Use of Renal Replacement Therapy in a Neonatal Foal with Postresuscitation Acute Renal Failure

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A 1-hour-old 64.1 kg Thoroughbred filly was presented to Iowa State University’s Lloyd Veterinary Medical Center because the foal was unresponsive and in cardiopulmonary arrest. Aggressive cardiopulmonary cerebral resuscitation was administered to the foal, which revived the foal; however, acute renal failure developed. Fluid retention and azotemia occurred although the foal was alert and able to suckle. A 6-hour renal replacement therapy session using hemodiafiltration and a continuous replacement therapy machine was administered to the foal at 3 days of age which lowered the foal’s azotemia and facilitated removal of some of the excess body fluid. Despite therapy, the foal developed pulmonary edema and was euthanized. Although the foal in this case did not survive, this report highlights the possibility of developing postresuscitation complications such as acute renal failure and describes the use of renal replacement therapy using hemodiafiltration as a viable option in neonatal foals with acute kidney injury.

Key words: Cardiac arrest; Cardiopulmonary resuscitation; Continuous renal replacement therapy; Hemodialysis.

Abbreviations:

ARF acute renal failure
CPA cardiopulmonary arrest
CPCR cardiopulmonary cerebral resuscitation
CrCl creatinine clearance
CRI continuous rate infusion
CRRT continuous renal replacement therapy
RRT renal replacement therapy
URR urea reduction rate

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included administration of a furosemide CRI (0.12 mg/kg/h IV). At 72 hours of age, the foal was ambulatory and alert, but due to progressive azotemia and fluid retention, renal replacement therapy (RRT) was elected with the goals of partial removal of excess body fluid and partial correction of azotemia to allow added time for the kidneys to regain function.

The foal was sedated with diazepam (0.08 mg/kg IV) and a 14 French, 28 cm, double lumen hemodialysis catheter was placed in the jugular vein using the Selding-ger technique and venous cutdown. The foal was administered a bolus (100 IU/kg) followed by a CRI (50 IU/kg/h) of unfractioned heparin and a commercial acrylonitrile-sodium methallyl sulfonate copolymer hollow-fiber hemodiafiltration set with a surface area of 1.5 m² was used with the noted initial RRT settings: blood flow rate of 50 mL/min, dialysate rate of 4000 mL/h, postfilter fluid replacement rate of 4000 mL/h and patient fluid removal rate of 300 mL/h (Table 2). Plasmalyte was used as the dialysate and replacement fluid. A 6-hour intermittent hemodiafiltration treatment was administered utilizing a continuous renal replacement therapy (CRRT) machine with vital parameters recorded every 30 minutes. The blood flow rate through the CRRT machine was gradually increased to a maximum of 280 mL/min and the patient fluid removal rate increased from 300 to 600 mL/h. The heart rate (mean 97 beats/min; range 80–100 beats/min) and respiratory rate (mean 28 breaths/min; range 12–44 breaths/min) remained stable but rectal temperature declined from 101.3°F at the start of the session to 94.6°F at the end. The PT and aPTT after 3 hours of RRT was 18.5 seconds (reference interval, 14.3–18.4 seconds) and 160 seconds (reference interval, 49.9–69.4 seconds), respectively. The foal sucked from the mare every 2 hours while being connected to the CRRT machine. The total fluid removal from the foal during the RRT session was 1703 mL correlating with a 1.1 kg loss in body weight (72.1 kg). The BUN and serum creatinine concentrations decreased from 63 mg/dL and 10 mg/dL, respectively, at the start of RRT to 42 mg/dL and 6.7 mg/dL at the end of RRT, respectively. The foal remained oliguric during the RRT session producing approximately 50 mL of urine over the 6-hour session.

