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Continuous Renal Replacement Therapy of Chronic Kidney Disease with Uncontrolled Azotemia in Six Dogs

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Abstract : The purpose of this case report was to present the treatment of continuous renal replacement therapy (CRRT) in dogs with end-stage CKD with uncontrolled uremia. Hemodialysis were carried out 6 patients who failed to improve clinical status with conventional management for CKD. Four dogs with urea reduction ratio (URR) range of 57-72% and 1 dog with URR of 37.3% showed good outcome with decreasing tendency of pre-dialysis Therefore, we suggest that CRRT could be recommended for use in CKD dogs with uncontrolled azotemia or uremia and should be monitor carefully throughout the CRRT.

Key words **:** Azotemia, Chronic kidney disease, Continuous renal replacement therapy, Dog, Hemodialysis, Urea reduction ratio.

Introduction

Continuous renal replacement therapy (CRRT) is a blood purification method by a combination of ultrafiltration and hemodialysis (12). CRRT has emerged as the preferred dialysis for patients with acute kidney injury (AKI), particularly those with hemodynamic instability in human medicine (2). It has been also widely used to treat chronic renal failure in critically ill patients with (1,9). CRRT has been investigated recently with emerging modality (3,6). Several papers are reported that the effectiveness of CRRT in dogs with AKI but lack of reports about the outcomes of CRRT in chronic kidney disease (CKD) patients. The purpose of this case report was to present the treatment of CRRT in 6 dogs with end-stage CKD and uncontrolled uremia and to evaluate the outcomes of such treatment.

Case

Six patients were refered to the Veterinary Medical Teaching Hospital of Seoul National University with anorexia and depression. Physical examination and blood analysis including complete blood count, serum chemistry, and electrolytes were carried out, and it was revealed severe azotemia. Although aggressive fluid therapy was conducted, azotemia was not resolved within normal range. Therefore, we decided to carry out hemodialysis for the patients. The signalments of six patients was presented in Table 1.

Following induction of general anesthesia with propofol and isoflurane, 7 or 8-Fr dual-lumen catheter (Gentle Cath; Nippon Sherwood, Tokyo, Japan) were inserted percutaneously into the external jugular vein using guide wire and vessel dialator technique for vascular access and the catheter were advanced to the right atrium or cranial vena cava. Thoracic radiography was used to confirm the appropriate position of the catheter tips in order to ensure that the distal tips were at the junction of the superior vena cava.

Hemodialysis was performed by Prisma system (CGH Medical, U.S.A.). Continuous venovenous hemodiafiltratoin (CVVHD), which uses a convective and diffusive solute clearance with ultrafiltration, was initiated for 3hr, and then changed into continuous veno-venous haemofiltration (CVVH) mode. CVVHD was used by automated renal replacement therapy and continuous fluid management unit; M10 preset [an acrylonitrile/sodium methallyl sulfonate (AN69) hollow

Table 1. Signalments of 6 Patients

no.	Breed	Age (years)	Body weight (kg)
1	Shih-Tzu	3	3.42
2	English Cocker Spaniel	5	8.12
3	Chinese Sharpei	1.5	8.62
4	American Cocker Spaniel	3	7.26
5	Shih-Tzu	3	4
6	Yorkshire Terrier	9	2.6

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fiber neonatal hemofilter/dialyzer with an effective surface area of 0.042 m^2, a filter priming volume of 3.50 ± 0.35 ml, and a total extracorporeal circuit blood volume of 50 ± 5 ml] or M60 preset [an acrylonitrile/sodium methallyl sulfonate (AN69) hollow fiber hemofilter/dialyzer with an effective surface area of 0.60 m^2, a filter priming volume of 49 ± 4.9 ml, and a total extracorporeal circuit blood volume of 41 ± 4.1 ml].

