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Rapid and Effective Elimination of Myoglobin with CytoSorb® Hemoadsorber in Patients with Severe Rhabdomyolysis

Frederic Albrecht[a] Stefan Schunk[b] Maren Fuchs[a] Thomas Volk[a]
Juergen Geisel[c] Danilo Fliser[b] Andreas Meiser[a]

[a]Department of Anesthesiology, Intensive Care and Pain Therapy, Saarland University Medical Center and Saarland University Faculty of Medicine, Homburg, Germany; [b]Department of Internal Medicine IV, Nephrology and Hypertension, Saarland University Medical Center and Saarland University Faculty of Medicine, Homburg, Germany; [c]Department of Clinical Chemistry and Laboratory Medicine, Saarland University Medical Center and Saarland University Faculty of Medicine, Homburg, Germany

Keywords
Acute kidney injury · Continuous renal replacement therapy · Hemoadsorber · Myoglobin · Renal replacement therapy · Rhabdomyolysis

Abstract
Introduction: Rhabdomyolysis is characterized by destruction of muscle fibers by various causes and is diagnosed by increased creatine kinase concentrations in the blood. Myoglobin released into the blood may cause acute kidney injury. In this randomized controlled study, we hypothesized that myoglobin elimination would be faster when a hemoadsorber was added to a continuous veno-venous hemodialysis (CVVHD). ***Methods:*** Four patients in the control group received CVVHD with a high cut-off hemofilter using high blood and dialysate flows for 48 h. Four patients in the CytoSorb group received the same treatment, but in addition, the hemoadsorber CytoSorb® was inserted in front of the hemofilter and replaced once after 24 h. Blood samples were drawn simultaneously before (pre) and after (post) the hemofilter or else the hemoadsorber, after 5 and 30 min, as well as after 2, 4, 8, and 24 h. All measurements were repeated the next day after the hemoadsorber had been renewed in the CytoSorb group. Primary outcome was the area under the curve (AUC) of the relative myoglobin concentrations as percent of baseline. To evaluate the efficacy of myoglobin removal, relative reductions in myoglobin concentrations during one passage through each device at each time point were calculated. ***Results:*** Patients in the CytoSorb group had a significantly lower AUC during the first 24 h (42 ± 10% vs. 63 ± 6%, $p = 0.029$) as well as during the observation period of 48 h (26 ± 7% vs. 51 ± 12%, $p = 0.029$). The relative reductions for myoglobin were considerably higher in the CytoSorb group compared to the control group during the first 8 h. ***Conclusion:*** Myoglobin concentrations declined considerably faster when CytoSorb was added to a CVVHD. When compared to a high-cut-off hemofilter, efficacy of CytoSorb in myoglobin elimination was much better. Because of saturation after 8–12 h an exchange may be necessary.

Introduction

Severe rhabdomyolysis may be caused by different mechanisms including trauma, ischemia, toxins, infections, or metabolic derangements [1]. Rhabdomyolysis is

karger@karger.com
www.karger.com/bpu

Correspondence to:
Frederic Albrecht, frederic.albrecht@uks.eu

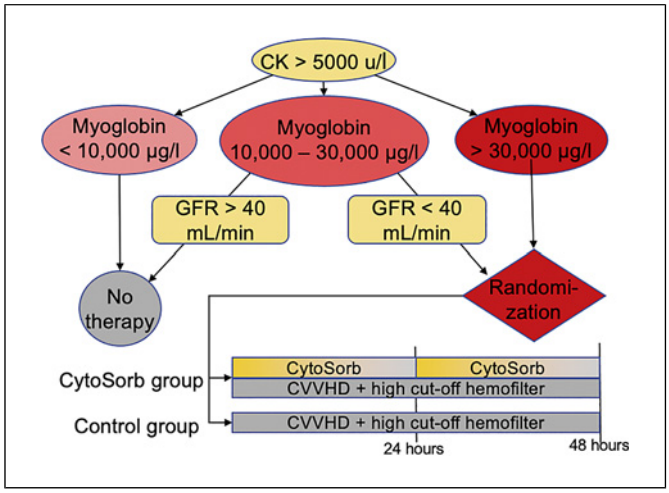

Fig. 1. Study plan: patient inclusion and treatment allocation. CK, creatine kinase; GFR, glomerular filtration rate; CVVHD, continuous veno-venous hemodialysis.