The creatinine clearance (CrCl), representing the volume of blood cleared of creatinine per minute excretion of urine (or in the case of RRT, effluent), was calculated. Because of mislabeled samples, CrCl was only calculated over the 4th and 5th hour time periods (Tables 2 and 3) using the following formula:

$$CrCl = \frac{\text{Uritrate} \ [\text{Cr}] \times \text{Effluent output} \ [\text{mL}]}{\text{Time} \ [\text{minutes}] + C_{20} \times C_{21}}$$

### Table 1. Clinicopathologic data from a newborn foal during and after the immediate postresuscitation period.

| Foal Age (hours) | 1a | 1.5a | 2b | 2.5a | 3a | 4b | 12a | Reference Interval a |
|-----------------|----|------|----|------|----|----|-----|----------------------|
| pH              | 6.604 | 6.721 | 6.971 | 7.027 | 7.223 | 7.262 | 7.347 | 7.34–7.36 |
| pCO₂ (mmHg)     | 100.0 | 53.8 | 39.3 | 63.4 | 43.0 | 52.4 | 56.4 | 42.3–48.1 |
| pO₂ (mmHg)      | 56.2 | 62.3 | 194.1 | 59.3 | 56.4 | 95.3 | 37.1 | 34.7–45.3 |
| SO₂ (%)         | 41.5 | 57.6 | 98.4 | 73.3 | 82.1 | 96.0 | 64.4 | 64.7–83.1 |
| HCT (%)         | 20 | 17 | 14 | 16 | 22 | 25 | 22 | 37–49 |
| HCO₃⁻ (mmol/L)  | 10.0 | 7.0 | 9.1 | 16.8 | 17.9 | 23.8 | 31.2 | 27.6–30.7 |
| Lactate (mmol/L)| 17.4 | 16.5 | 14.3 | 13.0 | 13.8 | 14.8 | 5.1 | 1.9–5.7 |

| Reference Interval a |
|---------------------|
| Venous blood. |
| Arterial blood. |

### Table 2. Clinicopathologic data a from a postresuscitation foal with acute renal failure before, during, and after a 6-hour CRRT session. Reference interval for serum samples.

| Foal Age (hours) | 1 | 4 | 24 | 48 | 72 | 76 | 80 | 81 | 82 | 96 | Ref Interval |
|-----------------|---|---|----|----|----|----|----|----|----|----|-------------|
| RRT (hours)     | +4 | +5 | +6 |
| Na⁺ (mEq/L)     | 139 | 140 | 135 | 129 | 127 | 127 | 128 | 124 | 127 | 124 | 127 | 125 | 137–145 |
| K⁺ (mEq/L)      | 5.4 | 3.6 | 3.7 | 3.8 | 4.5 | 4.5 | 4.4 | 4.1 | 4.3 | 4.1 | 4.9 | 5.1 | 2.7–4.8 |
| Cl⁻ (mEq/L)     | 109 | 94 | 94 | 90 | 89 | 89 | 94 | 99 | 94 | 100 | 96 | 95 | 102–114 |
| Phos (mg/dL)    | – | 6.1 | 5.0 | 6.3 | 6.5 | 5.5 | 3.6 | 5.6 | 3.5 | 5.6 | 6.1 | 2.6–5.0 |
| Ca²⁺ (mg/dL)    | – | 10.0 | 9.2 | 11 | 11 | 11.5 | 8.0 | 11.7 | 8.3 | 12 | 11.4 | 10.6–12.8 |
| HCO₃⁻ (mmol/L)  | 10 | 18 | 34 | 33 | 33 | 33 | 25 | 20 | 26 | 18 | 22 | 22 | 24.5–33.5 |
| BUN (mg/dL)     | 17 | 15 | 32 | 41 | 63 | 63 | 46 | 35 | 48 | 32 | 42 | 61 | 14–21 |
| Creat (mg/dL)   | 2.7 | 2.8 | 6.4 | 8 | 10 | 10 | 7.5 | 5.3 | 7.6 | 4.7 | 6.7 | 8.3 | 1.0–2.1 |

| Reference Interval |
|---------------------|
| Vitros 5,1 FS Chemistry System, Ortho Clinical Diagnostics, Raritan, NJ |
| Number in italics indicate values for effluent |

