Continuous renal replacement therapy for patients with acute kidney injury caused by melamine-related urolithiasis

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Background: **In 2008 there was an epidemic of renal disease affecting infants after consumption of melamine-tainted milk products. Most of the infected children were asymptomatic or with mild symptoms, and a few suffered from acute obstructive kidney injury secondary to melamine-contained renal stones (8 of 15 577 children screened at our hospital for urolithiasis). This study was intended to retrospectively review the management of acute kidney injury using continuous renal replacement therapy (CRRT) in the 8 children with acute kidney injury.**

Methods: **The 8 infants with acute kidney injury caused by melamine-related urolithiasis were referred to the pediatric intensive care unit at the hospital in late 2008. CRRT was given to treat their kidney injuries. Medical records of the infants were reviewed for demographic features, diagnosis, CRRT treatment, and outcomes.**

Results: **Before CRRT, hypertension was found in 6 of the 8 children. Varying degrees of oliguria, anuria, elevated levels of blood urea nitrogen (BUN) (13.11-35.6 mmol/L) and creatinine (Cr) (238.8-773.7 μmol/L) were observed in these patients. After CRRT, the levels of BUN, Cr and electrolytes decreased. Urine output and edema were improved clinically.**

Conclusion: **CRRT can rapidly improve renal function, avoiding such surgical interventions as lithotripsy, percutaneous nephrolithotomy, and ureteroscopy. It is an efficient modality to treat acute kidney injury caused by melamine-related urolithiasis.**

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Key words: **acute kidney injury;**
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Introduction

In September, 2008, there was an unprecedented epidemic of renal disease affecting infants after consumption of melamine-tainted milk products. Afterwards, it became mandatory to screen for urolithiasis in infants and young children throughout the country. From September to the end of the year 2008, 15 577 children who had been exposed to melamine-tainted powdered formula were screened at our hospital for renal stones.[1] Urolithiasis was found in 562 (3.6%) of these children.[1,2] Most of the children were asymptomatic but acute kidney injury secondary to renal stones obstruction were also found. Eight of the 562 children were diagnosed with acute kidney injury and admitted to the pediatric intensive care unit (PICU) in the hospital. Continuous renal replacement therapy (CRRT) was given to these patients. In this article we summarize our experience with CRRT for acute kidney injury caused by melamine-related urolithiasis.

Methods

The medical records of the 8 infants were reviewed in terms of age, sex, exposure history to contaminated formula (brand, melamine content, duration of exposure, use of formula alone or a combination of breast milk and formula), symptoms such as fever, unexplained crying during urination, edema, dysuria, hematuria, and passing of stones. Renal ultrasonographic findings before their admission to PICU and laboratory findings such as complete blood count, antistreptolysin-o test results, antinuclear antibody, complement C3,

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erythrocyte sedimentation rate, liver function tests, and blood coagulation were also reviewed. The infants were followed up regularly at the outpatient department.

Acute nephritis, rapid progressive nephrotic syndrome, systemic lupus erythematosus kidney injury, Henoch-Schonlein purpura nephritis, congenital urinary tract deformities, and kidney tumor were ruled out in all the 8 patients. They all had a history of consuming melamine-tainted powdered formula for more than 30 days.[3] Plain abdominal X-ray and ultrasonographic examinations showed evidence of renal stones (Table 1). These infants met the following criteria for acute kidney injury: an abrupt (within 48 hours) reduction of kidney function currently defined as an absolute increase of serum creatinine (Cr) of more than or equal to 0.3 mg/dl (≥ 26.4 μmol/L), a percentage increase of serum creatinine of more than or equal to 50% (1.5-fold over baseline), or a reduction of urine output (documented oliguria of less than 0.5 ml/kg per hour for more than six hours).[4]

CRRT was given by a PRISMA machine with a hemofilter when prisma M60 pre set filters (Gambro, PRISMA, Geneva, Switzerland) were used. Continuous veno-venous hemofiltration (CVVH) mode was performed; renal function and 24-hour daily fluid intake and output were monitored via a Foley catheter. The blood flow rate was 40-60 ml/L, replacement solution 20-30 ml/kg per hour, and fluid removal rate 2.5-3.7 ml/kg per hour. Loading dose of heparin was 20 U/kg and maintenance dose 10 U/kg per hour. Both femoral veins were catheterized with single-lumen catheter in all children. The composition of substitution fluid was as follows: 0.9% sodium chloride 1500 ml, 5% glucose 500 ml, 5% sodium bicarbonate 125 ml, 10% calcium gluconate 10 ml, 10% potassium chloride 6 ml, and 25% magnesium sulfate 0.75 ml.

