Journal of Pediatric Surgery (2013) **48**, 384–387

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Journal of Pediatric Surgery

www.elsevier.com/locate/jpedsurg

Posterior urethral valves: Creatinine velocity, a new early predictor of renal insufficiency

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Received 9 November 2012; accepted 12 November 2012

Key words:
Posterior urethral valves;
Neonate;
Chronic renal insufficiency;
Creatinine velocity;
C_{vel}

Abstract

Aim: Antenatal screening has led to early detection of posterior urethral valves (PUV). However, despite early intervention, a proportion of children will develop chronic renal insufficiency. We studied the trend of serum creatinine following urinary tract decompression during the neonatal period in infants as a possible predictor of chronic renal insufficiency.

Methods: Patients treated by endoscopic resection of posterior urethral valves between 1993 and 2004 were identified. From these, infants treated within the first 30 days of life were identified. Serum creatinine values taken within the first 5 days following initial drainage were recorded. A creatinine velocity for each patient was calculated by linear regression analysis. Creatinine was considered rising if velocity was >3 μmol/L/day, or falling if velocity was <−3 μmol/L/day. Chronic renal insufficiency was defined as CKD2 or higher.

Results: Sixty-four neonates had decompression of the urinary tract. Of these, 16 had rising creatinine despite drainage, 10 had a plateau in creatinine level, and 36 had falling creatinine following drainage. Insufficient data were available in two to calculate creatinine velocity. Progression to renal insufficiency was significantly higher in patients with an initial rise in creatinine (62.5%) than in those with plateau creatinine (40%) or falling creatinine (8.6%) ($P \leq 0.0005$ by Fisher exact test). Mean follow-up was 9.2 years.

Conclusions: Rising creatinine, even transiently, following urinary tract drainage in neonates with posterior urethral valves is significant and is a new and important indicator of long-term prognosis.

Congenital posterior urethral valves (PUV) are a cause of bladder outflow obstruction. The incidence of PUV was 1.4/10,000 births in a recent study from northern England and accounted for about 60% of all cases of fetal lower urinary tract obstruction [1]. Early identification and treatment of PUV in the neonatal period allows optimization of urinary tract function and therefore minimization of renal injury. Indeed the majority will retain a normal GFR into adulthood. However, about 30% will progress to chronic renal insufficiency (CRI) before adolescence [2].

Identification of risk factors for the development of renal insufficiency has been elusive. These might include negative prognostic indicators such as echogenic or cystic kidneys [3], high nadir creatinine (lowest serum creatinine during the first

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0022-3468/$ – see front matter © 2013 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.jpedsurg.2012.11.016

year of life) [3,4], bilateral reflux at diagnosis [5], and renal tubular acidosis [6]. The presence of a "pop-off" mechanism such as unilateral reflux, ascites or urinoma is seen as positive predictor for future renal function [7].

We derived a novel method of interpreting creatinine trend termed "creatinine velocity" (C_{vel}). Defined as the rate of change of creatinine, C_{vel} can be calculated using simple linear regression and expressed in μmol/L/day. We studied C_{vel} following initial bladder drainage as a prognostic indicator for long-term renal function.

1. Methods

All infants treated by endoscopic resection of posterior urethral valves between 1993 and 2004 were reviewed. Data collected included demographics, timing of intervention, serum creatinine and electrolyte values and outcomes including chronic renal insufficiency and renal replacement therapy.

As data were collected, a pattern emerged suggesting an early rise in creatinine predicts for poor renal outcome. We then studied creatinine following initial bladder drainage by correlating the C_{vel} with renal outcomes to determine whether it could be used as an early indicator of renal outcome.

Serum creatinine values taken within the first 5 days following initial bladder drainage were recorded. For each patient, C_{vel} was calculated by simple linear regression using Microsoft Excel 2007. This software uses simple linear regression to apply a line of best fit to the data, the slope of the which represents the creatinine velocity. Creatinine was considered to be rising if C_{vel} was >3 μmol/L/day, or falling if velocity was <-3 μmol/L/day. Chronic renal insufficiency was defined as CKD2 or higher according to Kidney Disease Outcomes Quality Initiative guidelines [8].

The Fisher exact test was used to compare renal outcome in the identified risk groups. Prognostic indicators were compared between normal renal function and renal impairment groups using the unpaired Student's *t*-test. Receiver operating curves (ROC) were used to identify optimal criterion and to compare the discriminating power of prognostic indicators. Data are expressed as mean (±SEM). $P<0.05$ was considered statistically significant.

2. Results

A total of 129 children were identified as having undergone transurethral resection of PUV during the study period. Of these, progress notes for 120 were reviewed (9 notes could not be retrieved). Sixty-four patients had had bladder drainage established within the first month of life. Of these, 43 (67%) had suspicion of PUV on antenatal screening. The remaining 21 children presented in a variety of ways including renal insufficiency ($n=7$), urinary tract infection (UTI) ($n=3$), urinoma ($n=6$), haematuria ($n=2$), weight loss ($n=1$), retention ($n=1$) and irritability ($n=1$).

C_{vel} could not be calculated in 2 children, due to lack of data (insufficient creatinine levels taken during 5 days following initial drainage) leaving 62 subjects for analysis. These were grouped according to their C_{vel} into either rising (group A, $n=16$), plateau (group B, $n=10$) or falling (group C, $n=36$) (Fig. 1).

Demographics for each group including mean birth weight, mean gestational age at birth and mean age at establishment of drainage are outlined in Table 1. Mean duration of follow-up was 9.2 years.

2.1. Outcomes

Of the 64 infants treated with bladder drainage within the neonatal period, 47 retained normal renal function and 17 (27%) developed chronic renal insufficiency (CRI). Chronic kidney disease (CKD) stages were CKD2 ($n=6$), CKD3 ($n=3$), CKD4 ($n=2$) and CKD5 ($n=6$) and are summarized in Table 2.

A total of 10 (62.5%) infants from group A went on to develop CRI compared with 4 (40%) infants from group B and only 3 (8.3%) from group C ($P<0.0005$). Children who developed renal impairment had a significantly higher C_{vel} than those who maintained normal renal function (5.6±6.9 versus −11.5±3.9; $P=0.026$).

As a test for future renal impairment, ROC analysis identified an optimal C_{vel} criterion value of >-0.6 μmol/L/day (sensitivity 78%, specificity 82%, area under the curve (AUC)=0.788; $P=0.0001$) (Fig. 2). Interpreted with −0.6 μmol/L/day as a cut-off, C_{vel} has a positive predictive value of 64% and negative predictive value 89%.

Of the 64 infants with early establishment of bladder drainage, 6 (9.4%) patients developed end-stage renal failure (ESRF), of whom 4 (6.3%) have received a renal transplant. Patients who developed ESRF included 3 (19%) of 16 from group A and 2 (20%) of 10 from group B. Only 1 (3%) of 33 from group C developed ESRF ($P=0.13$).

Highest creatinine reached in the weeks following diagnosis (peak creatinine) and nadir creatinine were also studied as prognostic indicators. Peak creatinine was significantly higher in patients who developed CRI than in those who maintained normal renal function (308±34.9 versus 168±15.7; $P=0.0001$). Nadir creatinine was significantly higher in patients who developed CRI than in those who maintained normal renal function (93±15.2 versus 40±15.7, $P\leq0.0001$). In an analysis by comparison of ROC curves, there was no significant difference between C_{vel}, peak creatinine and nadir creatinine as prognostic indicators (Fig. 3). Of course, C_{vel} is the only of these prognostic indicators that is invariably available by the fifth day of treatment, zenith and nadir being retrospective variables.