confirmed by increased blood creatine kinase (CK) concentrations. In parallel, myoglobin (Mb) is released from damaged muscle cells into the bloodstream and may cause acute kidney injury (AKI). The clinical picture was first described by Bywaters and Beall in 1941, when 4 patients with crush injuries developed renal failure and died 7 days after initial stabilization [2]. If patients survive the initial phase, renal function often recovers, but structural renal damage persists [1]. In the absence of war and natural catastrophes, the incidence of severe rhabdomyolysis may be as high as 78 per 100,000 hospital admissions, associated with a high mortality (32%) and 50% risk of AKI [3].

Extracorporeal techniques to rapidly remove Mb from the blood have therefore been in the focus of clinical research for decades [4]. Mb elimination can be achieved by hemodialysis or hemofiltration techniques using high cut-off filters and high volumes [5–8], whereas continuous veno-venous hemodialysis (CVVHD) or hemofiltration commonly used in intensive care units do not effectively eliminate Mb [7, 9–11]. Effective Mb removal by the CytoSorb® hemoadsorber (CytoSorbents Europe GmbH, Berlin, Germany) has been described in case reports [11–13] and retrospective studies [8, 14]. However, results from controlled trials are still not available.

In the present randomized study, we evaluated Mb elimination using the CytoSorb hemoadsorber compared to a high-cut-off hemofilter (EMIC®-2, Fresenius Medical Care, Bad Homburg, Germany). Specifically, we hypothesized that Mb elimination would be faster when CytoSorb is added to a CVVHD with the EMIC-2 hemofilter during the first 24 h. In addition, we measured the relative reduction of the Mb blood concentration during one passage through CytoSorb and EMIC-2, respectively.

Materials and Methods

The study was approved by the Local Ethics Committee (Saarland Medical Association, reference HA292/19), and registered at the German clinical trials register (DRKS00021049). Written informed consent was given by the patients or their legal representatives.

Adult patients with severe rhabdomyolysis could be included in the study. The patient inclusion and treatment allocation are shown in Figure 1. If the concentration of CK was above 5,000 IU/L, the Mb concentration was automatically determined. If the Mb concentration was above 30,000 µg/L, patients could be included in the study. Patients could also be included, if the Mb concentration was between 10,000 and 30,000 µg/L, and the glomerular filtration rate calculated from the CKD-EPI formula [15] was below 40 mL/min. Exclusion criteria were pregnancy, participation in another study, previous participation in the same study, lack of informed consent by the patients or their legal representatives, patients permanently unable to give consent, contraindication to or refusal to accept a renal replacement therapy, impossibility to insert a dialysis catheter or to generate high blood flows as high as 200 mL/min, as well as unavailability of a study assistant.

Randomization was accomplished by phone call to the hospital laboratory department, where a randomization list was kept. The internal jugular vein or the femoral vein were cannulated with a 13 French high-flow triple lumen catheter (Joline, Hechingen, Germany). Thereafter, continuous renal replacement therapy with a multiFiltrate Ci-Ca® CVVHD with regional citrate anticoagulation (Fresenius Medical Care AG & Co., Bad Homburg vor der Höhe, Germany) was connected. Patients in the control group were treated with a high blood flow of 200 mL/min and a dialysate flow of 4 L/h, using a high cut-off hemofilter (EMIC-2) for 48 h as standard care. In the CytoSorb group, the CytoSorb hemoadsorber was inserted in front of the hemofilter in the blood circuit and replaced once after 24 h while using the same flows and the same hemofilter as in the control group.

Blood samples were drawn simultaneously before (pre) and after (post) the hemoadsorber in the CytoSorb group, or else the hemofilter in the control group, at the following time points: 5 min, 30 min, as well as after 2, 4, 8, and 24 h. All measurements were repeated in both groups the next day after the hemoadsorber had been renewed in the CytoSorb group. In the control group, we renounced on the first blood sample after 5 min on day 2 since the EMIC-2 hemofilter had not been renewed. Instead, the 24-h values of day 1 were carried forward to the first values of day 2 in the control group. Blood concentrations of Mb, CK, and creatinine were determined.

