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Evaluation of Spot Urine Protein/Creatinine Ratio versus 24 Hour Urine Protein in Diagnosis of Hypertensive Disorders of Pregnancy

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Abstract:
Aim: *To determine if spot urine protein/creatinine (P/C) ratio can be used as an alternative method to 24 hour urinary protein for detecting significant proteinuria in patients with pre-eclampsia.*
Method: *Spot urine P/C ratio and 24 hour urine protein excretion was measured in 50 patients with pre-eclampsia. P/C ratio was determined in first morning midstream urine sample and total amount of protein excretion over 24 hours collection was measured on the next day. Correlation between the two parameters was measured and diagnostic cut off value was determined in relation to sensitivity and specificity, using the ROC curve analysis.*
Result: *A strong correlation was observed from r=0.94 with p<0.0001. Optimal cut-off value was 0.20 with 83.33% sensitivity and 87.5% specificity.*
Conclusion: *Spot urine P/C ratio may be a quick, convenient and accurate diagnostic test of significant proteinuria in patients of pre-eclampsia.*
Keywords: *proteinuria, protein/creatinine ratio, 24 hour urine protein, pre-eclampsia.*

I. Introduction

Hypertensive disorders, a common cause of maternal morbidity occurs in 2% to 8% of all pregnancies. The latest analysis by the World Health Organization suggests that, in developed countries, 16% of maternal deaths in pregnancy were a result of hypertensive disorders. As a result, obstetricians should always be on the alert for any sign of this hazardous complication. Clinical utility of spot urine P/C ratio as an alternative of 24hour urine protein excretion for detection of significant proteinuria in pre-eclampsia still remains unclear. While several international bodies have accepted it as a diagnostic test, it is still not accepted by the American Congress of Obstetricians and Gynaecologists and the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. In this study, we examined the correlation between spot urine P/C ratio and 24 hour urine protein in patients being evaluated for pre-eclampsia.

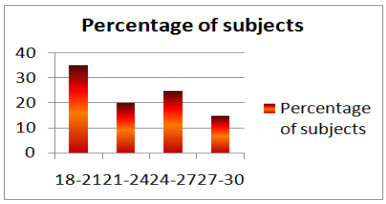
II. Material And Methods

This study was conducted over a period of six months from March 2012 to August 2012. A group of 50 patients were selected from those admitted in antenatal ward of Eden Hospital, Medical College, Kolkata. Inclusion criteria was hypertensive disorder in pregnancy with gestational age more than 20 weeks, and SBP>140mm Hg or DBP>90mm Hg. Exclusion criteria were coexisting urinary tract infection or bacteriuria, ruptured membranes, renal disorders, diuretic therapy, gestational diabetes, heavy exercise (>1hr of vigorous exercise on the day of urine collection), bed rest for more than 24 hours, and women who delivered before the 24 hour urine collection was completed.

Informed consent was obtained from all patients. First morning midstream sample of urine was collected and analysed for P/C ratio. Subsequent urine samples were collected over a 24hour period in a clean container and this was used to assess 24 hour urine protein excretion. Urine protein was measured by colorimetric method using pyrogallol red molybdate complex on Cobas Integra 400 autoanalyzer and urine creatinine was measured by Jaffe method on Hitachi 911 autoanalyzer instrument. Adequacy of 24 hour urine collection was assessed by comparing the total creatinine in the sample to the predicted creatinine estimated by the Cockroft-Gault equation for women.

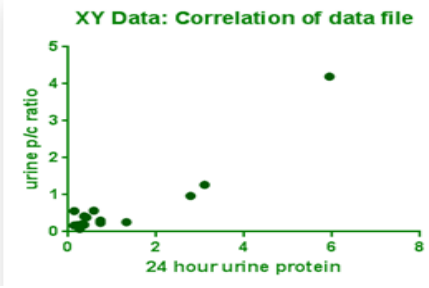
III. Results

80% of the patients were primigravida and 20% were multigravida. Age wise distribution is shown in the graph attached.