Immediately prior to use, the blood access lines and hemofilter/dialyzer were primed with 0.9% saline and a commercial dialysate, hemosol BO (Gambro, Hechingen, Germany) was used. The initial extracorporeal flow rate was based on a report of Shimokawa *et al*. (10). An extracorporeal blood flow rate of 20-30 ml/min was utilized in M10 preset, or 50-80 ml/min was used in M60 preset. A Dialysate flow rates of 200-250 ml/hr, replacement fluid flow rate of 100-200 ml/L, and ultrafiltration rates of 10-60 ml/hr were utilized. Dialysis time of one session was a period of 4-10 hr according to the severity of azotemia. At the beginning of the CRRT session, the venous line was connected to the inflow port of the circuit without discarding the rinse fluid. Heparin (15-25 U/kg/hr) was administered continuously as an anticoagulant throughout the CRRT procedure in all dogs. To maintain body temperature, heat support by hand warmers and fluid warmer, Prismaflo (Gambro) the circuit, dialysate, and replacement fluid were actively warmed throughout CRRT to prevent hypothermia.

Serum biochemistry, electrolytes and packed cell volume (PCV) results obtained at pre- and post-dialysis. Urea reduction ratio (URR) was calculated according to the percentage fall divided by the pre- blood urea nitrogen (BUN) during a dialysis session.

$$URR\ (\%) = (pre\_BUN - post\_BUN) / pre\_BUN \times 100$$

In addition, the BUN value of pre-dialysis of the first 5 sessions was plotted in linear fit.

The six dogs with CKD had CRRT treatment. Serum BUN and creatinine values were obtained during and between hemodialysis sessions in dogs and calculated URR also presented in Table 2. The level of BUN and creatinine dropped dramatically during the hemodialysis session then increases during the interdialysis interval before the next treatment. The BUN value was obtained and represented in slop for the first 5 sessions of pre-dialysis in each patient (Fig 1). URR, a parameter used to measure the adequacy of dialysis, was calculated according to the change in BUN over the entire session divided by the pre-BUN. Mean URR of 3 dogs were > 60% and 1 dog was 57.1%. 2 dogs were < 40% and 1 of them died after 3rd session.

Other serum biochemistry [P, total protein (T.P.), and albumin], electrolytes (Na, K, Cl) and PCV were estimated at pre- and post-dialysis and revealed hyperkalemia and hypernatremia at initial presentation. However, most of these laboratory serum results carried out at pre-dialysis were maintained within normal range (Fig 2).

Several adverse events results from either the underlying disease or dialysis treatments were recorded of six dogs during CRRT. We closely monitored the patients, 12 adverse events were recorded throughout the CRRT treatment. There were no signs of dyspnea, vomiting, or disequilibrium syndrome. But, excessive clotting associated with obstructed extracorporeal flow was examined 8 times due to a kinked catheter. In addition, respiratory arrest, cardiopulmonary arrest, seizure and bleeding were shown. Intermittent shivering was observed in all cases due to mild hypothermia (37.5~38ºC).

During the interdialysis period, dialysis-specific complications occurred in 4 dogs. Right atrial thrombosis was confirmed with echocardiography in 1 dog. Another dog developed excessive bleeding because of excessive heparinizа-

Table 3. Adverse events of intra and interdialysis in CRRT

intradialysis		interdialysis	
signs	episode	signs	episode
Dyspnea	None	Atrial thrombus	1
Vomiting	None	Bleeding	1
Dysequilibrium*	None	Dysequilibrium*	None
Clotting	8	Facial edema	2
Respiratory arrest	1		
Cardiopulmonary arrest	1		
Seizure	1		
Bleeding	1		
Intermittent Shivering	All		

*including disorientation, agitation, vocalization, acute blindness or coma

Table 2. BUN and Creatinine value of 6 patients at pre- and post-dialysis

Case no.	BUN		Creatinine		Mean URR (%)
	pre-dialysis	post-dialysis	pre-dialysis	post-dialysis	
1	85.3 ± 17.1	32.6 ± 8.9	5.3 ± 0.8	2.1 ± 0.6	61.7 ± 8.1
2	90.7 ± 23.2	27.5 ± 9.6	10.6 ± 3.3	2.9 ± 1.4	69.6 ± 8.8
3	108.7 ± 48.8	46.4 ± 26.0	12.9 ± 3.6	4.8 ± 2.7	57.1 ± 16.4
4	74.8 ± 21.7	46.5 ± 17.2	8.0 ± 2.9	3.8 ± 1.3	37.4 ± 14.5
5	84.1 ± 22.0	31.2 ± 11.2	5.2 ± 0.9	2.0 ± 0.5	63.3 ± 7.6
6	153.7 ± 59.7	88.2 ± 24.2	7.9 ± 1.9	4.8 ± 1.6	38.6 ± 20.3

