Aldosterone and renin-early and easy to measure prognostic biomarkers in serum and urine in posterior urethral valve.

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How to cite this article:
sharma K, Chowdhary S, Singh R, kumar Maurya A, Tiwari SH, Chourasia A, Suresh G**.** Pulmonary sequestration in a pediatric centre: A retrospective study. Iranian Journal of Pediatric Surgery 2024; 10 (2): 169-178.

DOI: https://doi.org/10.22037/irjps.v10i2.44954

Abstract

Introduction: Posterior urethral valve (PUV) is one of the most common causes of obstructive uropathy in the children. Approximately one -third of such children end in chronic kidney disease (CKD) in future despite good management. There are some clinical parameters that are assumed poor renal outcome indicators.

received: 31 March 2024
accepted: 17 August 2024
Published online: 15 October 2024

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Many novel biomarkers are coming in limelight for early detection of chronic kidney disease. Increase of renin and aldosterone values in serum and urine as a result of tubulointerstitial damage can be marked as an early biomarker for prognosis.
Therefore, this study focuses to assess the role of urinary and serum aldosterone and renin values in PUV patients before and after valve ablation.

Materials and Methods: This is a prospective observational study. It was conducted from September 2020 to August 2022 in the Department of pediatric surgery. The study group included 20 male babies with confirmed diagnosis of PUV. Clinical and radiological parameters were assessed. Plasma renin and aldosterone were measured using sandwich enzyme-linked Immunosorbent assay (ELISA) (ELK Biotechnology Co. LTD., Hubei, P.R.C.). Briefly, plasma samples or standard concentrations of the biomarker of interest were incubated in different 96-well ELISA plates coated with the appropriate antibodies. Statistical analyses were performed in Microsoft (MS) Excel using two-tailed Student's t-test. The Pearson test was used for correlation.

Results: Mean age of PUV patients was 2.72 years, whilst in the control group it was 2.58 years. Deranged renal function like raised urea and creatinine were significantly higher in the patient group than the control group. Median renin (82.89pg/ml) and aldosterone (71.76 pg./ml) in the patients with cases were significantly higher than the age-matched control group. In each age group, all levels of renin and aldosterone in urine and serum level were higher among patients than control.

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Keywords

- Posterior urethral valve
- Chronic Kidney disease
- Creatinine
- Biomarkers
- Aldosterone
- Renin

Median values of aldosterone level and renin fall significantly after corrective surgery. Levels of aldosterone level and renin correlated positively with serum and urea creatinine at presentation and follow-up.

Conclusion: Prognostic biomarkers are needed for PUV patients. Aldosterone and renin can be considered as early prognostic marker which are easy to measure in serum and urine.

Introduction

Posterior urethral valves are one of the most common causes of obstructive uropathy in the children. Posterior urethral valves can make varied amounts of damages to urinary tract such as acute retention, chronic renal disease, and in severe cases, pulmonary hypoplasia secondary to oligohydramnios. Posterior urethral valves are classified into three subtypes according to Young's criteria and is based on valve anatomy in posterior urethrae.[1]

Approximately one -third of PUV cases result in chronic kidney disease despite good management.[2] Some clinical parameters that accompany poor renal outcomes in PUV include late age of presentation (after two years of age), delayed fulguration (intervention after one month), high initial serum creatinine, failure of serum creatinine to return to physiologic level after one-month post-fulguration[3] and comorbidities like high grade of vesicoureteral reflux, and renal dysplasia.[4] Some suggest that late primary valve ablation after the first year of life is a risk factor for PUV.[5]

A recent study suggests the nadir creatinine within six week of valve fulguration as the only single factor for progression to chronic kidney disease in PUV patients.[6]

Another study reported that patients with post-ablation nadir creatinine above 0.85 mg/dl were at high risk for subsequent CKD.[7] Elevated nadir creatinine in the first year of life is generally regarded as the best

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predictor of adverse renal outcomes in these patients.[8]

Albumin in urine is the well-known biomarker of renal injury, but it occurs only after significant renal injury and not in tubulointerstitial disease. Cystatin C completely reabsorbed in tubule, and so undetectable in urine.[9]

