiafiltration to reduce blood myoglobin levels. Eighteen patients with severe AKI-associated rhabdomyolysis underwent RRT using ultrahigh-flow hemofilters (cut-off point 45 kDa). Myoglobin clearance during one session was between 90 and 94 ml/min, while its blood level dropped by 80%. Half of myoglobin was eliminated during the first 3–5 hours after the beginning of RRT, and 7% more of total myoglobin level were removed during the next hour of the session [60].

Some researchers believe that RRT based on the diffusion mechanism of mass transfer, also is highly effective in rhabdomyolysis complicated by AKI if a mass exchange device with a high cut-off point is used. Thus, the results of a study comparing the effectiveness of hemodialysis with dialyzers of various permeability in AKI-associated rhabdomyolysis showed that the use of a dialysis machines with 60 kDa cut-off point leads to a 50% reduction in myoglobin over 4 hours of RRT. In contrast, after hemodialysis using a standard machine with 15 kDa cut-off point, there was no decrease in blood myoglobin level [61]. A more recent study confirmed the effectiveness of prolonged hemodialysis using ultra high-permeability membranes for

AKI-associated rhabdomyolysis [62]. Moreover, there are reports of effective use of intermittent hemodialysis using ultra-high permeability machines [63].

Thus, the results of studies reported in the current literature indicate a sufficient efficacy of RRT based both on diffusion and convection mass transfer, using high and ultra-high permeability dialysis machines in the treatment of rhabdomyolysis, complicated by AKI, not only to replace the lost renal function, but also to remove factors of endogenous intoxication from the systemic circulation, primarily myoglobin, thereby preventing the progression and helping eliminate

AKI. Summarizing the research results, we can conclude that the preferred technique of RRT in rhabdomyolysis complicated by AKI is hemodiafiltration, which allows to remove myoglobin and endogenous toxins from the systemic circulation with greater efficiency due to implementation of diffusion and convectional mass transfer. For increasing the efficiency of RRT, dialysis machines with a higher cut-off point and longer duration of the RRT sessions can be used.

The Use of Plasma Separation Methods

To date, there are many studies devoted to the use of apheresis-based ECD methods. The most widely used is plasmapheresis, which consists in non-selective removal of plasma with all its substances, including myoglobin and molecules responsible for the development and maintenance of endogenous intoxication. The main advantages of plasmapheresis include technical simplicity, accessibility and relative low cost. All this makes it possible to perform plasmapheresis sessions in almost any hospital. In addition, the use of plasmapheresis in the treatment of patients with traumatic rhabdomyolysis at the pre-hospital stage in the field has been described. During plasmapheresis, plasma separation can be performed using special devices with plasma filters, gravitational method on a centrifuge or machine-free method [39].

There are few clinical observations of the use of plasmapheresis reported in literature. The application of this technique in a patient with exertional rhabdomyolysis, who underwent three sessions of plasmapheresis with the plasma replacement volumes of 1300-1500 ml was reported. This therapeutic approach was associated with a significant reduction in myoglobin in the blood and urine, the recovery of renal function was also noted [64]. Similar positive results were obtained when using plasmapheresis with a replacement volume of 29.3% (1000 ml) in a patient with long-term compression syndrome due to acute heroin poisoning [65]. Successful use of plasmapheresis in a patient on simvastatin and gemfibrozil with toxic rhabdomyolysis has also been reported [66]. The effectiveness of plasmapheresis in the management of rhabdomyolysis was explained by the removal of medium weight molecular factors of endogenous intoxication, including myoglobin, from systemic circulation. Elimination of these molecules can in some cases prevent damage of the target organs, including kidneys, and, as a consequence, improve the patient's condition and increase the likelihood of a favorable outcome [67]. Entire volume of myoglobin and other toxic substances is distributed throughout the fluid sectors of the body, hence a single plasmapheresis session with replacement of up to 50% of the circulating plasma volume would not lead to a steady decrease in the blood levels of these substances. This disadvantage limits the effective use of plasmapheresis in patients with rhabdomyolysis, complicated by AKI, for detoxification. Several sessions could partially mitigate this disadvantage due to an increase in detoxification efficacy by preventing the release of continuously produced endogenous toxins into the circulation. However, in most cases, even a series of sessions cannot provide the required detoxification [68].