URR: Urine Reduction Ratio

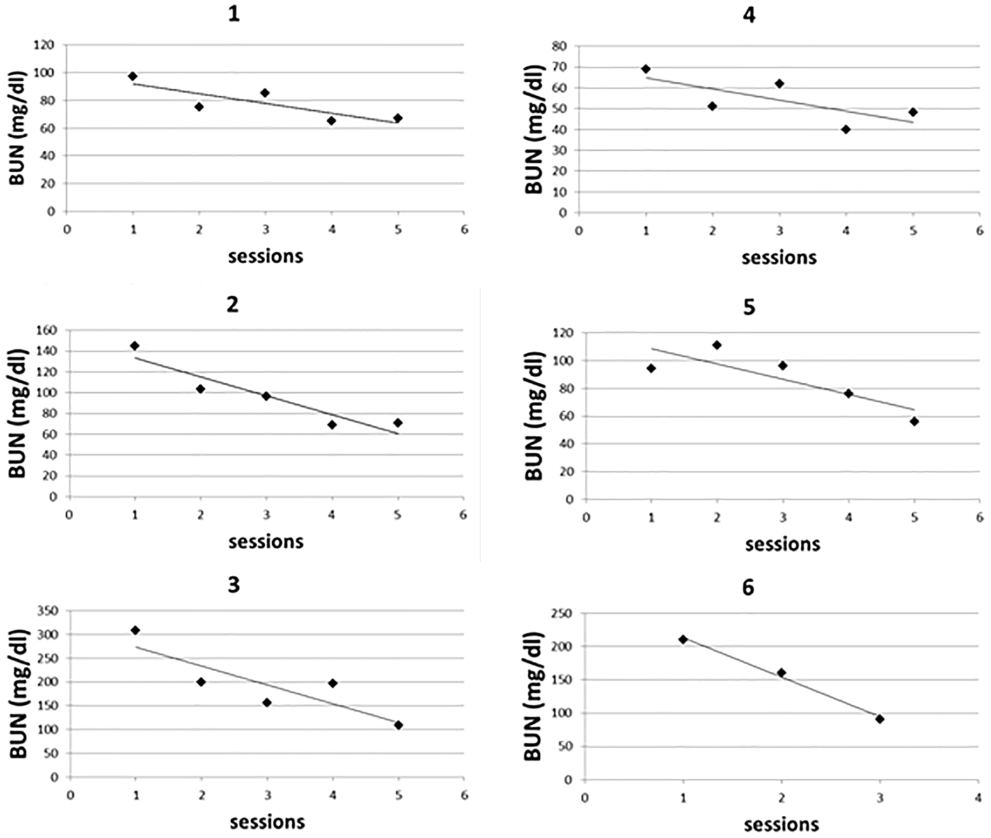

Fig 1. Changes in slop of BUN at pre-dialysis. BUN value at pre-dialysis of first 5 sessions represents (except case 6 dog) a decrease in urea appearance.

