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EFFECT OF PROLONGED-RELEASE PIRFENIDONE ON RENAL FUNCTION IN SEPTIC ACUTE KIDNEY INJURY PATIENTS

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ABSTRACT

Introduction: Acute kidney damage is severe medical consequence that has a poor prognosis on its own. AKI occurs in around one out of every five patients with non-severe sepsis, rising to two out of three in critically sick patients

Aim: in research we aimed to assess impact of PR-PFD on renal function in studied cases with sAKI.

Studied cases & techniques: This research was randomized, double-blind, parallel-design clinical trial showed in single university hospital.

Results: there was variation among studied groups as regard pH, serum Na & platelets at day1 & statistical variation among studied groups as regard pH, serum K and platelets at day1. In group A there was variation among day 1 and day 7 as regard creatinine, serum HCO3, serum K, serum Na, Hb, serum uric acid, leukocytes and platelets. In group B there was variation among day 1 and day 7 as regard creatinine, pH, serum K, Hb, leukocytes and platelets. In group C there was variation among day 1 and day 7 as regard creatinine, serum K, serum Na, serum uric acid, leukocytes and platelets.

Conclusion: In conclusion, PR-PFD was safe in terms of adverse events and improves kidney function when compared to placebo in patients with septic AKI. For our findings to be verified, more research is required.

Keywords: Pirfenidone; Renal Function; Septic Acute Kidney Injury.

Introduction

Acute kidney damage is severe medical consequence that has a poor prognosis on its own **[1]**. AKI occurs in around one out of every five patients with non-severe sepsis **[3]**, rising to two out of three in critically sick patients **[3]**. AKI causes around fifty percent of ICU studied cases to pass away, & those who survive episode are more likely to develop chronic kidney disease (CKD) **[4]**. AKI can now only be managed by relieving secondary hemodynamic & toxic renal insults & providing supportive measures, like dialysis. There are currently few pharmaceutical treatment alternatives accessible to stop & treat AKI.

Although there are several potential causes of AKI **[4]**, sepsis is the most significant one **[5]**. Regarding pathophysiology, patient traits, and clinical consequences, sepsis-associated AKI is different from nonsepsis AKI **[5]**. Once AKIN stage 3 develops, sAKI is common, severe, less

likely to resolve, and linked with greater mortality **[6]**. It has been proposed that tubular stress and subsequent tubular injury are caused by the glomerular ultrafiltration of toxic blood **[7]**. This theory contends that the glomerular filtrate becomes highly concentrated during sepsis and contains cytokines, chemokines, and complement fragments that may be hazardous to tubular cells **[8]**. Experimental findings **[9]** corroborate this "inflammatory" theory of AKI.

Renal responses to inflammation may involve loss of cell polarity, autophagy, digesting, and mitochondrial malfunction (mitophagy) to reduce energy consumption **[10]**. It is yet unclear how these intricate inflammatory processes impact renal function. Therefore, further therapies that might enhance the prognosis for AKI are required **[11]**. Experimental research supports PFD's anti-inflammatory and beneficial benefits in many AKI models **[12]**.

In this investigation, we showed double-blind, randomised clinical trial to assess impact of PR-PFDon renal function in studied cases with sAKI.

Studied cases & techniques:

This was single university hospital-based randomised, double-blind, parallel-design clinical trial. Research's population consisted of hospitalised septic AKI studied cases. Serum creatinine KDIGOcriteria were used to diagnose AKI, & Surviving Sepsis-3 campaign was used to describe sepsis.

Inclusion criteria: Septic studied cases with AKI years old eighteen to eighty five AKI by serum creatinine, based on KDIGO guide 2012 Acute Kidney Injury & acute on Chronic kidney disease.

Exclusion Criteria: Chronic kidney disease stage 3b, four & five known & sharpened, chronic dialysis, history of AKI & renal replacement treatment in previous 3 months, & pregnancy AKI caused by other than sepsis.

Aside from standard AKI therapy, studied cases were assigned to 1 of three study groups: Group A received 1200 mg of PR-PFD orally each twelve hours for seven daysFor seven days, Group B received six hundred mg of PR-PFDin morning & matched placebo at night. Group C received matched placebo orally each twelve hours for seven days.

Main goal was to reduce serum creatinine & rise urinary volume; secondary goals included variations in serum electrolytes, acid-base status, & mortality.

