Study of Spot Urinary Protein/Creatinine Ratio as an Alternative for 24-Hour Urinary Protein in Pre-Eclampsia in and around Chitradurga

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Abstract: Pre-eclampsia is defined as new onset of elevated blood pressure and proteinuria after 20 weeks of gestation. Urinary protein-creatinine ratio has been used to evaluate proteinuria in pre-eclampsia. The presence of proteinuria is seen as a possible indication of many complications in pregnancy and it remains central to the diagnosis of pre-eclampsia. It has both diagnostic and prognostic implications. 24 Hours Urine protein measurement is a standard method for the detection of proteinuria but it is time-consuming, needs more assistance from paramedical staff or nonmedical persons, the results are cumbersome if done not properly and need 24 hours' time. As an alternative, Spot sampling for a urine protein to creatinine (P/C) ratio has been investigated to determine the diagnostic accuracy of the protein to creatinine ratio (P/C) for the detection of remarkable proteinuria. A case control comparative study was done with women having pre-eclampsia and normal pregnant women admitted in Gynecology department of Basaveshwara Medical College Hospital & RC, Chitradurga according to the criteria. There was a good positive correlation between spot Urinary Protein /Creatinine Ratio and 24-hour Urinary protein excretion, with a correlation coefficient (r) of 0.980. The best cut-off which gave the maximum area under the curve was 0.14 for 300 mg, 0.36 for 1000 mg, 0.63 for 2000 mg, 0.76 for 3000 mg, 1.06 for 4000 mg and 1.40 for 5000 mg per 24h Urinary Protein excretion. A Urinary protein/creatinine ratio above 0.63 strongly predicts significant 24 hour urinary protein for more than 1 gram.

Keywords: Pre-eclampsia, Urinary Protein, Urinary Creatinine, Urinary Protein/Creatinine Ratio (P/C ratio).

INTRODUCTION

Pre-eclampsia is defined as development of hypertension and proteinuria (>300mg urinary protein in 24hrs) after 20th week gestation. Hypertension is defined as a blood pressure greater than 140/90mm Hg or a rise in blood pressure of 30/15 mm Hg from the base line confirmed by two measurements 6 hrs apart [1]. Pre-eclampsia is a leading cause of maternal and perinatal morbidity and mortality worldwide. Pre-eclampsia occurs in about 5-7% of pregnancies. It is known to affect the function of various organs involving metabolism.

The presence of proteinuria is seen as a possible indication of many complications in pregnancy, from urinary tract infection to chronic renal disease and it remains central to the diagnosis of pre-eclampsia in a hypertensive pregnancy. It has both diagnostic and prognostic implications [2]. Extensive changes occur in the renal system in pre-eclampsia. As a part of the end organ pathology pre-eclamptic glomeruli undergo structural changes with pronounced endothelial vacuolization and hypertrophy of the cytoplasmic organelles, first defined as glomerular endotheliosis [3]. The gold standard for measuring proteinuria is 24 hour urine collection, but a faster screening method is needed to save time and can initiate the treatment as early as possible. Spot urinary protein/creatinine ratio is however preferred for this purpose so there is a need of rapid, valid, accurate test to identify significant urinary proteinuria. This may lead to faster decision making, which is likely to reduce patients' anxiety, shorten length of hospital stay with patient's cost savings [4]. Many studies show a strong association between spot protein/creatinine ratio and 24 hour proteinuria, and the International Society for the Study of Hypertension in Pregnancy has accepted this test as a method for identification of significant proteinuria [5]. Protein/creatinine ratio of a single voided urine specimen has an important diagnostic role

in the management of preeclamptic women which necessitates further research in the field.

The aim of the study was to determine diagnostic accuracy of spot urine protein/creatinine ratio for the detection of remarkable 24 hour urinary proteinuria and to evaluate the protein/creatinine ratio for different proteinuria ranges in cases of pre-eclampsia.

MATERIALS & METHODS

This study was carried out in Basaveshwara Medical College Hospital & RC, Chitradurga from December 2013 to September 2014. A case control comparative study was done with Pre-eclampsia and normal pregnant women according to criteria. Samples were collected when patient were admitted in Gynecology department.