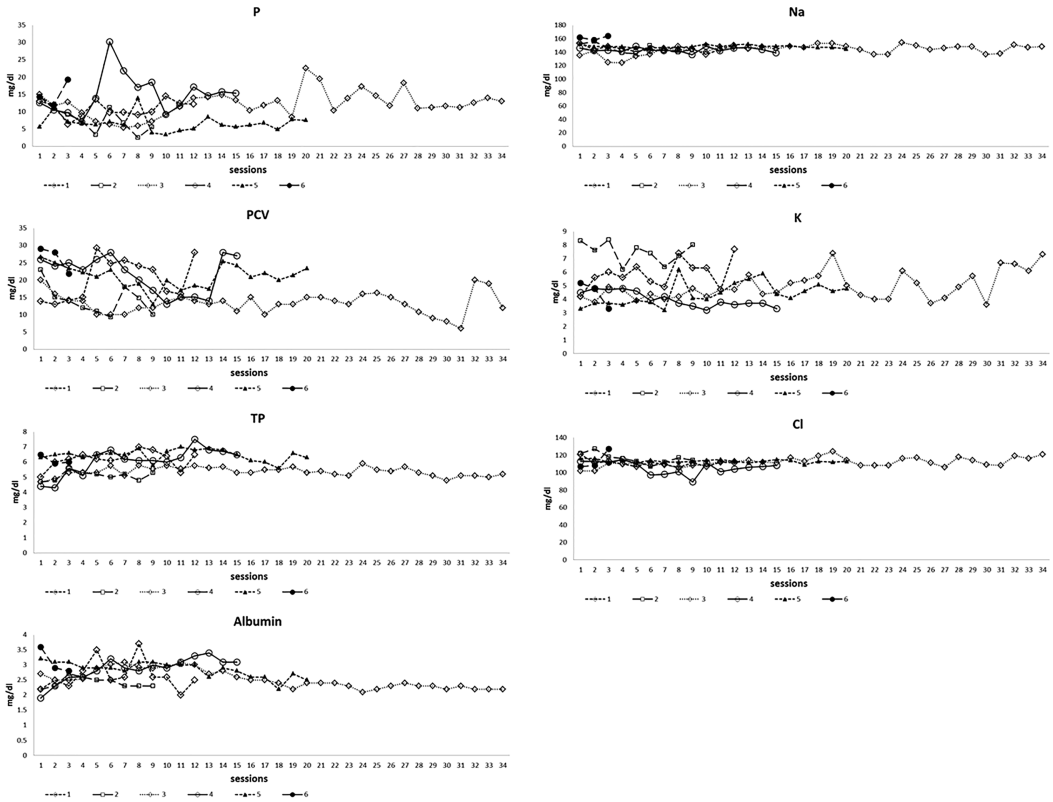

Fig 2. Serum chemistry and electrolytes of uremic dogs at each predialysis session. Phosphorus, total protein (T.P.), and albumin, electrolytes (Na, K, Cl) and packed cell volume (PCV) were estimated at pre- and post-dialysis. The serum and electrolytes results carried out at pre-dialysis were maintained within normal range.

tion. Facial and laryngeal edema with a tightly wrapped catheter bandage was detected in 1 dogs causing inspiratory stridor and was resolved after loosening the bandage. Dysequilibrium signs characterized by disorientation, agitation, vocalization, acute blindness or coma were not detected in all dogs.

Discussion

The change in slope show a decrease of urea associated with increasing "continuous" urea clearance. For the first 5 session, the pre-BUN level of all dogs was presented in slope which showed decreasing tendency. This means the decreasing slope is gradational recovery of renal function with CRRT treatment. After 5 sessions of each case, the pre-BUN level was increased or decreased, but those levels are usually maintained under 90 mg/dl.

The URR is defined as the percent reduction in blood urea nitrogen concentration during a single dialysis treatment. This is first popularized by Lowrie and Lew in 1991 as a method of measuring amount of dialysis that correlated with patient outcome (9). They suggested that the URR should be above 60%. In veterinary medicine, URR of up to 85% or greater are common in CKD patients but may lead to dialysis dysequilibrium syndrome (DDS) in patients with severe azotemia (5). In patients with BUN values > 150 mg/dl, it has been recommended that the URR should be limited to 30~50% (6,8). However, Cowgill *et al*. (4), suggested that CKD animals with severe uremia should be approached carefully until the pre-BUN is less than 100 mg/dl. Like this, adequacy standard for animals with CKD has not been built yet. From our study, to estimate excretion of urinary waste, URR, a parameter used to measure the adequacy of dialysis, was calculated throughout the sessions. Mean URR of 3 dogs were > 60%, 1 dog was 57.1% and 2 dogs were < 40%, and 1 of them died after 3rd session. Four dogs showed URR with a range of 57~72% and good outcome with decreasing tendency. The other 2 dogs, the level of pre-BUN was decreased for the first 5 sessions, however, the decreasing tendency was not well continued after that. Among them, a dog with severe azotemia at presenting time was accompanied with electrolyte imbalance and died after finishing 3rd sessions of hemodialysis (URR was only 15.93%). We can carefully suggest that the first 5 sessions of hemodialysis is important to predict outcome in CKD patient, but more case studies will be required to define that.

