

High cut-off and high-flux membrane haemodialysis in a patient with rhabdomyolysis-associated acute kidney injury

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Middle molecules are eliminated poorly with high-flux (HF) membranes irrespective of the use of haemofiltration or haemodialysis modes. Multiple middle molecule-induced diseases are causally linked to acute renal tubular injury, including cast nephropathy,¹ sepsis² and rhabdomyolysis.^{3,4} Effective removal of such molecules is thus highly desirable.⁵ In response to the limited elimination capacity of HF membranes, "high cut-off" (HCO) membranes were developed for effective middle molecule removal in addition to elimination of small solutes and fluid in patients with acute kidney injury (AKI). Several open-label studies have shown that application of such membranes can improve intermediate end points, such as disease severity for cast nephropathy^{6,7} and sepsis.⁸ Early, effective reduction of serum-free light chains appears to be associated with accelerated renal recovery in myeloma cast nephropathy.⁷

When serum myoglobin concentration rises above a critical point due to saturation of myoglobin-binding proteins, myoglobin in blood is mostly in the free (unbound) form.⁹ Circulating myoglobin (17 kDa) is freely filtered through the glomerular basal membrane, is involved in tubular cast formation, and is a source for tubulotoxic iron compounds.¹⁰ Lowering excessively increased serum myoglobin levels appears to be an important target for a potential renal recovery in patients who develop rhabdomyolysis-associated AKI.¹¹

Conventional HF membranes achieve limited serum myoglobin reduction rates, and studies have primarily reported on sieving coefficients rather than on serum myoglobin levels.¹² In an extensive case report, Naka and colleagues described their experience with a single patient, for whom they used continuous venovenous haemofiltration with HCO membranes in rhabdomyolysis-associated AKI and demonstrated an effective removal of myoglobin from the blood.¹³ Application of HCO membranes during haemodialysis with the potential to further increase myoglobin removal capacity has not yet been described.

We report our data on one session of extended haemodialysis using a HCO membrane (HCO 1100, Gambro, Lund, Sweden; 1.1 m² membrane effective surface area; in-vivo cut-off point of about 60 kDa) compared with that using a standard HF membrane (Polyflux H 140, Gambro; 1.4 m² membrane effective surface area; in-vivo cut-off point of about 15 kDa) in a patient with severe rhabdomyolysis-associated AKI.

ABSTRACT

In a patient with rhabdomyolysis-associated anuric acute kidney injury, an 8-hour haemodialysis session was performed with a large-pore, high cut-off (HCO) membrane (in-vivo cut-off, 60 kDa). Subsequently, during another 8-hour dialysis session, a standard high-flux (HF) membrane (in-vivo cut-off, 15 kDa) was used. Serum myoglobin levels were measured throughout both sessions. HCO haemodialysis reduced myoglobin serum levels by 50% within 4 hours (from 44 946 µg/L to 22 315 µg/L). In contrast, myoglobin serum levels increased from 21 430 µg/L to 34 336 µg/L during HF haemodialysis. Thus, HCO haemodialysis achieved a reduction in serum myoglobin level that is superior to any other renal replacement technique so far.

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Clinical record

An 85-year-old man with peripheral arterial occlusive disease (stage IV with necrosis of left heel) was treated at our intensive care unit for gram-positive septic shock due to community-acquired pneumonia; the patient had respiratory insufficiency and required mechanical ventilation. After effective treatment with piperacillin–tazobactam and clarithromycin, his condition improved and he was transferred to a general ward. Six days later, he suddenly developed cold and pale limbs. Critical ischaemia on both legs due to bilateral occlusion of common femoral artery was diagnosed on duplex sonography. An interventional angiography procedure was performed, but did not succeed in restoring blood flow. After surgical total thromboendarterectomy, he was readmitted to our ICU. Immediately after surgery, the serum myoglobin concentration was 46 768 µg/L (reference interval [RI], < 72 µg/L) — the highest concentration observed for this patient.

The patient developed severe rhabdomyolysis (on ICU readmission: creatine kinase level, 248 µmol/L [RI, < 3.2 µmol/L]; myoglobin concentration, 40 348 µg/L). Table 1 shows further results of biochemical analysis. Type 2 heparin-induced thrombocytopenia was suspected as the cause of the arterial thrombus due to decreasing platelet counts under heparin treatment, and was confirmed by enzyme-linked immunosorbent assay

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Table 1. Results of biochemical analysis during observation period