Inclusion Criteria

Primigravida with pre-eclampsia in the age group of 18-35 years above gestational age of 20 weeks, without any previous history of hypertension, dyslipidemia or other organ dysfunctions.

Exclusion Criteria

* History of Multigravida , diabetic mellitus, kidney disease
* History of chronic hypertension and proteinuria before conception or development of hypertension before 20 weeks of gestation
* Patients with chronic renal disease, pathological vaginal discharge
* Patients with history of recurrent urinary tract infection
* Molar pregnancy

Approval for the study was obtained from the Ethical Committee of the Hospital. Signed consent forms were also obtained from all participants before enrolling in the study. Demographic and general information such as age, number of pregnancy and gestational age were recorded. All patients underwent 24-hour urine collection, 24 hours urine was collected in all patients with assistance of nursing staff, each container was marked with patient's name, IPD number and collection time. Spot urine sample was collected in 10 ml sterilized glass vial to determine level of urinary protein/creatinine ratio just before 24 hour collection of urine. First voided morning urine sample was discarded.

Urinary protein level was determined by the Pyrogallol method in semi auto analyzer Erba Chem 5 Plus machine. Urinary creatinine level was measured by a modified Jaffe's method in fully auto analyzer Erba 200 machine.

RESULTS AND DISCUSSION

In our study, 50 cases of pre-eclampsia and 50 controls were included who had undergone 24-hour urine protein measurement and spot protein/creatinine ratio measurement. Variables of the preeclamptic patients are presented in Table-1. The mean maternal age was 22.78 ± 4.23 years (range 18-35 years) in pre-eclampsia patients (range 18–35). The mean body mass index (BMI) was 26.92 ± 2.64 kg/m^2 in pre-eclampsia patients. Mean blood creatinine level was 0.87 ± 0.31 mg/dl. The mean 24 hour urinary protein excretion was 1.6 ± 1.3 g (range 0.3–.5.5gm) in pre-eclampsia patients. The mean spot protein/creatnine ratio ratio was 0.55 ± 0.36 (range 0.21-1.65) in pre-eclampsia patients. 48% women had a 24-hour urine protein excretion of 1gm or higher, and 18 % women had a 24-hour urine protein excretion of 3 gm or higher and 4 % women had a 24-hour urine protein excretion of 5 gm or higher.

Figure-4 shows scatter diagram for the relationship between the spot protein-creatinine ratio and 24-hour protein excretion in Pre-eclampsia cases. There was a good positive statistical correlation between the spot protein creatinine ratio and 24-hour protein excretion, with a correlation coefficient (r) of 0.980.

The test performance was shown in table-2 and figure-4. Relation of spot P/C ratio with 24 hour urinary protein collection is shown in Table-2 & Figure-4.