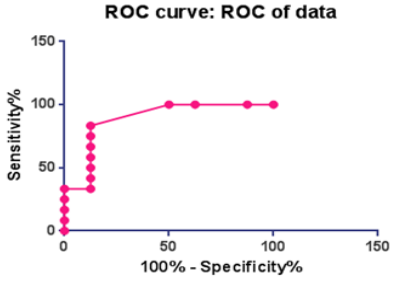
Data was analysed using SPSS 16 and Graph pad Prism 6 softwares. Results were considered significant when p<0.05. Demographic and baseline data were represented as mean±SD and percentage, where appropriate. The correlation between spot urine P/C ratio and 24 hour urine protein was analysed using Pearson correlation test. Sensitivity, specificity and predictive values of the spot urine P/C ratio at various cut-offs for prediction of significant proteinuria were estimated considering the 24hour urinary protein as the gold standard. The receiver operating characteristic (ROC) curve was used and the area under the curve(AUC) was calculated.

Mean urine P/C ratio was 0.547±0.91 and mean urine 24 hour protein excretion was 0.938±1.43gm/day. Using Pearson correlation coefficient, there was a positive correlation between 24 hour urinary protein and spot urine P/C ratio (r=0.9364) with 95% confidence interval between 0.8432 to 0.9749 and P value<0.0001(two-tailed).



ROC curve was calculated taking urine protein excretion >300mg/day as the gold standard. Area under ROC curve = 0.885, with standard error = 0.085, 95% confidence interval between 0.71 to 1.05 and P value = 0.004. The optimal spot P/C ratio cut-off point was 0.20 for 300mg/24hours protein excretion with sensitivity 83.33%, specificity 87.5% and likelihood ratio 6.67.

Cut-off	Sensitivity	95% CI	Specificity%	95% CI	Likelihood ratio
> 0.1245	100.0	73.54% to 100.0%	12.50	0.3160% to 52.65%	1.143
> 0.1750	100.0	73.54% to 100.0%	37.50	8.523% to 75.51%	1.600
> 0.1850	100.0	73.54% to 100.0%	50.00	15.70% to 84.30%	2.000
> 0.2000	**83.33**	**51.59% to 97.91%**	**87.50**	**47.35% to 99.68%**	**6.667**
> 0.2250	75.00	42.81% to 94.51%	87.50	47.35% to 99.68%	6.000
> 0.2500	66.67	34.89% to 90.08%	87.50	47.35% to 99.68%	5.333
> 0.2800	58.33	27.67% to 84.83%	87.50	47.35% to 99.68%	4.667
> 0.3450	50.00	21.09% to 78.91%	87.50	47.35% to 99.68%	4.000
> 0.4050	41.67	15.17% to 72.33%	87.50	47.35% to 99.68%	3.333
> 0.4900	33.33	9.925% to 65.11%	87.50	47.35% to 99.68%	2.667
> 0.5650	33.33	9.925% to 65.11%	100.0	63.06% to 100.0%	
> 0.7700	25.00	5.486% to 57.19%	100.0	63.06% to 100.0%	
> 1.120	16.67	2.086% to 48.41%	100.0	63.06% to 100.0%	
> 2.735	8.333	0.2108% to 38.48%	100.0	63.06% to 100.0%	



IV. Discussion

Pre-eclampsia, which accounts for most hypertensive disorders of pregnancy, is defined as a systolic blood pressure level of 140mm Hg or higher or a diastolic blood pressure level of 90 mm Hg or higher that occurs after 20 weeks of gestation with proteinuria.1

Pre-eclampsia poses a great hazard to both the mother and the fetus with adverse outcomes, thereby necessitating early detection for proper management. It is a multisystem endothelial disease that leads to glomeruloendotheliosis, and in severe cases it may lead to renal impairment and failure. The glomerular basement membrane becomes permeable to proteins, including albumin, and detection of these components in urine is key to the diagnosis. Significant proteinuria exposes the pregnant woman to hazards such as coagulopathy, liver disease, and stroke.2-5 Serious perinatal morbidity occurs in the form of preterm delivery (often iatrogenic) and foetal growth restriction. Measuring proteinuria is mandatory for diagnosis and evaluation of the severity of pre-eclampsia.