Results

Of the 8 children, 6 were boys and 2 girls, aged from 9 to 33 months (median: 18 months) (Table 1). Milk products consumed by the 8 children were produced by the Sanlu Group (Shijiazhuang, Hebei Province, China; melamine levels reported as exceeding 2.5 ppm[5]). The mean duration of melamine-tainted formula consumption was 11.1 months (range: 5-18 months). Bilateral calculi at the ureters were confirmed in all the 8 children by ultrasound examinations of the urinary system before admission (Table 1). The calculi were sand-like and less dense than calcium oxalate ones. Four children (patient 2, 3, 5 and 6) presented with hydronephrosis, 2 (patient 6 and 7) with diffused pathological changes in bilateral kidneys, and 4 (patient 2, 6, 7 and 8) with unilateral or bilateral dilated upper ureters. Oliguria or anuria was found in all 8 children and hematuria in one of them. Six children (patient 1-6) had hypertension on admission and no dysuria or urinary frequency was found. Gastrointestinal tract symptoms such as vomiting and diarrhea were not observed. In the first 6 hours after admission to PICU, the average urine output in the 8 children was equal or less than 0.5 ml/kg per hour. Twelve hours after admission, they were anuric and subsequently developed edema with increased levels of Cr and blood urea nitrogen (BUN). Three (patient 4, 6 and 7) of them showed electrolyte abnormalities such as hyperkalemia. The mean levels of BUN and creatinine were 24.4 mmol/L and 484.4 μmol/L, respectively. The highest levels of BUN and Cr were 33.1 mmol/L and 725.4 μmol/L, respectively. Because

Table 1. Characteristics of the 8 patients diagnosed with acute kidney injury

Patient no.	Gender	Age (mon)	Body weight (kg)	Duration of melamine-contaminated formula consumption (mon)	Symptoms and courses	Stones location	Blood pressure (mmHg)
1	Female	11	9	11	Oliguria for 2 days	Bilateral kidneys and ureters	115/71 (88)
2	Male	33	18	16	Anuria for 2 days	Bilateral kidneys and left ureters	129/85 (102)
3	Male	13	10	13	Anuria for 2 days	Bilateral kidneys and ureters	119/86 (95)
4	Female	9	11	7	Oliguria for 1 day	Left kidney and bilateral ureters	125/80 (97)
5	Male	21	13	18	Fever and oliguria for 3 days	Bilateral kidneys and ureters	112/69 (85)
6	Male	17	12	10	Anuria for 2.5 days	Bilateral kidneys and ureters	132/88 (105)
7	Male	25	16	9	Anuria for 1 day	Bilateral ureters and kidneys	87/58 (65)
8	Male	15	13	5	Hematuria for 2 days and anuria for 1 day	Bilateral ureters and kidneys	89/55 (69)

Table 2. Main parameters of the 8 patients after CRRT

Patient no.	Filtration duration (h)	Fluid removal (ml)	Serum K^+ (mmol/L)		Renal function		Urine output (ml/kg per h)
			Before CRRT	After CRRT	Before CRRT	After CRRT	
1	40	728	5.4	2.9	BUN 23.2 mmol/L Cr 319 μmol/L	BUN 3.33 mmol/L Cr 44.2 μmol/L	2.37
2	15	740	4.6	3.1	BUN 26.3 mmol/L Cr 500 μmol/L	BUN 2.96 mmol/L Cr 52.1 μmol/L	3.89
3	13	476	3.2	3.7	BUN 13.11 mmol/L Cr 773.7 μmol/L	BUN 4.79 mmol/L Cr 23.3 μmol/L	2.9
4	16	519	5.8	4.1	BUN 35.6 mmol/L Cr 467 μmol/L	BUN 3.2 mmol/L Cr 80.8 μmol/L	2.76
5	27	846	4.9	3.6	BUN 28.65 mmol/L Cr 593.6 μmol/L	BUN 4.15 mmol/L Cr 37.6 μmol/L	2.48
6	32	1130	6.0	3.5	BUN 33.1 mmol/L Cr 725.4 μmol/L	BUN 5.97 mmol/L Cr 56.2 μmol/L	3.19
7	15	632	5.6	4.2	BUN 19.1 μmol/L Cr 257.5 μmol/L	BUN 8.6 mmol/L Cr 107.4 μmol/L	2.83
8	11	328	3.7	3.3	BUN 16.27 mmol/L Cr 238.8 μmol/L	BUN 9.07 mmol/L Cr 138 μmol/L	4.55

CRRT: continuous renal replacement therapy; BUN: blood urea nitrogen; Cr: creatinine; RBC: red blood cell; WBC: white blood cell.

all 8 children presented with oliguria or anuria in a very short duration after admission, none of them received urinalysis before CRRT.