**Table-1: Comparison of variables between cases and controls**

| Variables	Cases	Controls
Patient age (years)	22.58 ± 3.81	22.98 ± 3.65
Gestational Age (weeks)	28 ± 4	27 ± 5
BMI (kg/m^2)	26.92 ± 2.64	23.58 ± 4.35
Spot Urinary Protein (mg/dl)	27.56 ± 17.15	4.40 ± 2.00
Spot Urinary Creatinine (mg/dl)	50.38 ± 7.92	83.34 ± 17.49
Spot Urinary P:C ratio	0.55 ± 0.36	0.05 ± 0.03
24 hour Urinary Proteinuria (mg)	1620 ± 1365	139 ± 54
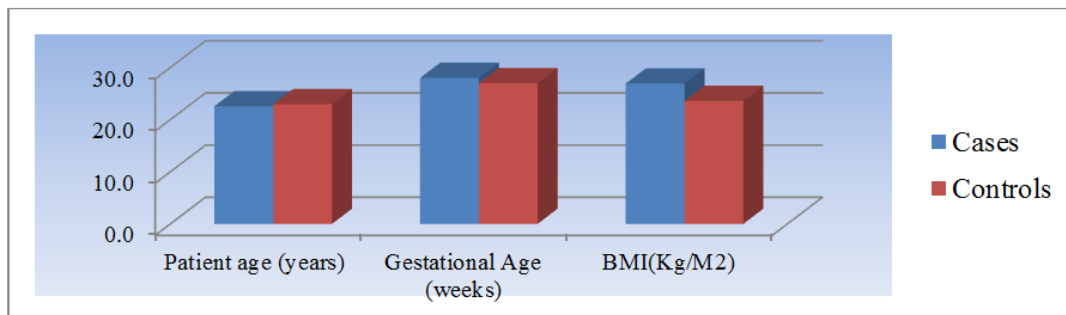
Fig-1: The Age(in Years) distribution of Pre-eclampsia cases and normal controls were 22.58±3.81 and 22.98±3.65 respectively, The Gestational age (in weeks) distribution of Pre-eclampsia cases and normal controls were 28±4 and 27±5 respectively. The Body Mass Index (in kg/M^2) distribution of Pre-eclampsia cases and normal controls were 26.92±2.64 and 23.58±4.35 respectively
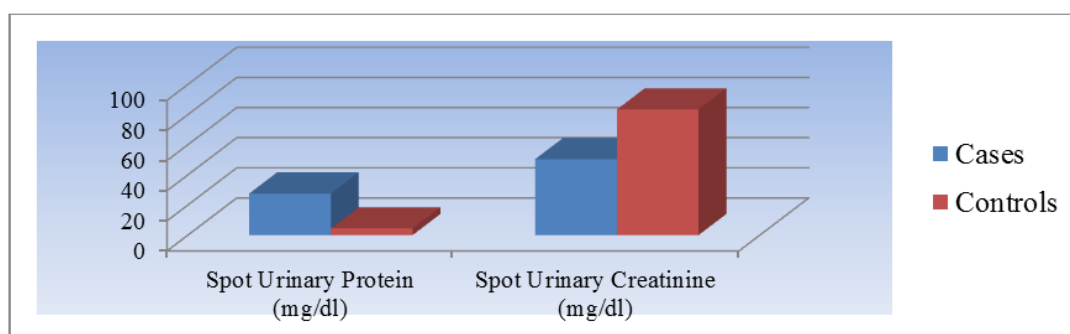
Fig-2: The Spot Urinary Protein of Pre-eclampsia cases and normal controls were 27.56±17.15 and 4.40 ±2.00 (p< 0.001 Highly Significant),The Spot Urinary Creatinine of Pre-eclampsia cases and normal controls were 50.38±7.92and 83.34 ±17.49 respectively.(p< 0.001 Highly Significant)
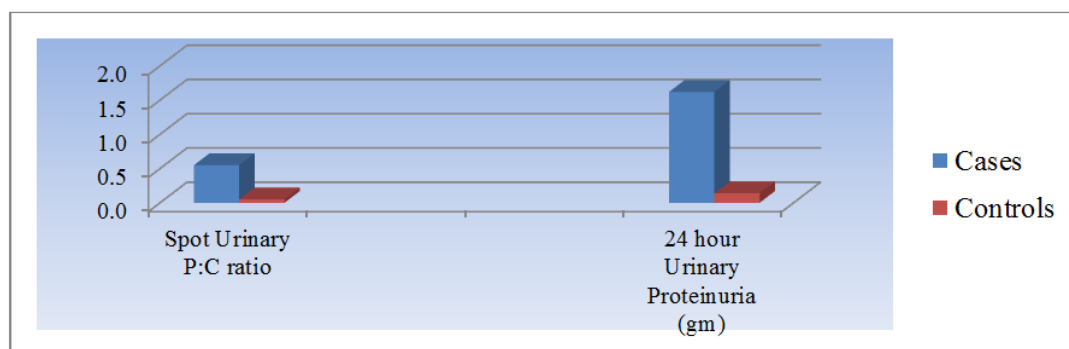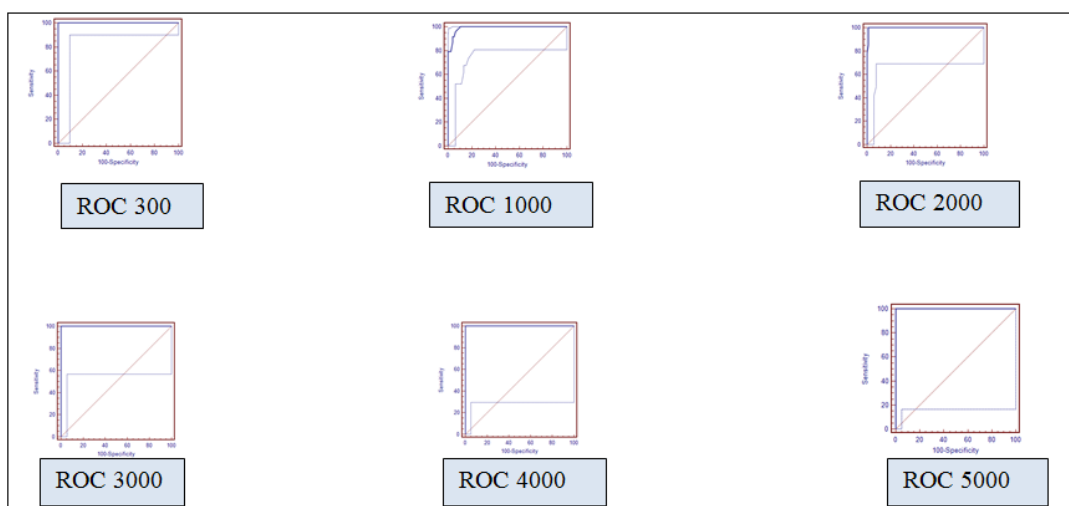