For the primary endpoint, the area under the curve (AUC) of the patients' Mb-pre concentrations as percent of baseline over 24 h was calculated and compared between groups with Mann-Whitney U

Table 1. Primary and secondary endpoints of the study

Primary endpoint	AUC of the patient concentration as percent of baseline					
Mb	over 24 h			over 48 h		
Secondary endpoints	Relative reduction of the concentration during one passage through each device ($[C_{pre} - C_{post}]/C_{pre}$) at the following time points					
Mb	5 min	30 min	2 h	4 h	8 h	24 h
Creatine kinase	5 min	30 min	2 h	4 h	8 h	24 h
Creatinine	5 min	30 min	2 h	4 h	8 h	24 h

C_{pre}, concentration in front of the device; C_{post}, concentration after the device under investigation.

test. The same evaluation was performed over the whole study period of 48 h. As secondary endpoints, the relative reductions at each time point were calculated as the difference between Mb-pre and Mb-post divided by Mb-pre, expressed as percentage, and compared between groups with Mann-Whitney U test. The same calculations were performed with CK and creatinine concentrations. All primary and secondary endpoints are summarized in Table 1.

Presented *p* values are nominal and are not corrected for multiple testing. As we did not notice significant differences in relative reductions at the specified time points between the two study days, data of the 2 days were pooled together for each group. Because of lack of appropriate data, an a priori power analysis was not possible. For practical reasons and because of limited resources, we planned an interim analysis after 8 patients and determined the maximum number of patients to be 15.

Results

A planned interim analysis was executed after randomization of 8 patients; of those, all concluded the study. We found a significant difference in the primary outcome, consequently recruiting was stopped. A post hoc power analysis yielded an actual power of 93% (effect size of 2.5, α-error 0.05, one-tailed comparison).

Patients in the CytoSorb group were younger compared to the control group and had higher CK plasma concentrations before randomization. Otherwise, patients' biometric data, medical conditions that led to rhabdomyolysis, Mb and creatinine concentrations, and glomerular filtration rates before randomization were similar. All patients suffered from AKI grade II or III according to *Kidney Disease Improving Global Outcomes*. Full patient details are shown in Table 2. Further baseline parameters before randomization and individual patient data are shown in the online supplementary Table (for all online suppl. material, see https://doi.org/10.1159/000534479).

Primary Outcome

Patients in the CytoSorb group had a significantly lower AUC of the Mb concentrations as percent of baseline during the first 24 h (42 ± 10% vs. 63 ± 6%, $p = 0.029$) as well as during the whole observation period of 48 h (26 ± 7% vs. 51 ± 12%, $p = 0.029$, Fig. 2a). Decline of raw values of the Mb concentrations in the CytoSorb group is steep during the first hours but flattens out thereafter. The time course of this effect seems independent of the initial height of the Mb concentration (Fig. 2b).

Secondary Outcomes

The relative reductions for Mb (17.8 kDa) were considerably higher in the CytoSorb compared to the control group during the first 8 h of therapy (Fig. 3a). In the CytoSorb group, the mean values as high as 76% at 5 min were falling to 10% at 8 h. In contrast, in the control group, mean relative reductions for Mb remained below 10% at all time points.

Relative reductions for CK (80 kDa) were low and short-lived with CytoSorb (5 min: 15%; from 2 h: <5%) and close to zero with the EMIC-2 filter (Fig. 3b). Relative reductions for creatinine (0.1 kDa) were close to zero with CytoSorb and remained around 40% with EMIC-2 (Fig. 3c).

We did not notice any adverse events associated with the use of the extracorporeal circuit of the CVVHD plus hemofilter or with the hemoadsorber. All systems were used with the specified blood and dialysate flows without malfunction or interruption during the observation period.

Discussion

In this randomized controlled study, we found a considerably and significantly faster decline of Mb blood concentrations, when the CytoSorb hemoadsorber was added to CVVHD compared to CVVHD alone. This was the case, although in both study groups, high blood flows and high cut-off hemofilters were used.