Similarly, other novel biomarkers are coming in limelight for early detection of chronic kidney disease in PUV.[10] Obstructive uropathy in PUV result in stress in tubule-interstitial compartment that causes decreased renal plasma flow due to arteriolar constriction. The drop in the glomerular filtration rate determines the activation of the renin–angiotensin system, resulting in increased plasma renin activity (PRA) and aldosterone levels.[11-12] This results in increase of PRA and aldosterone values in serum and urine as consequences of tubular obstructive stress.[13]

Therefore, this study focuses to assess the role of urinary and serum aldosterone and renin values in PUV patients before and after valve ablation. Furthermore, it marks as early and sensitive prognostic biomarkers in PUV patients. These biomarkers are more sensitive and specific than the traditional biomarkers (serum creatinine, serum cystatin C, and albuminuria) as prognostic marker for CKD in PUV.

Materials and Methods

This is a prospective study. It was conducted from September 2020 to August 2022 in the department of paediatric surgery. The study was approved by the institute's ethical committee. The study group included 20 male babies with confirmed diagnosis of PUV. Control group include non-renal diseases patients like neck sinuses, hemangioma, cystic hygroma pre sternal sinus and they are of similar age group. Informed consent was taken prior to study. PUV patients were undergone endoscopic procedure and valve ablation. Preoperative urine samples were collected in operative room. The follow-up was done clinically by urinary stream and radiologically with voiding cystourethrography (VCUG). The follow-up was planned at 6 months following cystoscopic valve ablation. Furthermore, serum urea and creatinine, electrolytes, anthropometric data were recorded. Ultrasonography (on each follow-up) to assess postvoid urine residue (PVUR) in addition to VCUG (6 months follow up) for

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ascertaining ratio of the posterior urethra to anterior urethra diameter were performed.

All collected urine and plasma samples were centrifuged at 10,000 rpm for 20 min. The supernatant was collected and two divided aliquots were stored at −80°C.

Plasma renin, aldosterone, were measured using sandwich enzyme-linked Immunosorbent assay (ELK Biotechnology Co. LTD. Hubei, P.R.C.). Briefly, plasma samples or standard concentrations of the biomarker of interest were incubated in different 96-well ELISA plates coated with the appropriate antibodies. Biotinylated antibodies were added, followed by HRP addition, with washing in buffer solution. After incubation with the HRP solution, further washing was performed and a chromogenic substrate added, and the reaction stopped with a kit-based stop solution after fifteen minutes. Optical density was taken as per manufacturer's protocols and the concentration calculated by extrapolation against a standard curve. Statistical analyses were performed in MS Excel using two-tailed Student's t-test. The Pearson test was used for correlation.

Result

Twenty patients with PUV were included in study for two years. The median age at the time of valve ablation in PUV cases was 2.5 (1.20–3.87) years and none were diagnosed antenatally. This might be due to less awareness in parents and low seriocomic status. Mandelia et al[7] found the median age at the time of valve ablation was 5 months (range 3 days to 9 years). A study by Mac Rae Dell et al., age of the patient range was 3.2 years to 14.5 years.[8] The most common symptoms are fever and recurrent urinary tract infection (UTI) with deranged renal function in 14 (70%) cases. Dribbling of urine was present in 6 (30.0%) while 10 (55%) present with acute retention and sepsis.

Mean age of PUV patients was 2.72 years, whilst in the control group it was 2.58 years.

Deranged renal function like raised urea and creatinine were significantly higher in the patient group than the control group. Median renin (82.89pg/ml) and aldosterone (71.76 pg./ml) in the patients with PUV were significantly higher than the age-matched con troll group **(Table 1).**

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In each age group, all levels of renin and aldosterone in urine and serum level were higher among patients than control **(Table 1).**

Table 1: showing Pre-operative & Post-operative values (serum and urine) of Renin and Aldosterone.