Fig-3: The Spot Urinary Protein Creatinine Ratio of Pre-eclampsia cases and normal controls were 0.55± 0.36 and 0.05±0.03 respectively.(p< 0.001 Highly Significant),24 Hour Urinary Proteinuria of Pre-eclampsia cases and normal controls were 1620±1365 mg and 139±54 mg respectively (p< 0.001 Highly Significant)
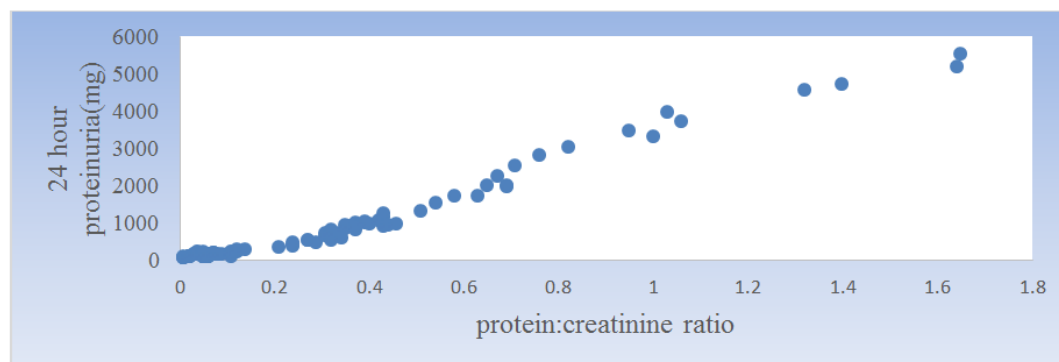
Fig-4: Relation between 24-h protein excretion and spot urine P/C ratio

Table-2: Spot urinary P/C ratio and different ranges of 24-h Urinary protein in preeclamptic patients

24 hour urine Protein (mg/day)	Spot P/C ratio (ROC analysis)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
300	0.14	100	100	100	100
1000	0.36	100	89.47	75	100
2000	0.63	100	98.84	93	100
3000	0.76	100	100	100	100
4000	1.06	100	100	100	100
5000	1.4	100	100	100	100

Fig-5: ROC curves showing the performance of spot urine P/C ratio for different 24 protein ranges in preeclamptic patients