In order to increase the detoxification efficiency, some researchers have proposed to modify the plasmapheresis technique. The main idea of this modification was an increased volume of plasma replacement (more than 50% of the circulating plasma volume). Meanwhile, a direct correlation between the volume of replacement and the efficacy of removal of toxic substances from the blood has been revealed. Thus, the successful use of plasmapheresis in the treatment of rhabdomyolysis caused by fibrates in a patient with terminal chronic kidney disease was reported [69]. The number of publications on successful use of non-selective plasmapheresis in the management of rhabdomyolysis is limited.

The authors of current publications mainly focus on the disadvantages of non-selective plasmapheresis. This method of ECD has restrictions on the plasma replacement volume, which should not exceed 1.5–2.0 times circulating plasma volume, corresponding to 4–6 liters of plasma. Such volume of replacement of the total volume of body fluid, where endogenous toxins are distributed, is not enough to achieve a significant and sustained reduction of toxic substances.

The use of non-selective plasma exchange is inevitably accompanied by a decrease in the blood levels of albumin, immunoglobulins and clotting factors, which can cause serious complications.

Thus, presently, most researchers do not recommend wide and routine use of non-selective methods of apheresis, such as plasmapheresis and plasma exchange, in rhabdomyolysis, due to insufficient safety and limited effectiveness [51, 68, 70].

Selective plasma exchange can potentially have wider application. This option of plasma exchange is safer and more effective compared with the non-selective plasma exchange. Selective plasma exchange consists in filtration of water and some substances dissolved in blood plasma through a microporous membrane. The range of substances eliminated from the blood depends on the pore size of the membrane and, accordingly, the molecular weight of the substances in the blood plasma. The maximum molecular weight of the eliminated substances is comparable to that of albumin (about 66 kDa) or less. This specific feature of the method makes it possible to remove toxic substances with an average molecular weight from the bloodstream and retain important large molecular weight substances, including immunoglobulins and coagulation factors [71].

There exist a variety of plasma separators which differ in the membrane pore size, determining the cut-off point and sieving ratio and, accordingly, the spectrum of substances removed from the plasma. The amount of albumin removed from the plasma directly depends on the pore size of the membrane. Depending on the goals and blood albumin level, the most appropriate plasma separator for clinical use can be selected [71, 72]. The use of plasma separator with smaller pore size leads to less albumin loss and allows elimination of a narrower range of endogenous toxins compared to the plasma separators with larger pore size [71]. If we compare non-selective plasma exchange with selective one, the latter has a greater detoxification effect due to a larger volume of plasma replacement with the same volume of transfusion media (fresh frozen plasma and/or albumin solutions) [73]. Based on a review of the literature on the subject, selective plasma exchange is used mainly in the treatment of hepatic failure [74]. The data of its use in rhabdomyolysis, though, are lacking.

Although there is some evidence of the successful use of plasmapheresis and non-selective plasma exchange in the treatment of patients with rhabdomyolysis for prevention of AKI or its progression, most authors believe that the existing data cannot conclusively demonstrate the positive impact of these methods on the outcome. In addition, some researchers point out that the use of apheresis methods in early rhabdomyolysis can delay intensive therapy or hamper its delivery.