Randomization was done in Excel software in one: one: one fashion & nephrology staff members who were blind to allocation groups gave drugs to every studied case daily.

Every studied cases underwent thorough clinical history & physical test, which contained blood pressure, heart & respiratory rates, oxygen saturation, ventilatory parameters in mechanically assisted ventilation studied cases, & strict fluid balance. On regular basis, the complete blood count, serum creatinine, serum urea, BUN, serum electrolytes, & urinalysis parameters were measured.

Statistical analysis: data was fed into computer & analysed withIBM SPSSsoftware package version twenty. IBM Corporation, Armonk, New York Numbers & percentages were used to define qualitative data. Kolmogorov-Smirnov exam was used to confirm distribution's normality. Range, mean, standard deviation, median, & interquartile range were used to define quantitative

data. Importance of obtained outcomes was determined at five percent level.

Used tests were: Chi-square test: For categorical variables, to compare among variable groups. **Oneway ANOVAtest:** For normally distributed quantitative variables, to compare among more than 2 studied groups. **Kruskal-Wallis test:** For abnormally distributed quantitative variables, to compare among more than 2 studied groups. **Paired t-test:** For normally distributed quantitative variables, to compare among two repeated measures. **Wilcoxon test:** For abnormally distributed quantitative variables, to compare among two repeated measures

Table (1): Comparing among studied cases based on baseline & clinical data

	Group A (n = thirty)		**Group B (n = thirty)**		**Group C (n = thirty)**		**p**
Years old							
Range.	34 – 77		35 – 70		36 – 72		0.647
Mean ± SD.	55.67 ± 13.2		53.03 ± 10.45		55.27 ± 11.41		
Sex	No.	%	No.	%	No.	%	
Female	9	30.0	12	40.0	12	40.0	0.650
Male	21	70.0	18	60.0	18	60.0	
Comorbidities							
COPD	0	0.0	1	3.3	1	3.3	0.600
CHF	2	6.7	1	3.3	2	6.7	0.809
DM	11	36.7	12	40.0	12	40.0	0.954
HTN	12	40.0	10	33.3	15	50.0	0.418
Clinical data							
Oligoanuria	6	20.0	3	10.0	7	23.3	0.372
Septic shock	7	23.3	6	20.0	10	33.3	0.468
Cardiogenic shock	7	23.3	4	16.7	6	20.0	0.602
Surgical case	7	23.3	14	46.7	11	36.7	0.166
Mechanical ventilation	11	36.7	11	36.7	8	26.7	0.638

SD: **Standard deviation**

χ^2: **Chi square test** **F: Oneway ANOVA**

p: p value comparison among studied groups

*: significant at $p \leq 0.05$

Table finds that there was no variation among studied groups as regard baseline and clinical data.

Table (2): Comparing among studied cases based on studied variables

	Group A (n = thirty)	**Group B (n = thirty)**	**Group C (n = thirty)**	**p**
Creatinine				
Day one	2.38 (1.44 – 3.46)	2.01 (1.77 – 2.38)	2.42 (1.96 – 2.71)	0.091