[By ROC analysis, the best cut-off of spot urinary protein /creatinine ratio that gives the maximum area under the curve was 0.14 for 300 mg per 24 hour urinary protein (AUC: 1, 95% CI: 0.96–1, p=1),0.36 for 1,000 mg per 24 hour urinary protein(AUC: 0.99, 95% CI: 0.95–0.99, p<0.0001),0.63 for 2,000 mg per 24 hour urinary protein (AUC: 0.99, 95% CI: 0.96–1, p<0.0001) , 0.76 for 3,000 mg per 24 hour urinary protein(AUC: 1, 95% CI: 0.96–1.P=1) ,1.06 for 4,000 mg per 24 hour urinary protein(AUC: 1, 95% CI: 0.96–1,P=1) , and 1.40 for 5,000 mg per 24 hour urinary protein(AUC: 1, 95% CI: 0.96–1,P=1].

Our study shows that sensitivity and specificity of urinary protein creatinine ratio is 100 % at cut off value of 0.76, It suggests that Spot urinary protein /creatinine ratio is able to diagnose all cases of Pre-eclampsia not even missing a single case and also able to exclude all non preeclamptic cases. The advantage of Spot urinary protein/ creatinine ratio method is that we don't need to wait for 24 hours urinary protein for diagnosis of pre-eclampsia .We can initiate the treatment without delay. We investigated the correlation between spot urinary protein/creatinine ratio and 24-hours proteinuria in patients with Pre-eclampsia. There was a good positive statistical correlation between the spot protein creatinine ratio and 24-hour protein excretion, with a correlation coefficient (r) of 0.980.

Our observations are in accordance with the Work of Durnwald and Mercer [6] who assessed lower correlation coefficients of 0.56 and 0.41 and cautioned against substituting spot protein /creatinine ratio for the 24 hour urine protein collection. Al and colleagues [7] reported significant association between 24-hour protein and random protein-creatinine ratio (r = 0.56, p < 0.01). With a cut off protein creatinine ratio greater than 0.19 as a predictor of significant proteinuria, sensitivity and specificity were 85% and 73%. Positive and negative predictive values were 46% and 95% respectively. Wheeler and colleagues [8] studied in their study, that the protein /creatinine ratio of 0.46, 0.82 and 3.0 represented 1000 mg/ 24 h 2000 mg/ 24 hr and 3000 mg/24 hr, respectively. All of these were characterized by excellent accuracy. The urine protein /creatinine ratio of 0.21 corresponded with a protein excretion rate of 300 mg /24 hr. The area under curve was 0.8% indicating good accuracy which supports our findings. Nahid Shah Bazian *et al*., [9] found the strong correlation between the spot protein /creatinine ratio and 24 hr urine protein excretion (r = 0.84, p < 0.001). The optimal spot protein /creatinine ratio cut off point was 0.2 for 300 mg/ 24 hr of protein excretion, with a sensitivity, specificity, positive predictive value and negative predictive value of 91.2%, 87.8%, 94.4% and 96.8% respectively. Similar to our study, Methven *et al*., [10] found that the protein /creatinine ratio was

more sensitive and more specific for the detection of proteinuria >0.5–1 g/day in patients chronic kidney disease in a non-pregnant population. Antunes *et al.*, [11] reported that for greater degrees of proteinuria, the correlation between the P/C ratio and 24-hour urine excretion with primary glomerulopathies was lower in a non-pregnant population. In addition, Guy *et al.*, [12] determined a correlation between 24-hour urine protein measurement and albumin-creatinine ratio when this was >1 g/day in a non-pregnant population with renal disease.

CONCLUSION

Based on the finding of our study, we can conclude that, spot urinary protein /creatinine ratio in hospitalized patients with pre-eclampsia can be used as a screening test as a good alternative and predictor for significant proteinuria with high accuracy. The advantage of Spot urinary protein creatinine ratio method is that we don't need to wait for 24 hours urinary protein for diagnosis of pre-eclampsia. This quick method with high accuracy is very useful to prevent fetal and maternal morbidity and mortality in India. Therefore, it could be used as a rapid alternative test in patients with poor clinical status in order to prevent any delay in the implementation of treatment. We believe that the urinary protein/creatinine ratio should be considered as a potential alternative for 24-hour urine collection for proteinuria in pregnant women to detect pre-eclampsia.

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