	Reference interval	9 hours before HD	0 hours (start of HCO-HD)	4 hours	6 hours	8 hours (start of HF-HD)	10 hours	12 hours	16 hours
Creatine kinase (μmol/L)	< 3.2	351.81	343.07	318.80	351.07	364.10	225.66	335.92	369.00
Creatine kinase MB (μmol/L)	< 0.4	5.58	5.78	—	—	—	—	10.96	12.00
Creatinine (μmol/L)	59–104	142	177	—	—	—	—	76	64
Alanine transaminase (μmol/L)	0.17–0.83	2.17	—	—	—	—	—	—	—
Aspartate transaminase (μmol/L)	0.17–0.83	10.23	—	—	—	—	—	—	—
pCO ₂ (mmHg)	35–45	33.3	42.90	41.50	—	36.40	—	32.80	31.70
pH	7.35–7.45	7.47	7.25	7.26	—	7.29	—	7.25	7.17
Standard bicarbonate concentration (mmol/L)	23–27	25.5	18.20	17.90	—	17.90	—	15.20	12.30
Base excess (mmol/L)	–2 to +3	0.3	–7.30	–7.60	—	–7.80	—	–11.70	–15.60
Glucose (mmol/L)	3.5–5.5	15.00	14.90	8.40	—	6.20	—	4.20	2.30
Lactate (mmol/L)	0.55–2.2	3.1	4.00	7.50	—	7.30	—	10.00	12.50

HCO = high cut-off. HD = haemodialysis. HF = high-flow. — = not done.

(ELISA; GTI Diagnostics, Aachen, Germany). Heparin therapy was immediately discontinued, and intravenous treatment with argatroban, a direct thrombin inhibitor, was started for anticoagulation.

Nine hours after surgery, the patient's serum myoglobin concentration was stable (44 946 μg/L) and he developed anuric AKI and lactic acidosis (pH, 7.0; base excess, –9.0 mmol/L, lactate concentration, 7.3 mmol/L [RI, 0.55–2.2 mmol/L]), with the need for renal replacement therapy. Therefore, we commenced extended haemodialysis with an HCO membrane for 8 hours followed by HF haemodialysis for another 8 hours. Both sessions were conducted with a Genius 90 single-pass batch dialysis system (Fresenius Medical Care, Bad Homburg, Germany), allowing comparison of myoglobin removal from the serum during HCO and HF haemodialysis using the same dialysis machine, dialysis duration, blood and dialysis flow and filtration rate. Ultrafiltration in both settings was 50 mL per hour. Blood and dialysate flows on the Genius system were set at 220 mL per hour. The Genius system has been increasingly used for slow low-efficiency daily dialysis, a mode of blood purification that is characterised by high efficiency and cardiovascular stability.^{14–16}

Within 4 hours of HCO haemodialysis, serum myoglobin levels fell by about 50%. During the following 2 hours, HCO haemodialysis further reduced serum myoglobin concentration slightly (Figure 1). After 6 hours of HCO haemodialysis, a plateau in serum myoglobin concentration was reached. After 8 hours of HCO haemodialysis, the dialyser was switched to a HF haemodialysis. After this change, myoglobin serum levels rose from 21 430 μg/L to 34 336 μg/L, an increase of 63% (Figure 1).

At the time of dialyser exchange, we found no clinical signs of a changed condition that could explain an increase in myoglobin production or release. Cardiovascular stability

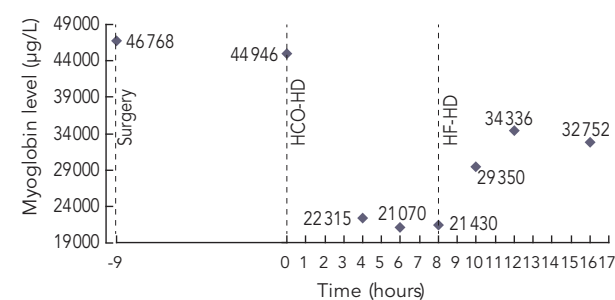
(noradrenaline dose ranged between 22 and 26 μg/kg/h during HCO and HF haemodialysis) and ventilation indices were similar during HCO and HF haemodialysis (inspiratory pressure, 18 mmHg; positive end-expiratory pressure, 5 mmHg; respiratory rate, 22 breaths/min; FiO₂, 35%). At the time of dialyser exchange, there were no signs of worsening inflammatory processes such as sepsis (during haemodialysis, body core temperature ranged from 36.3°C to 37.8°C and C-reactive protein concentration was 90 mg/L [RI, < 5.0 mg/L] before haemodialysis was commenced).

After the two haemodialysis sessions, dialysis treatment was ceased because of multiple organ failure and poor prognosis. The patient died the following day.

Discussion

For our patient, we chose to use HCO membrane haemodialysis because of the advantageous ratio of effective elimination

Figure 1. Serum myoglobin concentration over time during HCO-HD and HF-HD



HCO = high cut-off. HD = haemodialysis. HF = high-flow.