Day 7	1.55 (0.66 – 2.39)	1.31 (0.9 – 1.94)	0.87 (0.69 – 1.32)	0.233
p1	<0.001*	0.002*	<0.001*	
Urinary output				
Day 1	1252 (650.75 – 1909.5)	1407.5 (969.25 – 2025.5)	1254.5 (975.5 – 1734)	0.421
Day 7	1232 (1069.25 – 1486)	1220.5 (697.75 – 2008.5)	1592 (1060.75 – 1857)	0.211
p1	0.673	0.086	0.141	
Serum pH				
Day one	7.39 ± .07	7.33 ± .06	7.32 ± .09	<.001*
Day seven	7.39 ± .08	7.35 ± .06	7.33 ± .1	.013*
p1	0.774	<0.001*	0.222	
Serum HCO3				
Day 1	20.8 ± 5.88	21.53 ± 4.96	20.47 ± 4.17	0.706
Day 7	21.48 ± 6.56	21.36 ± 4.84	20.49 ± 4.43	0.737
p1	0.042*	0.346	0.921	
Serum K				
Day 1	4.09 ± 0.89	4.76 ± 1.18	4.63 ± 1.73	0.121
Day 7	3.18 ± 0.85	3.95 ± 1.29	3.1 ± 1.69	0.027*
p1	<0.001*	<0.001*	<0.001*	
Serum Na				
Day 1	139.62 ± 7.62	131.8 ± 9.13	126.35 ± 21.26	0.002*
Day 7	135.88 ± 7.85	131.99 ± 8.99	126.98 ± 20.99	0.051
p1	<0.001*	0.396	0.008*	
Hb				
Day 1	10.18 ± 1.8	10.66 ± 1.65	10.38 ± 2.24	0.627
Day 7	9.71 ± 1.74	9.87 ± 1.71	10.45 ± 2.28	0.300
p1	<0.001*	<0.001*	0.231	
Serum uric acid				
Day 1	5.3 (4.13 – 6.05)	5.55 (3.18 – 7.45)	6.9 (3.28 – 9.88)	0.333
Day 7	5 (3.6 – 5.7)	5.65 (3.58 – 7.7)	6.65 (3.1 – 9.68)	0.196
p1	<0.001*	0.063	<0.001*	
Leukocytes				
Day 1	11.7 (8.55 – 16.8)	14.35 (9.55 – 19.83)	12.65 (8.63 – 16.05)	0.272
Day 7	10.35 (5.8 – 15.73)	11.4 (6.48 – 16.65)	9.75 (6.03 – 12.63)	0.298

p1	<0.001*	<0.001*	<0.001*	
Platelets				
Day 1	203.5 (145.75 – 260.5)	270 (202.25 – 339.5)	278.5 (165.25 – 420)	0.020*
Day 7	227 (173.5 – 291)	310 (213 – 355)	326 (197.25 – 439.75)	0.008*
p1	<0.001*	<.001*	<0.001*	

SD: **Standard deviation**

F: Oneway ANOVA test **H: Kruskal-Wallis test**

t: Paired t-test **Z: Wilcoxon test**

p: p value comparison among studied groups

p: p value comparison among day 1 & day 7

*: significant at $p \leq 0.05$

Table finds that there was variation among studied groups as regard pH, serum Na & platelets at day1 & statistical variation among studied groups as regard pH, serum K and platelets at day1.

In group A there was variation among day 1 and day 7 as regard creatinine, serum HCO3, serum K, serum Na, Hb, serum uric acid, leukocytes and platelets.

In group B there was variation among day 1 and day 7 as regard creatinine, pH, serum K, Hb, leukocytes and platelets.

In group C there was variation among day 1 and day 7 as regard creatinine, serum K, serum Na, serum uric acid, leukocytes and platelets.

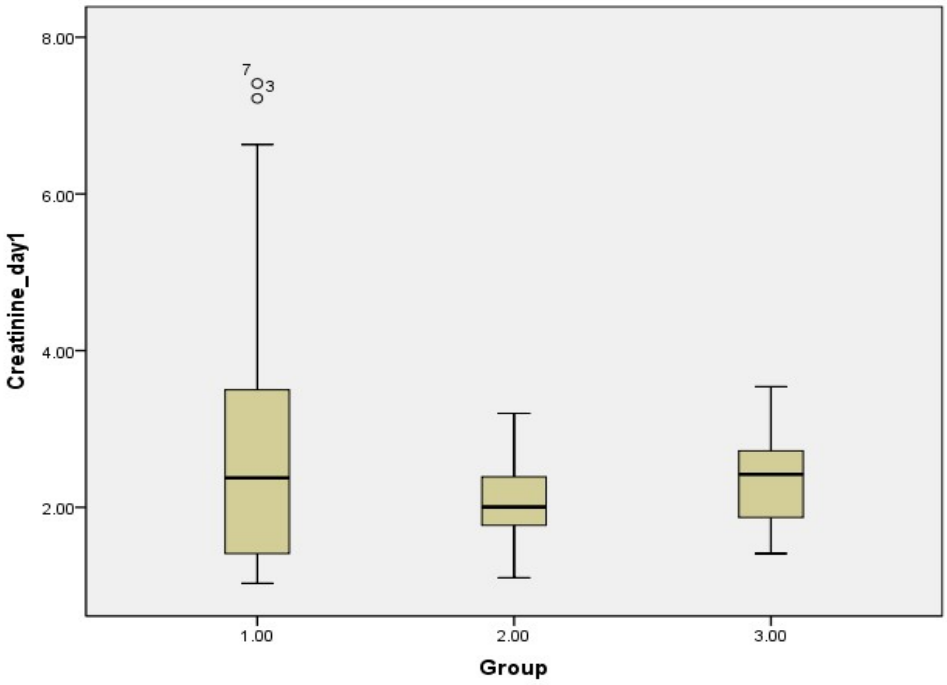

Fig (1): Comparing among studied cases based on creatinine day 1.