Severe rhabdomyolysis may be caused by different mechanisms and the underlying condition may by itself determine survival and renal outcome. Bywaters described the clinical course of 70 patients with crushing injuries after being buried under debris during air raids in the London Blitz. Those who survived the initial days

Table 2. Baseline parameters before randomization

	CytoSorb group (n = 4)	Control group (n = 4)	SMD
Age, years	43 [28–56]	69 [63–72]	−1.68
Male sex	4	3	
Height, cm	175 [165–178]	176 [168–184]	−0.34
BMI, kg/m^2	25.1 [23.8–28.2]	29.5 [20.9–34.8]	−0.23
Mb, µg/L	24,406 [22,498–60,236]	20,171 [13,335–31,758]	0.62
CK, units/L	29,960 [5,502–68,655]	12,056 [6,265–16,113]	−2.49
Creatinine, mg/dL	4.0 [1.7–4.6]	2.5 [1.9–3.8]	0.39
GFR, mL/min	18.1 [13.7–19.6]	28.8 [13.3–36.6]	−0.8
Urine, L/24 h	345 [148–2,950]	463 [326–1,180]	0.31
AKI KDIGO grade II	0	1	
AKI KDIGO grade III	4	3	
Underlying condition			
Lower limb ischemia	3	3	
Myositis	0	1	
Long lie trauma	1	0	

Data are presented as median [IQR] or numbers. SMD, standardized mean difference; BMI, body mass index; GFR, glomerular filtration rate; AKI KDIGO, acute kidney injury according to Kidney Disease Improving Global Outcomes.

became anuric and developed a typical clinical picture. At around the seventh day, about one-third suddenly became polyuric, whereas all others died [16].

After the muscle injury, Mb concentrations rise rapidly with a peak after 12 h. As long as renal function remains intact, Mb is rapidly eliminated by the kidney. With a molecular weight of only 17.8 kDa, it is readily filtrated by the glomerulus, reabsorbed by the proximal tubule, and metabolized. However, when the capacity of the proximal tubule is exceeded, Mb molecules pass further down, form casts, and may obstruct and disrupt the nephron. Other mechanisms like oxidative and inflammatory damage as well as vasoconstriction have also been proposed [1]. Already, Bywaters demonstrated in rabbit experiments that Mb does play a major role in the pathogenesis of kidney injury [16].

Therefore, rapid Mb elimination seems crucial to decrease the incidence and severity of AKI, and many techniques have been proposed in the past. If renal replacement therapies are used to eliminate large molecules, high-cut-off hemofilters with large pores as well as large volumes of dialysate and/or replacement fluid are required for efficient removal, and filtration techniques seem superior to pure dialysis. In early case series using high cut-off filters and very high fluid volumes, Mb clearances up to 100 mL/min were reported [5–7]. If high-cut-off filters were used with continuous techniques as commonly used in the intensive care unit setting with much lower fluid volumes, Mb clearances were negligible [9–11]. If continuous techniques were combined with the CytoSorb hemoadsorber, marked decreases of Mb serum concentrations were reported [8, 11, 13, 14]. A marked decrease of Mb concentration was also found, when CytoSorb was used as a standalone application [12]. However, all these were case reports or retrospective studies without proper control group, and none did actually measured Mb elimination by the device.

Efficacy of Mb elimination can be measured as percent reduction in Mb blood concentration during one passage through a hemoadsorber or a hemofilter, respectively. Multiplying this value with the plasma flow will yield Mb clearance. In our study, we found these relative reductions by CytoSorb to be very high at first (around 80% and 40%), but then decreasing to about 10% after 8 h, indicating a saturation effect. Although we were using a high-cut-off hemofilter, which according to the specifications by the manufacturer will allow elimination of molecules up to 45 kDa, its relative reductions were very low, below 10% from the beginning.

After about 8 h the hemoadsorber becomes saturated. Interestingly, very high Mb concentrations at the onset of hemoadsorption do not seem to expedite saturation (see Fig. 2b). We rather assume that other molecules from the blood with similar size may occupy the hollow cavities of the hemoadsorber, thereby impeding further adsorption of Mb. We therefore recommend renewing CytoSorb after 8–12 h if further reduction in Mb concentrations seems indicated. It should be considered that after treatment Mb concentrations may increase again because of re-distribution from other tissues or ongoing muscle destruction.