Sorption Methods of Extracorporeal Detoxification

Creation of new selective adsorptive devices capable of removing a certain range of endogenous toxins from the bloodstream has prompted the study of the effectiveness of sorption ECD techniques in rhabdomyolysis. The interest in this subject grew when the CytoSorb adsorption device (Cytosorbents Corp., USA) was developed for extracorporeal binding of endogenous toxins with molecular weight less than 55 kDa. This feature allows the removal of medium molecular weight substances, which include various interleukins and other cytokines, pathogen-associated and damage-associated molecular patterns (PAMP and DAMP). The CytoSorb device can effectively eliminate substances with a high concentration. At the same time the efficiency of their elimination decreases as their concentration in blood falls. This effect is due to the physical and chemical sequelae of hydrophobic interactions, which prevent complete removal of some mediators from the bloodstream [70, 75, 76]. Based on the above properties, selective hemoadsorption using the CytoSorb device has been most widely used in sepsis and septic shock. The majority of published works is devoted to this use of hemoadsorption [77]. However, given the molecular weight of myoglobin, which is 17.8 kDa, selective hemoadsorption using the CytoSorb device can lead to a clinically effective removal of myoglobin from blood and theoretically improve treatment results. Thus, in the last few years, publications on clinical observations of the use of the CytoSorb adsorption device for selective hemoadsorption in rhabdomyolysis started to appear. One of them reports the results of treatment of a patient with traumatic rhabdomyolysis complicated by AKI. Extracorporeal detoxification started with prolonged RRT using an ultrahigh permeability hemofilter. The chosen strategy was not successful in reducing the manifestations of disease. Due to the lack of improvement, selective hemoadsorption was added to the intensive therapy, which resulted in blood myoglobin reduction amidst persisting tissue ischemia [78]. A team of researchers from India described rhabdomyolysis with AKI, which developed as a result of fever induced by influenza B and enterovirus infection. Treatment with selective hemoadsorption using the CytoSorb device was successful [79]. We also found a case report of a patient with 3,4-methylenedioxymethamphetamine poisoning complicated by rhabdomyolysis and multiple organ failure. Selective hemoadsorption performed on the CytoSorb adsorption device was associated with a significant decrease in the levels of intoxicating agent, myoglobin, and interleukin-6. Treatment of this patient also had a favorable outcome [80].

One of the largest published studies on this subject was conducted by a team of German researchers. It included 43 patients with severe rhabdomyolysis. The inclusion criteria were AKI with anuria, blood myoglobin level above 5,000 ng/ml before selective hemoadsorption which was done using CytoSorb adsorption device for at least 90 min. Serial assessment of the blood myoglobin concentration was performed 24–36 hours before hemoadsorption, immediately before the ECD session and 12–24 hours after the start of perfusion. The results of the study showed a significant decrease in blood myoglobin level during selective hemoadsorption. The median myoglobin content was reduced by 29% [81].

The literature data on selective cytokine hemoadsorption using the CytoSorb device in rhabdomyolysis complicated by AKI indicate a fairly high efficiency of this ECD method, which is primarily due to efficient elimination of myoglobin from the systemic circulation. These mechanisms can also contribute to nephroprotective effect, consisting in the prevention of further progression of renal damage and / or in the regression of the existing AKI. Despite these results, the effectiveness of selective hemoadsorption using the CytoSorb device cannot be considered confirmed, since the body of evidence on the subject consists mainly of individual clinical observations. In addition, a large published study on this problem has several flaws due to the lack of a control group [81]. Based on the available data, it is difficult to make a definitive conclusion about the impact of including selective cytokine hemoadsorption on the outcome of patients with rhabdomyolysis complicated by AKI.

In addition to CytoSorb, other adsorption devices for selective hemoadsorption have been developed that can potentially eliminate myoglobin from the bloodstream. Such devices include Desepta (Hemos-DS, Russia), Efferon CT (Efferon, Russia), HA330 (Jafron Biomedical, PRC). These devices were registered in Russia and have been used in practical medicine. However, there are no data on the effectiveness of these devices for selective hemoadsorption in patients with rhabdomyolysis complicated by AKI in the literature so far.

Conclusion

Based on the literature review on rhabdomyolysis, we can see that treatment of patients with rhabdomyolysis, especially severe, remains a challenging issue to date. The greatest interest of researchers is focused on using various methods of ECD along with the other intensive therapy options, for effective elimination of myoglobin, the main factor of endogenous intoxication and AKI development in rhabdomyolysis, from the circulation. Available research results do not provide the necessary evidence of the effectiveness of plasma replacement techniques of ECD. Techniques based on mass exchange devices with high cut-off point are considered to be the most effective. Most authors recognize hemodiafiltration as the most effective of RRT methods. Studying the effectiveness of combined use of RRT and selective hemoadsorption appears to be a promising area of research.

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