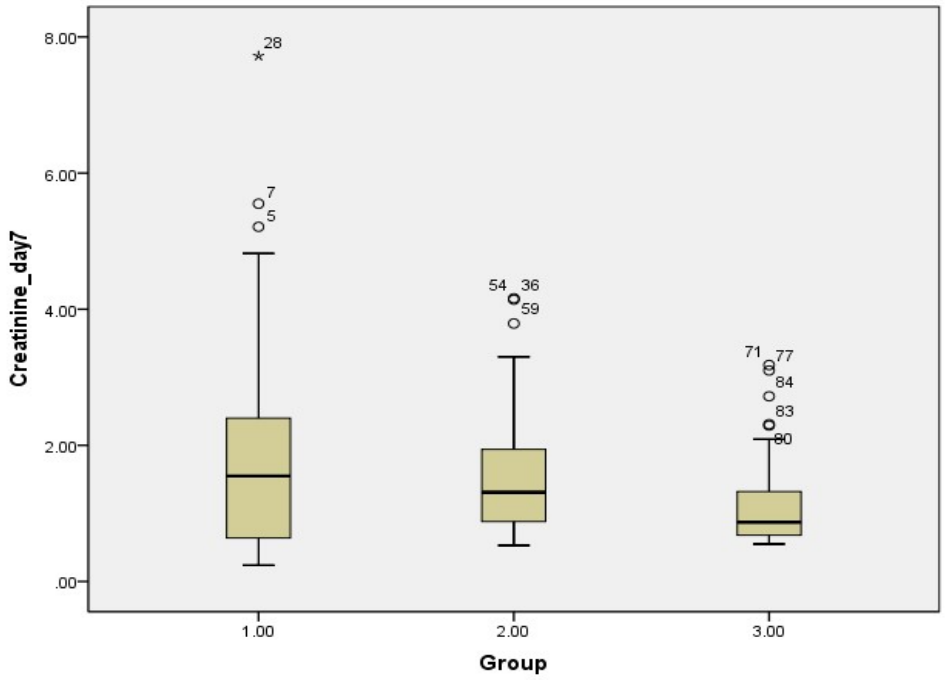

Fig (2): Comparing among studied cases based on creatinine day 7.

Table (3): Comparing among studied cases based mortality

	GroupA (n = thirty)		**GroupB (n = thirty)**		**Group B (n = thirty)**		**p**
	No.	percent	No.	%	No.	%	
Died	10	33.3	7	23.3	6	20.0	0.468

χ^2: **Chi square test**

p: p value comparison among studied groups

*: significant at $p \leq 0.05$

Table finds that there was no variation among studied groups as regard mortality.

Discussion

Based on this theory, throughout sepsis, glomerular filtrate contains cytokines, chemokines, & complement fragments that can be toxic to tubular cells **[6]**. Experiment results reinforce "inflammatory" hypothesis of AKI **[7]**.

There are numerous proinflammatory & anti-inflammatory variables that vary quickly when sepsis advances **[8]**. Previous research suggests that PFD has anti-inflammatory impact. PFD was beneficial in reducing TNF-α & IL-6 levels, reducing proteinuria & NAG activity, attenuating interstitial fibrosis, & reducing expression of fibrotic markers & macrophage infiltration in nephrectomized rat model. PFD therapy reduced TNF-α, IL-6, & nitric oxide synthase-2 expression in M1 macrophages, indicating its effectiveness in early & late stages of kidney damage **[9]**.

Difference in TNF-α levels among Chen et alstudy.'s & our outcomes could be described by

aetiology of AKI. We investigated this event in human sepsis, which is thought to have robust inflammatory response than nephrectomized model; another explanation could be drug dosing & administration schedule. To best of knowledge, this is 1st period PR-PFDhas been tested in sAKI, & we are unable to compare outcomes to those of other clinical researches.