Key messages

- High cut-off membranes used in dialysis settings reduce serum myoglobin level substantially and more rapidly than previously reported for continuous haemofiltration.
- Elimination capacity of myoglobin for high cut-off membranes is superior to that of high-flux dialysers.

of middle molecules while preserving serum albumin.⁸ We used extended haemodialysis to maximise serum myoglobin reduction and to pursue a therapeutic option for the patient, who had severe, presumably ongoing, rhabdomyolysis with subsequent anuric AKI. To our knowledge, we describe the highest reported rate of serum myoglobin level reduction within a single haemodialysis session.

Before the commencement of HCO haemodialysis, serum myoglobin concentrations were stable over 9 hours. However, we achieved rapid, effective reduction of serum myoglobin concentrations during HCO haemodialysis. In contrast, the myoglobin concentration immediately and substantially increased during HF haemodialysis, presumably due to ongoing myoglobin production and release into the serum in the presence of limited removal capacity of HF dialysis membranes. Other explanations seem unlikely and, clinically, there was no new muscular ischaemic or traumatic event at the time of filter change from HCO to HF membranes.

Gondouin and Hutchison described a myoglobin sieving coefficient of 0.9 for the Gambro HCO 1100 dialyser, making a reduction of serum myoglobin levels by this intervention in our patient likely.¹¹ Similar to our serum reduction rate of about 50%, serum level, reduction of free light chains by 35%–70% were reported by Hutchison and colleagues using the HCO 1100 dialyser.¹⁷

Estimated sieving coefficients for myoglobin in conventional HF membranes ranged between 0.11 and 0.14,¹² reflecting the limited capacity of serum myoglobin during HF haemodialysis that we observed in our patient.

Previously, Naka and colleagues reported a 50% reduction of serum myoglobin concentration after 17 hours of HCO continuous venovenous haemofiltration.¹³ Further, their report showed increasing myoglobin clearance when higher ultrafiltration rates were used during continuous haemofiltration. Common dialysis settings for chronic kidney damage patients are set up with blood flow rates at 350 mL/min, dialysate flow rates of 500 mL/min and about 500–1500 mL ultrafiltration per hour. We hypothesise that HCO haemodialysis with higher blood and dialysate flow rates might be even more effective for myoglobin removal.

Over time, dialysis membrane pores may become congested by a protein layer.¹⁸ Therefore, switching the HCO dialyser when a plateau elimination of the substance is reached, which

was about after 6 hours in our patient, might have further increased effectiveness for myoglobin elimination.

Finally, there are strengths and limitations of this case study. In an anuric patient, glomerular filtration rate is zero; therefore, myoglobin reduction was achieved exclusively by the HCO membrane and not by the kidney. No wash-out period was allowed between HCO and HF haemodialysis, as the patient needed immediate and ongoing renal replacement therapy. Dialysis membranes (HCO/HF) were not randomly allocated as only one patient was treated with both dialysers. We did not specifically measure pre- and postfilter myoglobin levels, as our primary end point was serum myoglobin reduction, a patient-related outcome.

Conclusion

Extended haemodialysis using an HCO membrane achieved a substantial reduction in serum myoglobin levels much more rapidly than previously reported with haemodialysis dialysers or during continuous haemofiltration settings. After the membrane was switched to a HF membrane, myoglobin levels rose substantially within hours.

Additional efforts should be made to further evaluate renal replacement therapies techniques using HCO filter membranes in patients who develop rhabdomyolysis-associated AKI. Whether early, effective reduction of blood myoglobin load will preserve kidney function or accelerate renal recovery and improve patient outcomes remains to be determined in larger patient cohorts.

Competing interests

None declared.

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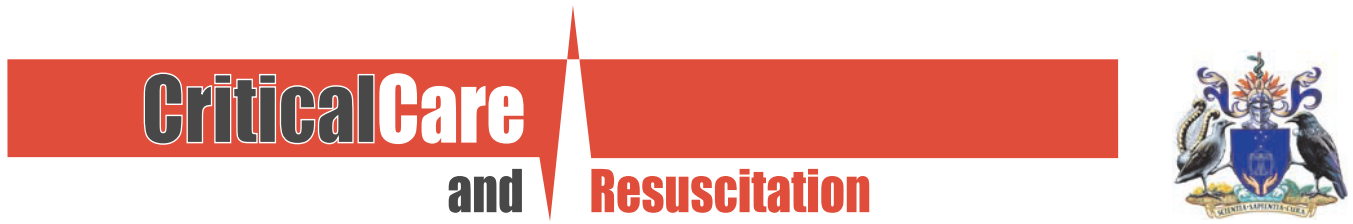
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