The mean duration of CRRT was 21.1 hours (range: 11-40 hours). After CRRT, the mean level of BUN decreased from 24.4 mmol/L to 5.3 mmol/L, the mean level of Cr decreased from 484.4 μmol/L to 67.5 μmol/L, and the mean level of serum potassium decreased from 4.9 mmol/L to 3.6 mmol/L (Table 2); edema resolved. Blood pressure of the 6 children with hypertension returned to normal after CRRT and after 5 days of treatment in the PICU, the patients were transferred to the pediatric nephrology ward. They were hospitalized for 12 days including those days in ICU. The general condition of the 8 children was good at discharge from the hospital. All renal indices including renal function, electrolytes and urine output were normal. In 4 children who had residual stones at discharge, 2 children were found to have the remaining stones removed at one-month follow-up, and the other 2 had stones removed 2 months later. All children had normal renal function at a 6-month follow-up.

Discussion

Melamine, also known as cyanuramide, is used in manufacturing household utensils and ornaments. It is a triazine compound with a molecular formula of $C_3H_6N_6$. As an essential component in flame retardants, glues, and plastics, it is not used for human or animal consumption.[6,7] Unfortunately, because it contains 66% nitrogen by mass, it was used unscrupulously as a food additive to give the false measurement of a higher protein content on food-quality tests.[8,9] Once absorbed into the body, melamine adheres to other substances, aggregates, and facilitates crystal formation in the urinary tract.[8,10,11] The nephrotoxicity of melamine was first reported after an outbreak of pet food contamination with melamine in 2007.[9,12] In experimental murine and rat models, chronic melamine exposure resulted in the formation of kidney stones and bladder stones.[13]

Melamine is also proved to induce urolithiasis in children who were fed with melamine-tainted milk products for a certain period of time.[14] The mechanism of stone formation by melamine is unclear at present. Animal studies in the past few years showed the tubular crystals mainly contained melamine and cyanuric acid. Sun et al[15] analyzed the melamine-associated stone specimens from 13 children with renal failure using liquid chromatography-mass spectrophotometry, and confirmed that the composition of stones was primarily uric acid and melamine. Melamine-induced kidney stones differing from radiopaque calcium oxalate and phosphate stones were radiolucent and thus not revealed by radiographic examinations.[3,16,17] Therefore, ultrasonographic examination is the best method for detecting kidney stones in children who have consumed melamine-contaminated formula.[3]

Unlike urolithiasis with other causes in children, which have well-described urinary symptoms and signs, most children with melamine-related urolithiasis were asymptomatic.[18] Since melamine induced stones were less echogenic and dense, with a "sandy" appearance on ultrasound,[2] it is more likely to be expelled after administration of a considerable amount of fluid. For

mild patients without renal failure, we prescribed conservative treatment including intravenous hydration, diuresis, alkalification of urine, and traditional Chinese medicine (Regimen *Herba Lysimachie* granules for oral intake) to eliminate renal calculi.[1]

The 8 children in the present study had been fed with high-content melamine tainted powdered formula for a long duration. All the patients were less than 36 months of age. Though we cannot do blood or stone analysis for melamine, but due to clinical suspicion and results from governmental agencies, the cause of urolithiasis in these patients are thought to be melamine toxicity. Excluding other causes, we found acute kidney injury was caused by melamine-related urolithiasis in these children. CRRT other than intermittent hemodialysis was considered suitable for these patients. This was also due to the fact that melamine is presumed to be tissue bound and have shown to be slow releasing,[19] like lithium poisoning.[20]

CRRT was reported to be effective in children with acute kidney injury.[21,22] In our study the patients were selected for CVVH at superfiltration ratio independent of blood pressure. Compared with other modes of blood purification, CVVH showed large blood flow, better superfiltration ratio, and longer use of filter. These can avoid the complications of arterial cannulation such as bleeding, embolism and thrombosis.

Of the multitude modes of CRRT, both CVVH and continuous venovenous hemodiafiltration have higher clearances of certain substance poisoning such as lithium poisoning.[20] Moreover, CVVH was used to improve the renal function of the patients with acute kidney injury induced by melamine-tainted milk products. We controlled the optimal clotting time, used relative lower blood flow speed, and made sure every pump pressure was within the normal range. When the urine output increased in CRRT, stone evacuation was monitored. Gross hematuria in several patients was thought to be caused by minor injury of the urinary tract secondary to stone passage.

CRRT for renal failure in children is still in its infancy in China. Skillful central vein cannulation is a prerequisite for CRRT. For older pediatric patients, bilumen cannula is an option of choice. For children younger than 3 years old, the diameter of bilumen cannula is too wide. Hence bilateral femoral cannulation is proposed. The femoral vein is optimal for CRRT because of its relatively wide diameter, superficial position, and easy accessibility.

Our study has certain limitations. The blood or urine melamine level of these 8 patients were not compared before and after CRRT due to the limited facility. For the limited condition as well, we did not analyze the stone composition.

In conclusion, acute kidney injury induced by melamine-tainted milk products in children requires immediate diagnosis and treatment. Ultrasonography examination is a reliable method for diagnosis of the disease. CRRT can rapidly restore renal function and avoid surgical intervention such as lithotripsy, percutaneous nephrolithotomy and ureteroscopy. It is indicated for patients with acute kidney injury caused by melamine-related urolithiasis.

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