Renal responses to inflammation may involve loss of cell polarity, digestion, autophagy, and mitophagy, all of which reduce energy consumption **[8]**. The impact of these intricate inflammatory processes on renal function is still unclear. Consequently, there is requirement for additional interventions that could enhance the prognosis for AKI **[9]**. In various AKI models, experimental studies have demonstrated anti-inflammatory & beneficial impacts brought about byPFD **[12]**.

In double-blind, randomised clinical trial, we investigated impacts of PR-PFD on renal function in sAKI studied cases.

In thesis we demonstrated that there was no variation among studied groups as regard baseline & clinical data.

Chávez-Iñiguez et al. [13] found that among twenty eight in group A, thirty in group B, & thirty in group C, there was no variation among studied groups as regard baseline data.

In this study we found that there was variation among studied groups as regard pH, serum Na & platelets at day1 & statistical variation among studied groups as regard pH, serum K and platelets at day1.

Cho et al. [14] found that with pirfenidone treatment, monthly modification in GFR enhanced from baseline median of -0.61 ml/min per 1.73 m2 to -0.45 ml/min per 1.73 m2. This difference represents twenty five percent advancement in rate of decline.

Lima-Posada et al. [15] found that from day 1 (4.37 6 0.90) to day seven, Group B with pirfenidone sCr improved (0.94 6 1.15). UO trajectory in Group B enhanced more than in Group A & placebo, although there were no variations among three study groups.

Matsumoto et al. [16] found that Pirfenidone suppressed renal function decline up to six months after starting therapy ($p<.001$), with tendency to suppress renal function also at twelve months after therapy ($p =.136$).

Similarly, nonrandomized pilot trial by **Ojeda-Duran et al. [17]** Above sixty-month period, researchers assessed security of new formulation of prolonged release pirfenidone in eighteen studied cases with CKD, particularly those with focal & segmental glomerular hyalinization. This research reveals that prolonged release pirfenidone found renal function decline in CKD studied cases. Whereas levels of eGFR, creatinine, cystatin C, urea, haemoglobin, & hepatic transaminases did not change in this research, proteinuria did. When compared to pirfenidone preparations used in earlier researches, this new pharmaceutical formulation showed minor side effects & enhanced tolerance.

Research by **Takakura et al. [18]** Prophylactic pirfenidone treatment reduced fibrosis by eighty percent while improving proteinuria, serum blood urea nitrogen, & creatinine levels.

Shimizu et al. [19] PFD therapy attenuated renal damage in rat model with unilateral obstruction & induced renal function recovery prior to ureteral obstruction removal, & same

group demonstrated that PFD inhibits collagen accumulation in remanent kidney in rats with partial nephrectomy. Even so, septic AKI may have different physiopathological mechanism & may respond differently to same drug.

Pirfenidone could improve glomerular fibrosis but may not be effective in reducing proteinuria. Provided that pirfenidone pretreatment may defend against proteinuria, pirfenidone pretreatment could be beneficial in avoiding proteinuria in secondary glomerular diseases like diabetic nephropathy **[19]**

In this that there was no variation among studied groups as regard mortality.

Chávez-Iñiguez et al. [13] found that mortality rate did not vary between groups (p=0.38). When compared to placebo, studied cases who received PFD at any dose had nonsignificant (p=0.21) risk ratio for death of 1.1 (ninety five percent CI 0.93-1.48).

Cho et al. [14] found that there was insignificant reduction of mortality rate among studied cases who received PFD at any dose (p <.001).

We are aware of the following limitations of our study: this was single-center research, sample size was small, & we did not consider urinary output when classifying AKI; statistical analysis may have been underpowered for primary & secondary results; & lastly, follow-up was only allowed to last for 7 days. We are aware that these results cannot be applied to other populations because of these restrictions.

In conclusion, PR-PFD was safe in terms of adverse events and advance kidney function when compared to placebo in patients with septic AKI. For our findings to be verified, more research is required.