Urinary dipstick test is commonly used as a bedside method for detection of proteinuria because of its simplicity and low cost. However, it gives fluctuating results during the day related to changes in water intake, exercise, diet, postural changes or improper training regarding use of dipstick. The urinary dipstick test results 3+ and 4+ have very low positive predictive values are, therefore, not valid for diagnosis of severe pre-eclampsia.

Urine collection over 24 hours is considered the traditional comparator for quantification of proteinuria in pregnancy, when significant proteinuria is defined as proteinuria of 300mg/24 hours or more6,7. The urine requires refrigeration and its collection is cumbersome, time consuming, and potentially misleading if collected inaccurately. Also, it may not be possible to complete the urine collection when delivery occurs, leading to undetermined proteinuria status and an unsubstantiated diagnosis of pre-eclampsia. Timed collections delay clinical diagnosis and cause risk to mother and fetus. Moreover, it may result in prolonged hospital stay when a hypertensive disorder of pregnancy is being investigated, thereby increasing patient anxiety and healthcare costs.

Because of the disadvantages of 24 hour urine collection, alternatives for the diagnosis of proteinuria in pregnancy have been considered. Urine P/C ratio is considered to be a more rapid and accurate diagnostic test for proteinuria. Measurement of protein-creatinine (P/C) ratio in a spot urine sample provides quantitative estimation of proteinuria, and also avoids the influence of variations in urinary solute concentration and is independent of the degree of dilution of urine.2,8,9 This is hypothesized to be preferable to a random spot urine alone because ratio of two stable excretion rates, creatinine and protein, would cancel out the time factor and thus provide a better estimate of 24 hour protein excretion.3

Urine protein excretion is customarily expressed as the amount of protein excreted per unit of time, factored for body surface area. Since creatinine production and excretion are also related to body size (as well as age and sex), good correlation is expected between the P/C ratio and quantitative urinary protein excretion in individual patients9-12 .The substitution of a spot urine P/C ratio for a 24 hour urine protein would have significant implication including prompt clinical decision making. It would reduce healthcare costs and lead to patient satisfaction. The object of our study was to compare these two methods of assessing significant proteinuria.

Our study shows that P/C ratio correlated well with the gold standard of 24 hour urine protein. Results are consistent with most of the previous studies. Study by Durnwald and Mercer, 2003 and Aggarwal N et al, 2008 showed poor correlation coefficient.5,6 But it may be noted that it had recruited outpatients while our study had patients being tested after admission. So there were no dropouts and more accurate sample collection and handling. Torng et al., 2001 reported an increased cut-off value while Young et al., 1996, and Robert et al.,1997, reported decreased cut-off values.13,14

The results obtained in this study indicate that spot urine P/C ratio is highly accurate for detecting significant proteinuria. The cut–off value that best predicted significant proteinuria of a random PCR was 0.2mg/mg since this cut – off yields a high diagnostic performance with a sensitivity of 83.33% and specificity of 87.5% and likelihood ratio 6.67. The main concern in the clinical use is the false negative test results, because these cases may be missed. Undetected cases of pre-eclampsia have a risk of significant morbidity and mortality15-17. On the other hand, false positive results may result in excessive monitoring of the mother and risk of preterm delivery. So the optimal cut off value was selected considering a reasonable sensitivity with specificity to balance the missed cases with false positives.18-20

From the results obtained in our study, we conclude that spot urine protein-creatinine ratios can predict significant proteinuria with high accuracy. It can be used as an alternative to dipstick in emergency situations, and also as a substitute for 24 hour urine protein estimation.

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