Complications related to hemodialysis has been well described in human CRRT (7). Especially, potential clinical complications include bleeding, hematomas, thrombosis, infection, sepsis, allergic reactions, hypothermia, nutrient losses, insufficient blood purification, hypotension and arrhythmias. Adverse events were carefully examined during intra and interdialysis in CRRT treated dogs. 12 adverse events were recorded during the total 93 sessions of CRRT. Clotting (due to a kinked catheter), respiratory arrest, cardiopulmonary arrest, seizure, bleeding and hypothermia were observed during intradialysis. During the interdialysis period, dialysis-specific complications occurred such as atrial thrombosis and bleeding.

Coagulation and filter clotting is most significant complication. If filter clotting occurs, the blood within the entire extracorporeal circuit (ECC) should be discarded and this contributes to the development of blood loss anemia. To prevent clotting and prolong the filter life, Diehl *et al.* (6) suggest that increasing pre-filter replacement fluid rate or considering to use heparin as an anticoagulant. Heparin is the most common choice as an anticoagulant in veterinary medicine but bleeding and thrombosis may develop. For alternatives, citrate or nafamostat mesilate can be used. However, nafamostat mesilate is not appropriate for CRRT in dogs, because of severe vomiting (11) and in case of citrate, there are the risk of ionized hypocalcemia and metabolic alkalosis (6). In these cases, we administered heparin sodium as a dosage with 15~25 U/kg/hr. During the total 93 sessions, 8 times clotting were occurred due to a kinked catheter. Bleeding and thrombosis are other complications could be induced frequently by inappropriate heparin dose during interdialysis period. Appropriate and low-dose heparin management based on standard heparin protocol (10) was applied and filter clotting was not occurred in this study. However, bleeding and thrombosis of the CRRT circuit were inevitable. For this reason, careful monitoring of the patient and the ECC and careful activated clotting time determinations could make adequate anticoagulation throughout the CRRT.

Overall, this report is hemodialyzation of 6 dogs using CRRT in CKD with uncontrolled azotemia. Before beginning of CRRT, azotemia was not respond to medication and all they presented uremic sign including uremic breath. Three to 19 sessions of hemodialysis were carried out in each dog and a dog died showing severe electrolytes imbalance after 3rd sessions of hemodialysis. For the first 5 sessions, the levels of pre-dialysis BUN were progressively decreased on subsequent days demonstrating recovery of residual renal function. Thus, the dogs that accompanied URR range of 57~72% showed good outcome. Although complications such as bleeding and thrombosis were inevitable with the standard heparinized protocol, CRRT provided well control of electrolytes and fluid state throughout the total 93 sessions in 6 dogs. Therefore, we suggest that CRRT can be recommended for use in CKD dogs with uncontrolled azotemia and should be monitor carefully throughout the CRRT.

Conclusion

The dogs that accompanied URR range of 57~72% showed good outcome. CRRT could be recommended for use in CKD dogs with uncontrolled azotemia or uremia. Adverse events, such as obstructed extracorporeal flow, atrial thrombosis, and excessive bleeding due to heparinization, facial edema, respiratory and cardiopulmonary arrest were recorded. Therefore, patients should be monitored carefully throughout the CRRT.

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개선되지 않는 질소혈증 동반한 만성신부전 환자에서 지속적 신대체 요법의 적용

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요 약 : 본 케이스는 요독증이 해소되지 않는 말기 만성 신부전 환자에서의 지속적 신대체요법에 관한 보고이다. 본원에 내원하여 만성신부전으로 진단 내려진 6마리의 환자에서 수액요법과 같은 일반적인 대증요법에 개선이 없었다. 따라서 혈액투석방법을 진행하였다. 평균 57-72%의 요소감소율을 보인 4마리의 환자와 37.3%의 요소감소율을 보인 1마리의 환자견에서 좋은 개선을 보였다. 하지만 6마리의 환자견에서의 93회 혈액투석 동안 체외흐름 폐색, 항응고제 사용에 의한 과도한 출혈등과 같은 부작용이 12회 발생하였다. 따라서 요독증이 개선되지 않는 만성 신부전 환자에서의 지속적 신대체요법은 유용하다 할 수 있으며 혈액투석동안 면밀한 부작용 관찰이 중요하다 여겨진다.

주요어 : 만성신부전, 지속적신대체법, 투석, 요소감소율, 요독증