Values	Pre-Post Aldo (plasma pg/ml)		Pre-Post Aldo (urine pg/ml)		Pre-Post renin (plasma pg/ml)		Pre-Post renin (urine pg/ml)		Pre-Post Creatinine (mg/ml)		Pre-Post Urea(mg/ml)	
Minimum	63.08	32.46	75.80	38.2	64.75	31.54	76.35	.5992	.8	.599	69.20	11
Maximum	85.33	89.65	97.31	95.20	87.20	89.65	97.06	1.635	2.30	1.63	155	189
Median	73.04	52.57	84.96	58.56	73.12	51.59	83.86	.8751	1.92	.87	106.5	68.07
Standard Deviation	6.288	4.639	6.499	4.271	6.724	4.601	6.843	.0701	.297	.070	15.26	12.45
p-value	<.0001		<.0001		<.0001		<.0001					

Median values of aldosterone level and renin fall significantly after corrective surgery. The Aldosterone level correlated positively with serum creatinine at presentation (correlation coefficient 0.6702, P-value < 0.001); blood urea at initial presentation (correlation coefficient 0.684, P-value < 0.001); serum creatinine at follow-up (correlation coefficient 0.7437, P- value < 0.001); blood urea at follow-up (correlation 0.603, P-value < 0.001) **(Table 2).** The renin level correlated positively with serum creatinine at presentation (correlation coefficient 0.6451, P-value < 0.001); blood urea at initial presentation (correlation coefficient 0.743, P-value < 0.001); serum creatinine at follow-up (correlation coefficient 0.7969, P- value < 0.001); blood urea at follow-up (correlation 0.8148, P-value < 0.001) **(Table 2).**

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Table 2: showing post-operative correlation of Aldosterone & renin with creatinine

	Post -op Ald Vs Creatinine (Serum)	Post -op Ald Vs Creatinine (Urine)	Post -op renin Vs Creatinine (Serum)	Post -op renin Vs Creatinine (Urine)
r-value	.7851	.7437	.7969	.8142
p-value	<.0001	<.0001	<.0001	<.0001

Discussion

PUV is the most common cause of obstructive uropathy in children and second most common cause for renal transplantation. Even after good management, chronic renal disease is the end result in 11%-51% patients.[5-7-14] A lot of research has been going on factors effecting outcome in PUV. Prognostic indicators in PUV is limited by various inadequate definition of variables, though nadir creatinine (below 0.8 mg/dL) is consistent and independent prognostic indicator.[7-8.14-16] We need sensitive and specific biomarkers that can select babies requiring early and more aggressive intervention. Urinary and serum biomarkers instead of hazardous radiological exposure is demand of time now. Urinary obstruction in PUV results in rise in local pressure, decrease renal flow (due to afferent arteriolar constriction) and thus result in activation of the renin–angiotensin system. This results in increased plasma renin activity (PRA) and aldosterone levels.[11-12] Development of tubular resistance to renin and aldosterone as a consequence of tubular obstructive stress can also determine an increase in both PRA and aldosterone levels.[13] Previous studies also suggest rise in plasma renin activity in PUV patients.[17] Similarly Rise in renin was observed in patients with PUV significantly in present study. In a previous study regarding long-term follow-up of 312 cases of PUV, 52% had a normal life with normal renal parameters without

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any sequelae of PUV. The remaining 48 %had progressed towards ESRD (28%), chronic renal failure (14%) and renal rickets (6%).[18] In another study evaluating plasma renin activity (PRA) in PUV patients, mean PRA was elevated in all patients before valve ablation, irrespective of age, and decreased after valve ablation.[19] A strong association of PRA with renal damage was found on multivariate analysis of various known risk factors. PRA also had prognostic significance regarding future renal function.[20-21] Renin is relatively unstable but aldosterone is easy to calculate and more specific than prior biomarkers in research as presented in study.

Conclusion

Prognostic biomarkers are needed for PUV patients. Aldosterone and Renin can be considered as early prognostic marker which is easy to measure in serum and urine.

Ethical Consideration

Approval was obtained from the ethics committee of Banaras Hindu university, institute of medical sciences, Varanasi, India. (ECR/526/Inst/UP/2014/RR-20 dt 19.5.2020)

Acknowledgment

Acknowledgement: We are highly grateful to the MRU(Multidisciplinary research unit) of the institute for the laboratory work and statistical analysis.