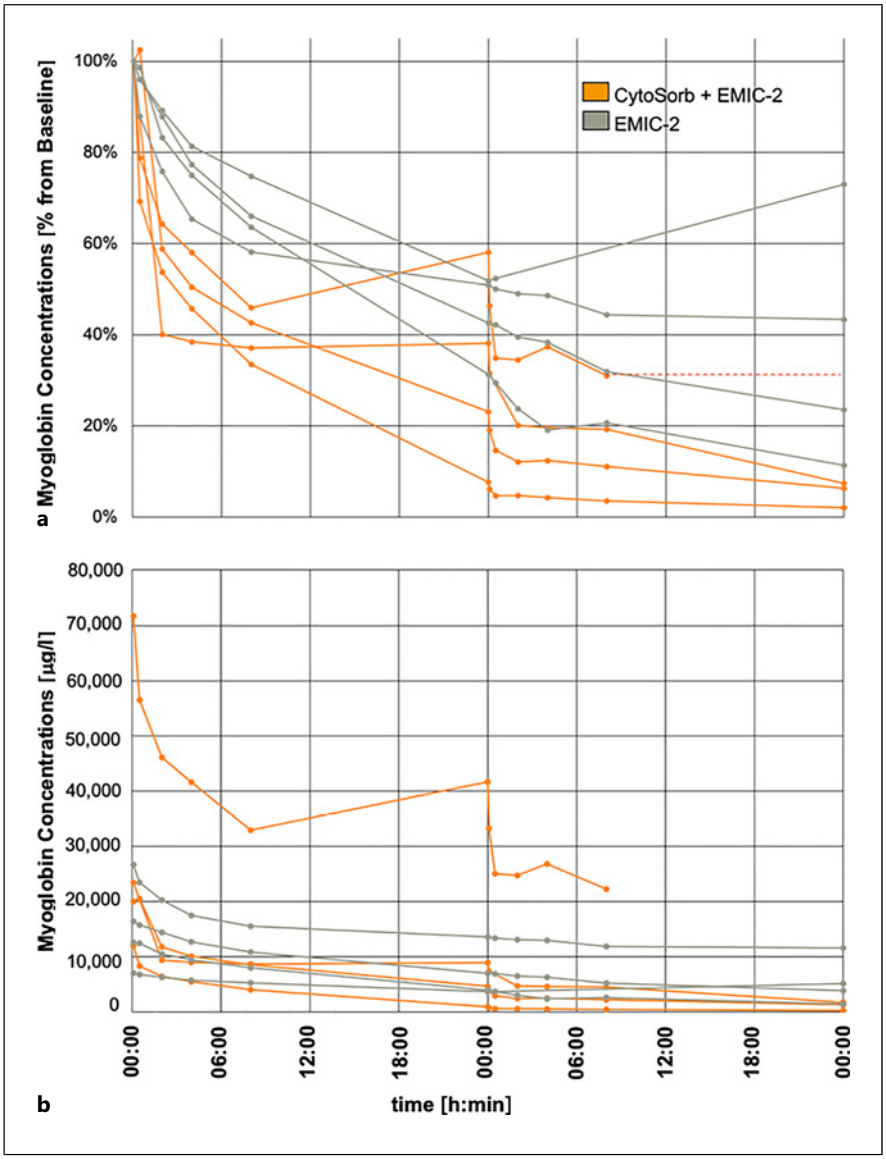

Fig. 2. Mb concentrations of individual patients as percent of baseline (**a**) or else as raw data (**b**) over 48 h. Patients in the CytoSorb group had a significantly lower AUC during the first 24 h (**a**: mean ± SD, 42 ± 10% vs. 63 ± 6%, $p = 0.029$) as well as during the whole observation period of 48 h (26 ± 7% vs. 51 ± 12%, $p = 0.029$). For 1 patient in the CytoSorb group with missing data, the last observation was carried forward (**a**: dotted line).

An early treatment with rapid Mb elimination seems crucial to prevent AKI because not only the height of the concentration but also exposure times are important. In most intensive care units, continuous renal replacement therapies are available, and a hemoabsorber can easily be added, whereas extended high-volume hemofiltration or dialysis techniques are less available as an emergency treatment, e.g., during nightshifts or on weekends.

Relative reductions for CK were low and short-lived with CytoSorb and close to zero with the EMIC-2 filter. Negative values may be explained as a concentration effect, as ultrafiltration was used in all patients to obtain negative fluid balances.