**Note:**
- "aVenous blood.
- "bArterial blood."
Renal Replacement Therapy in a Neonatal Foal

Table 3. Renal replacement data for a foal with acute renal failure. Total procedure time was 6 hours and 40 minutes with a 5-hour and 2-minute actual run time.a

| RRT (hours) | Actual Time |
|-------------|-------------|
|             | 1,220       | 1,300 | 1,400 | 1,500 | 1,600 | 1,700 | 1,800 | 1,900 | Total |
| Patient Fluid Removal (mL) | 0 | 72 | 171 | 239 | 300 | 345 | 425 | 151 | 1,703 |
| Replacement Fluid Prefilter (mL) | 0 | 1,267 | 3,614 | 3,772 | 3,297 | 3,080 | 3,399 | 1,190 | 19,619 |
| Dialysate (mL) | 0 | 1,261 | 3,610 | 3,816 | 3,289 | 3,060 | 3,397 | 1,188 | 19,621 |
| Effluent (mL) | 0 | 3,394 | 7,395 | 7,827 | 6,886 | 6,485 | 7,221 | 2,529 | 41,737 |

aProcedure time indicates the total time in which patient was interfaced with RRT machine; run time indicates time in which blood was being processed through filter but does not include time where system was on standby to allow for fluid bag changes, emptying of effluent bags, and correcting alarms.

The urea reduction ratio (URR), representing the percentage decrease in urea over the RRT session, was calculated using the following formula:

\[
\text{URR} = \frac{\text{pre-BUN} - \text{post-BUN}}{\text{pre-BUN}} \times 100
\]

The CrCl over the 4th and 5th hour times were 81.1 and 66.8 mL/min of effluent, respectively. Creatinine clearance expressed based on body weight (mL/kg/min) was 1.27 and 1.04 mL/kg/min, respectively. The URR over the CRRT session was 33%.

During and after the RRT session, the foal was continued on the CRI of furosemide. The body temperature continued on the CRI of furosemide. The body temperature returned to 100.6°F 6 hours after completion of the RRT session, and vital parameters were within acceptable ranges. The foal produced approximately 90 mL of urine over the next 12 hours; however, the following morning (96 hours old), the foal’s BUN and serum creatinine increased to 61 mg/dL and 8.3 mg/dL, respectively and the body weight increased to 76.4 kg along with worsened facial, pectoral and limb edema. Furthermore, labored respiratory effort (respiratory rate 32 breaths/min) and blood-tinged froth were noted from both nares. Based on the deterioration of clinical condition, continued lack of substantial urine production, exhausted financial resources, and poor prognosis, the foal was euthanized.

Postmortem examination confirmed diffuse subcutaneous, pulmonary, and renal edema with tri-cavitary effusion. The lungs, kidneys, and heart had multifocal petechial hemorrhages and generalized loss of body fat was present. Microscopic changes within the kidney included multifocal infarction associated with multiple intravascular thrombi and necrosis and sloughing of tubular epithelial cells accompanied by evidence of epithelial cell regeneration. Centrilobular necrosis was present within the liver, and multifocal neuronal necrosis was identified within the brain. This constellation of lesions was interpreted as secondary to hypoxic injury. In addition to pulmonary edema, a mild bronchopneumonia with intra-alveolar squames was observed, with the latter observation considered indicative of in-utero stress.