Funding/Support

Not applicable

Conflict of interests

There is no conflict of interest

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References

1. Nasir AA, Ameh EA, Abdur-Rahman LO, et al: Posterior urethral valve. World J Pediatr. 2011 Aug;7(3):205-16 .
2. Alsaywid BS, Mohammed AF, Jbril SM, et al: Renal outcome among children with posterior urethral valve: When to worry? Urol Ann (2021) 13:30–5.
3. Velhal R, Jain A, Nayan A, et al: Impact of surgical intervention on progression to end-stage renal disease in patients with posterior urethral valve. Afr J Urol (2021) 27:158.
4. Farhat W, McLorie G, Capolicchio G, et al: Outcomes of primary valve ablation versus urinary tract diversion in patients with posterior urethral valves. Urology (2000) 56:653−7.
5. Sarhan O, El−Ghoneimi A, Dawaba M, et al: Early versus late primary valve ablation: Does it affect the prognosis in children with posterior urethral valves. J Pediatr Urol (2008).
6. Wu CQ, Blum ES, Patil D, et al: Predicting childhood chronic kidney disease severity in infants with posterior urethral valve: A critical analysis of creatinine values in the first year of life. Pediatr Nephrol (2021) 37:1339–45.
7. Coleman R, King T, Nicoara CD, et al: Nadir creatinine in posterior urethral valves: How high is low enough? J Pediatr Urol (2015) 11:356. e1–5.
8. Hennus PM, van der Heijden GJ, Bosch JL, et al: A systematic review on renal and bladder dysfunction after endoscopic treatment of infravesical obstruction in boys. PLoS One (2012).
9. Conti M, Moutereau S, Zater M, et al: Urinary cystatin c as a specific marker of tubular dysfunction. Clin Chem Lab Med (2006) 44:288–91 .
10. Uwaezuoke SN, Ayuk AC, Muoneke UV, et al: Chronic kidney disease in children: Novel biomarkers as predictors of disease. Saudi J Kidney Dis Transplant (2018) 29:775–84.
11. Chevalier RL, Kaiser DL: Chronic partial ureteral obstruction in the neonatal guinea pig. I. Influence of uninephrectomy on growth and hemodynamics. Pediatric research. 1984 Dec;18(12):1266-71.

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12. Chevalier RL, Peach MJ, Broccoli AV: Hemodynamic effects of enalapril on neonatal chronic partial mureteral obstruction. Kidney international. 1985 Dec 1;28(6):891-8.
13. Rodríguez-Soriano J, Vallo A, Oliveros R, et al: Transient pseudohypoaldosteronism secondary to obstructive uropathy in infancy. The Journal of pediatrics. 1983 Sep 1;103(3):375-80.
14. Ansari MS, Gulia A, Srivastava Aneesh, et al: Risk factors for progression to end-stage renal disease in children with posterior urethral valves. J Pediatr Urol 2010:261–4.
15. DeFoor W, Clark C, Jackson E, et al: Risk factors for end stage renal disease in children with posterior urethral valves. J Urol 2008; 180:1705–8.
16. Bilgutay AN, Roth DR, Gonzales Jr ET, et al. Posterior urethral valves: risk factors for progression to renal failure. J Pediatr Urol 2016;12, 179 e1-7.
17. Bajpai M, Pratap A, Tripathi M, et al: preliminary observations on the significance of plasma renin activity as a prognostic marker. J Urol 2005; 173:592e4.
18. Gangopadhya AN: The experience of managing posterior urethral valve (PUV) over a period of 22 years: A single center study. J Indian Assoc Pediatr Surg 2003; 8:133e9.
19. Bajpai M, Singh A: Plasma renin activity: an early marker of progressive renal disease in posterior urethral valves. J In- dian Assoc Pediatr Surg 2013 OcteDec;18(4):143e6.
20. Bajpai M, Singh A: Plasma renin activity: an early marker of progressive renal disease in posterior urethral valves. J In- dian Assoc Pediatr Surg 2013 OcteDec;18(4):143e6.
21. Panigrahi P, Chowdhary S, Sharma SP, et al: Role of urinary transforming growth factor beta-B1 and monocyte chemotactic protein-1 as prognostic biomarkers in posterior urethral valve. Journal of Indian Association of Pediatric Surgeons. 2020 Jul 1;25(4):219-24.

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