References

1. Lameire N. H., Bagga A., Cruz D. Acute kidney injury: an increasing global concern," *The Lancet*, 2013; 382(9887): 170–179.
2. Murugan R., Karajala-Subramanyam V., Lee M. Acute kidney injury in non-severe pneumonia is associated with an increased immune response and lower survival," *Kidney International*, 2010; 77(6): 527–535.
3. Hoste E. A. J., Bagshaw S. M., Bellomo R. Epidemiology of acute kidney injury in critically ill patients: the multinational AKI-EPI study," *Intensive Care Medicine*, 2015; 41(8): 1411–1423.
4. Case J., Khan S., Khalid R., Khan A. Epidemiology of acute kidney injury in the intensive care unit, *Critical Care Research and Practice*, 2013; Article ID 479730, 9.
5. Zarjou A, Agarwal A. Sepsis and acute kidney injury, *Journal of the American Society of Nephrology*, 2011; 22(6): 999–1006,.
6. Peters E, Antonelli M, Wittebole X, Nanchal R, François B, Sakr Y. A worldwide multicentre evaluationn of the influence of deterioration or improvement of acute kidney injury on clinical outcome in critically ill patients with and without sepsis at ICU admission: results from the intensive care over nations audit, *Critical Care*, 2018; 22: 188.

7. Bellomo R, Kellum J. A, Ronco C. Acute kidney injury in sepsis, *Intensive Care Medicine*, 2017; 43(6): 816–828.
8. Gómez H, Kellum J. A. Sepsis-induced acute kidney injury," *Current Opinion in Critical Care*, 2016; 22(6): 546–553.
9. Dellepiane S, Marengo M, Cantaluppi V. Detrimental cross-talk between sepsis and acute kidney injury: new pathogenic mechanisms, early biomarkers and targeted therapies, *Critical Care*, 2016; 20: 61.
10. Mariano F, Cantaluppi V, Stella M. Circulating plasma factors induce tubular and glomerular alterations in septic burns patients," *Critical Care*, 2008; 12(2): R42.
11. Pickkers P, Ostermann M, Joannidis M. The intensive care medicine agenda on acute kidney injury," *Intensive Care Medicine*, 2017; 43(9): 1198–1209.
12. Chen J.-F, Ni H.-F, Pan M.-M. Pirfenidone inhibits macrophage infiltration in 5/6 nephrectomized rats," *American Journal of Physiology-Renal Physiology*, 2013; 304(6): F676–F685.
13. Chávez-Iñiguez, J. S., Poo, J. L., Ibarra-Estrada, M., García-Benavides, L., Navarro-Blackaller, G., Cervantes-Sánchez, C., et al. Effect of Prolonged-Release Pirfenidone on Renal Function in Septic Acute Kidney Injury Patients: A Double-Blind Placebo-Controlled Clinical Trial. International Journal of Nephrology, 2021.
14. Cho, M. E., Smith, D. C., Branton, M. H., Penzak, S. R., Kopp, J. B. Pirfenidone slows renal function decline in patients with focal segmental glomerulosclerosis. Clinical Journal of the American Society of Nephrology, 2007; 2(5), 906-913.
15. Lima-Posada, I., Fontana, F., Pérez-Villalva, R., Berman-Parks, N., Bobadilla, N. A. Pirfenidone prevents acute kidney injury in the rat. BMC nephrology, 2019; 20(1): 1-9.
16. Matsumoto, J., Sunohara, K., Mori, Y., Nagaya, H., Inaba, S. Effects of pirfenidone on renal function in patients with interstitial pneumonia. Renal Failure, 2021; 43(1): 879-881.
17. Ojeda-Duran, S. A., Lyra-Gonzalez, I., Meza-Rios, A., Lucano-Landeros, S., Sandoval-Rodriguez, A., Vazquez-Del Mercado, M., et al. Evaluation of safety of a newly formulated pirfenidone in chronic kidney disease: a non-randomized pilot study in mexican patients. Journal of Renal and Hepatic Disorders, 2020; 4(1): 22-30.
18. Takakura, K., Tahara, A., Sanagi, M., Itoh, H., & Tomura, Y. Antifibrotic effects of pirfenidone in rat proximal tubular epithelial cells. Renal Failure, 2012; 34(10): 1309-1316.
19. Shimizu, T., Kuroda, T., Hata, S., Fukagawa, M., Margolin, S. B., Kurokawa, K. Pirfenidone improves renal function and fibrosis in the post-obstructed kidney. Kidney international, 1998; 54(1), 99-109.