The equine industry involves a continuous cycle of breeding mares and monitoring pregnancy and parturition leading to the common presentation of newborn foals in various levels of critical illness, and at times cardiopulmonary arrest (CPA), to equine clinicians. To date, very few case reports describing CPCR in foals have been published in the literature and the low numbers of cases that have been described have not survived the initial CPA.1 As a result of the dearth of reported cases, postresuscitation complications have not been detailed in foals, as compared to the numerous complications, commonly referred to as postcardiac arrest syndrome, observed in people.2,4 These complications include brain injury, myocardial dysfunction, and acute kidney injury (AKI).2,4 Organ dysfunction results from a combination of insults including ischemia-reperfusion injury and the systemic inflammatory response syndrome,2,4 Cytokines, adhesion molecules, impaired vasculature, increased inflammation, hypoperfusion, and endotoxin contribute to organ injury, dysfunction and potentially organ failure.2,4 The reported incidence of AKI in people after CPA and CPCR ranges from 12 to 80%, depending on how AKI is defined.5,5–7 The duration of postresuscitation hypotension might be associated with AKI as hypotension was significantly longer in people with AKI as compared to the non-AKI group.3 The complete mechanism by which AKI develops post-CPA and CPCR is not fully elucidated; however, initial ischemic injury to the kidney during CPA and resuscitation might cause sublethal renal tubular injury; subsequently, reperfusion injury, hypoperfusion, or both from circulatory shock may result in further injury.3,7 In the case here, ischemia and low oxygen carrying capacity due to low hemoglobin concentration along with increased activity of the coagulation system likely contributed to the development of acute renal failure (ARF) as tubular necrosis, a lesion related to ischemia, as well as multifocal infarction and intravascular thrombi were noted on microscopic examination.8 The lack of thrombi within other organs suggests that the renal thrombi were secondary to renal damage or a direct cause of AKI rather than a systemic coagulopathy. Further microscopic evidence of ischemia included infarcts to the central nervous system (centrilobular necrosis), brain, and liver (centrilobular necrosis), but clinical manifestations of these lesions were not apparent. Another variable that might contribute to development of AKI in this case was the administration of hetastarch, which has been associated with AKI and decreased outcome in dogs;9 however, nephrotoxicity has not been demonstrated in equine patients.
Renal replacement therapy including intermittent hemodialysis, intermittent hemodiafiltration, CRRT, and peritoneal dialysis, has been rarely implemented in adult horses and foals.\textsuperscript{10-13} In 1 case, a 4-day-old foal with oxytetracycline-induced ARF was anesthetized on 3 separate occasions to allow intermittent hemodialysis treatments over a 4-day period and was reportedly healthy at 2 years of age.\textsuperscript{12} Intermittent and continuous peritoneal dialysis has also been used in a few horses to treat ARF with some success.\textsuperscript{10,13} Intermittent hemodialysis, hemodiafiltration, and CRRT are a blood purification modality available on CRRT machines and is similar to intermittent hemodialysis in that the patient’s blood is passed through thousands of straw-like semipermeable membranes contained within a dialyzer.\textsuperscript{14} However, in addition to diffusion principles that promote blood purification in intermittent hemodialysis, hemodiafiltration uses convection (solvent drag) and adsorption (adhesion) to facilitate blood purification.\textsuperscript{14,15} Hemodiafiltration employs a slow and gradual purification process, as compared to intermittent hemodialysis, allowing better control of blood pressure surges associated with blood volume imbalances and can also remove fluid volume overload as well as assist in clearance of nephrotoxic drugs, toxins, and toxic metabolites.\textsuperscript{15,16} The foal presented here tolerated the CRRT procedure well for the 6-hour session and was maintained in lateral recumbency by hospital staff during the procedure; additional sedation or anesthesia was not required. Furthermore, the foal was not agitated during the procedure; additional sedation or anesthesia was not required. Furthermore, RRT continued while the foal was asleep in the future.

Subjectively, anticoagulation was adequate for the case here (18.5 seconds) was similar to healthy adult horses (mean PT 20.6 seconds); however, prolongation of the PT (160 seconds) was not as dramatic as healthy adult horses (PTT > 245 seconds) despite using the same dose of heparin.\textsuperscript{11} A difference in the pharmacokinetics or pharmacodynamics to heparin might explain the differences noted between adult horses and neonatal foals.\textsuperscript{20} Subjectively, antiocoagation was adequate for the case here as there was no evidence of clotting within the dialyzer (dark blood, blood streaks or fibrin) nor increased pressures within the circuit.\textsuperscript{21}