War events or natural catastrophes may result in large numbers of patients with crush injuries, like most recently at the Turkish-Syrian border [17], and many of these will suffer from rhabdomyolysis and possibly AKI. In these cases, rapid elimination of Mb could be achieved with CytoSorb, which can be added to a dialysis machine but can also be used stand-alone with its own external, pump-driven blood circuit available from the manufacturer.

Limitations

The patients studied presented with a variety of possible causes of rhabdomyolysis and a wide range of Mb concentrations. Evaluating the percent fall in Mb therefore seems appropriate.

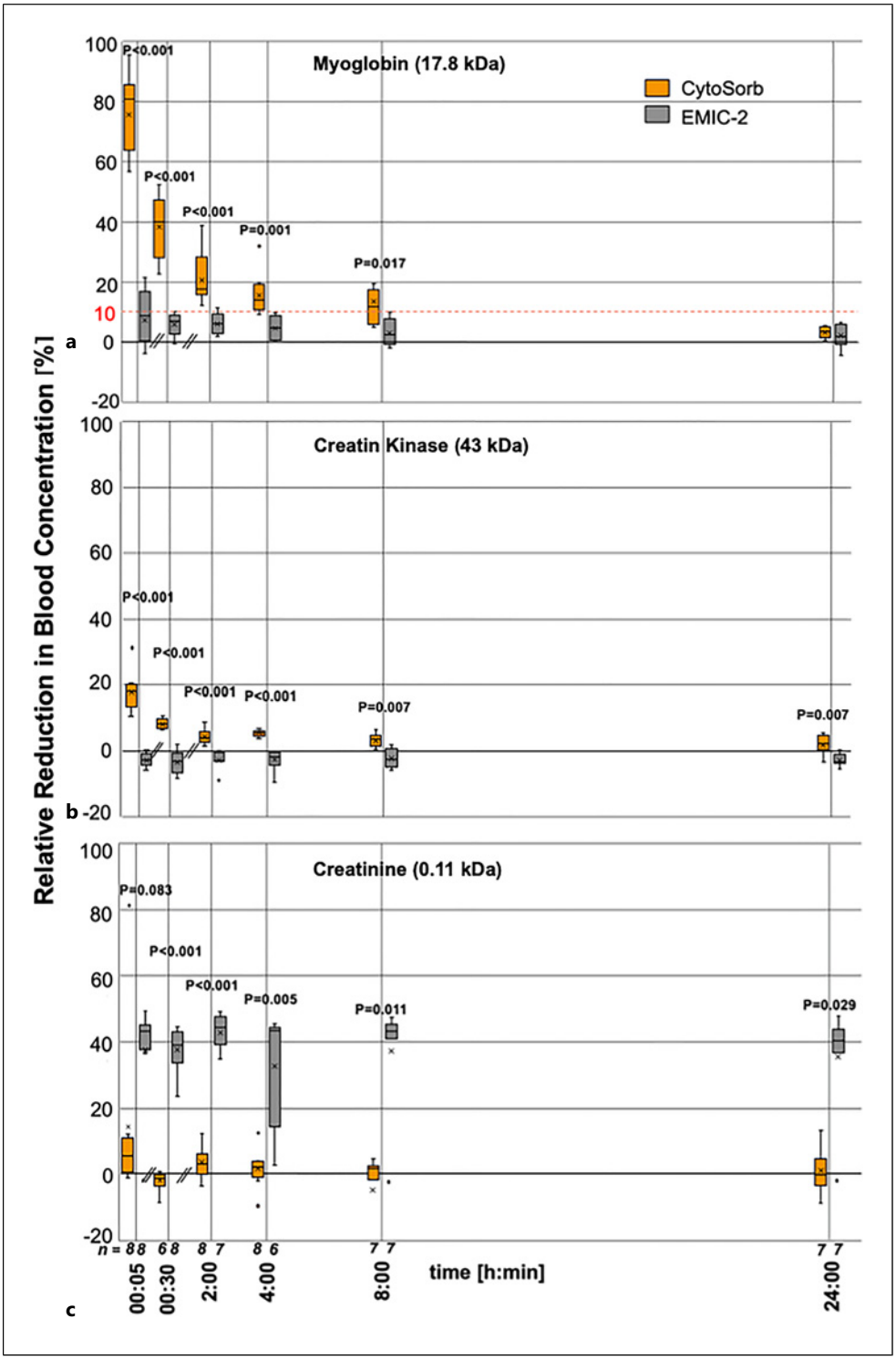

Fig. 3. Box plots (box = quartiles, -- = median, x = mean, antennas = minimum and maximum values, dots = outliers) of the relative reductions of the concentrations of Mb (**a**), creatine kinase (**b**), and creatinine (**c**) during one passage through the hemoadsorber (CytoSorb) or through the high-cut-off hemofilter (EMIC-2) at the prespecified time points. Data from the two study days were pooled together. The number of observations represented by each box is indicated above the time line. *p* values indicate significant differences between the study groups at each time point (Mann-Whitney U test).

Obviously, patients in the CytoSorb group profited from both hemoadsorption and CVVHD alike. A faster decline in Mb concentration was thus expected, but the extent of this with the AUC being reduced by one-third during 24 h and by 50% when looking at 48 h compared to the control group seems clinically meaningful. We cannot exclude other kinetic pathways like renal elimination, hepatic metabolism, or else further Mb release from ongoing rhabdomyolysis (which was the case in 1 CytoSorb patient), but when evaluating the relative reductions in Mb concentrations during passage through the different devices, it is compelling to assume that the observed difference in our main outcome measure is due to the additional hemoadsorption by CytoSorb. Mb levels were not measured in the dialysate. Although the Mb clearance can be calculated from the relative reductions, the amount of Mb collected in the dialysate could have been used to double check.

A uniform threshold for the toxicity of Mb does not exist and probably depends on various factors. According to our study plan, we included patients with Mb concentrations above 30,000 μg/L, when glomerular filtration rate was above 40 mL/min, but also with Mb above 10,000 μg/L, when the glomerular filtration rate was impaired. These a priori chosen limits were consented with our nephrology department, but we do acknowledge that they are arbitrary. We calculated glomerular filtration rate from the latest available serum creatinine before starting the therapy, which may overestimate the glomerular filtration rate if the serum creatinine is on the rise. Measuring creatinine clearance from the urinary ratio divided by serum creatinine would have yielded more precise results. However, this would have implied collecting urine over 24 or at least 12 h and would thus have delayed therapy.

A significantly younger age and significantly higher CK plasma concentrations before randomization in the CytoSorb group may be explained with the small number of patients. Obviously, because of the limited number of patients in this pilot study, outcome comparisons are not meaningful.

We did not measure Mb concentrations between 8 and 24 h. Thereby, we may have missed the point when Mb adsorption by CytoSorb becomes zero or negligible. Therefore, we cannot state whether saturation of the adsorber is complete after 10, 12, or 16 h. But considering the small relative reductions at 8 h, renewal of the adsorber after 8 h or a little later according to convenience, seems indicated.

Conclusion

In this randomized controlled study, Mb concentrations declined considerably faster when the hemoadsorber CytoSorb was added to a continuous hemodialysis. When compared to a high-cut-off hemofilter, efficacy of CytoSorb in Mb elimination was much higher. Because of saturation, CytoSorb should be renewed after 8–12 h if further Mb elimination is indicated. Further randomized controlled trials are justified to examine the influence of CytoSorb on AKI or survival as primary outcome parameters.

Statement of Ethics

This study protocol was reviewed and approved by the Local Ethics Committee (Saarland Medical Association, reference HA292/19), and registered at the German clinical trials register (DRKS00021049). Written informed consent was given by the patients or their legal representatives.

Conflict of Interest Statement

A.M. received honoraria for lectures from CytoSorbents Europe GmbH, Berlin, Germany. All other authors declare no conflict of interest.

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Author Contributions

F. Albrecht and A. Meiser contributed to the conception and design of the work, to the analysis and interpretation of data for the work, and drafting of the manuscript. S. Schunk and D. Fliser contributed to the acquisition, analysis, and interpretation of data for the work. M. Fuchs contributed to the acquisition, analysis, and interpretation of data for the work and drafting of the manuscript. T. Volk contributed to the conception and design of the work, the analysis and interpretation of data, and critically reviewing the manuscript. J. Geisel contributed to the acquisition and analysis of data for the work. All authors reviewed the manuscript critically for important intellectual content and approved the final version to be published. All authors agreed to be accountable for all aspects of the work.

Data Availability Statement

Relevant data are reported in the article. Further inquiries can be directed to the corresponding author.

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