The CrCl in the foal presented here was 81.1 and 66.8 mL/min of effluent, over the 4th and 5th hours respectively, as compared to an average of 68.9 mL/min of effluent in healthy adult horses.\textsuperscript{11} In comparison, 1 report described a CrCl of 40.9 mL/min and 12.5 mL/min with continuous and intermittent peritoneal dialysis, respectively, in an adult horse with ARF.\textsuperscript{10} However, when body weight of the patient is considered, the CrCl in this report (1.27 and 1.04 mL/kg/min) was much higher than that measured in healthy adult horses (0.127 mL/kg/min) undergoing RRT, thus suggesting that RRT has more potential to effectively treat azotemia in foals as a result of their smaller blood volume as compared to adult horses.\textsuperscript{11} Additionally, CrCl in the foal in this report was more efficient than peritoneal dialysis described in adult horses which documented a CrCl of 0.105 mL/kg/min and 0.03 mL/kg/min with continuous and intermittent dialysis, respectively.\textsuperscript{10} Moreover, both the serum creatinine concentration and BUN (URR) dropped by 33% over the RRT session in the foal presented here. Of note, the case presented here was treated on an emergency basis, which prohibited more calculated sample and data collections. Therefore, solute clearance could only be calculated at arbitrary time points. While a full discussion regarding the factors that contribute to clearance of uremic solutes is beyond the scope of this case report, the variables reported (i.e., prereplacement fluid, dialysate, effluent) are reported to illustrate relevant dialysis prescription parameters that are determinants of solute clearance and serve as a starting point for future cases. With the feasibility of this RRT platform demonstrated in this case, the opportunity to better characterize solute clearance should be seized in the future.

Fluid retention was noted in the foal described here, evidenced by 9.1 kg gain in body weight and generalized edema over the first 48 hours of life. During the RRT session, total fluid removal from the foal (1703 mL) correlated with a 1.1 kg loss in body weight (72.1 kg), suggesting that intermittent hemodiafiltration can effectively remove excess fluid volume from neonatal foals with volume overload. Renal replacement therapies are designed to remove excess fluid from the body, but hemodynamic stability is dependent on refilling of the intravascular space with fluid from the interstitium.\textsuperscript{21} The speed at which the intravascular space is replenished (plasma refill rate) dictates and limits the amount of intravascular fluid that can be removed.\textsuperscript{21} Hemodiafiltration allows slow and constant removal of fluid from the patient, providing hemodynamic stability
as excess fluid is removed whereas intermittent hemodialysis is associated with more rapid fluid shifts and less hemodynamic stability. Thus, hemodiafiltration may be a therapy for treating hypervolemia in horses with AKI or congestive heart failure.

In summary, although the foal in this report did not survive, this report highlights RRT as a novel and viable therapeutic option for foals with ARF. Although the incidence of CPA and postcardiac arrest syndrome in foals is not known, clinicians and support staff should be familiar with CPRC techniques, maintain a properly equipped facility to allow rapid administration of CPCR, and be aware of postcardiac arrest complications. In addition, RRT may be a viable option to facilitate recovery from anuric or oliguric ARF and facilitate removal of excess fluid volume in neonatal foals. In retrospect, longer (i.e. 10–12 hours) and repeated (2–4 sessions) RRT session may have improved outcome and allowed further correction of azotemia and removal of excess fluid from the patient, both of which might have provided more time to recover renal function. This point serves to highlight some of the current limitations of RRT in foals to allow modification of this treatment modality in future clinical cases. First, treatment times must be extended to allow adequate time for solute and excess fluid removal. Second, a team of veterinarians and support staff must be available to perform extended or continuous treatments. Lastly, RRT-induced hypothermia must be addressed by warming fluids involved in RRT along with provision of external methods of warming the patient. Notwithstanding, this case is the first to describe the postcardiac arrest complications (ARF) and RRT in a neonatal foal, but further investigation are needed to advance equine critical care.

Footnotes

a Epinephrine, IMS Limited, El Monte, CA
b Dobutamine, Hospira Inc., Lake Forest, IL
c Plasmalyte, Baxter Healthcare, Deerfield, IL
d 6% Hetastarch, Braun Medical, Bethlehem, PA
e Lactated Ringer’s Solution, Abbott Laboratories, North Chicago, IL
f Cefiofur, Zoetis Inc., Kalamazoo, MI
g Furosemide, Merck, Madison, NJ
h 20% Mannitol, Nova Tech Inc., Grand Island, NE
i Diazepam, Hospira Inc., Lake Forest, IL
j Dialysis Catheter, Medcomp, Harleysville, PA
k Heparin, Fresenius Kabi, Lake Zurich, IL
l Prismaflex M150 hemofilter set, Baxter Healthcare, Deerfield, IL
m Prismaflex, Baxter Healthcare, Deerfield, IL

Acknowledgment

Conflict of Interest Declaration: Authors declare no conflict of interest.

Off-label Antimicrobial Declaration: Cefiofur was used off-label.

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