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ORIGINAL ARTICLE

Analysis of Proteinuria Estimation Methods in Hypertensive Disorders of Pregnancy

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Abstract

Purpose of the Study The gold-standard 24-h urine collection method for protein estimation is inconvenient and is associated with a delay in laboratory analysis. This study was undertaken to compare sulphosalicylic acid test, urine dipstick test, urine protein-to-creatinine ratio with 24-h urine protein estimation in pre-eclampsia cases.

Methods This is a comparative study and consists of a single group of 764 subjects. This study was conducted in the Department of Obstetrics and Gynaecology in collaboration with the Department of Biochemistry, JIPMER, Pondicherry, India, from February 2011 to January 2014. The subjects included were 764 pre-eclampsia women. A first voided morning sample was obtained for sulphosalicylic acid test, dipstick test, urine protein and creatinine estimation and urine culture, and subsequent urine samples were collected for the 24-h urine protein estimation.

Main Findings For significant proteinuria, sulphosalicylic acid test with 1 + proteinuria has sensitivity, specificity,

PPV and NPV of 59, 48, 39, 67, whereas with 2 + has sensitivity, specificity,PPV and NPV of 44, 88, 75 and 67%, respectively, dipstick test with 1 + proteinuria has sensitivity, specificity, PPV and NPV of 71, 52, 54 and 70%, whereas with 2 + has sensitivity, specificity,PPV and NPV of 49, 87, 75 and 69%, respectively. The spot urine protein-to-creatinine ratio and 24-h urine protein were significantly correlated ($r = 0.98$; $p < 0.0001$). The cut-off value for the protein-to-creatinine ratio as an indicator of protein excretion $\geq$ 300 mg/day was 0.285. The sensitivity, specificity PPV and NPV were 100, 99, 100 and 99%, respectively.

Conclusion The spot urine protein-to-creatinine ratio is a better method for estimation of proteinuria in pre-eclampsia.

Keywords Sulphosalicylic acid test · Urine dip stick test · Urine protein-to-creatinine ratio · Proteinuria in pre-eclampsia

Introduction

Hypertensive disorders of pregnancy complicate up to 10% of pregnancies and remain a major cause of maternal morbidity and mortality [1]. Antenatal care involves a screening programme, with the measurement of blood pressure and proteinuria taken more frequently towards term, and this information is used to detect hypertensive disorders of pregnancy.

Pre-eclampsia is a multisystem disorder of unknown aetiology, and it is characterized by the development of hypertension (140/90 mmHg or higher) with proteinuria after 20 weeks of pregnancy in previously normotensive and non-proteinuric patients [1, 2]. Proteinuria is defined as the presence of 300 mg or more of protein in a 24-h urine specimen [2]. The gold-standard 24-h urine collection method for protein estimation is not without errors, and the most obvious error is variable and incomplete collection. This test is inconvenient and is associated with a delay in laboratory analysis and availability of results. Lack of storage facilities, staff inadequacy and transportation also add to the difficulty. In some cases, delivery may occur before completion of 24-h urine collection, and the patient often requires hospital admission to complete the test.

Besides, there are many methods of proteinuria estimation like sulphosalicylic acid test, dipstick test and urine protein-to-creatinine ratio. [3] Each test has their demerits hence we need reliable test with early available results.

Purpose of the study This study was undertaken to compare sulphosalicylic acid test, urine dip stick test, urine protein-to-creatinine ratio with 24-hour urine protein estimation as a method of protein estimation in pre-eclampsia cases.

Methods This is a comparative study and consists of a single group of 764 subjects. This study was conducted in the Department of Obstetrics and Gynaecology in collaboration with the Department of Biochemistry, JIPMER, Pondicherry, India, from February 2011 to January 2014. This study was approved by the JIPMER Research Committee and Institute Ethics Committee on 13 January 2011 (IEC No. 2011/1/1 and dated 24/02/2011). The subjects included were 509 pre-eclampsia women. A first voided morning sample was obtained for sulphosalicylic acid test, dipstick test, urine protein and creatinine estimation and urine culture, and subsequent urine samples were collected for the 24-h urine protein estimation.

Inclusion Criteria

Pregnant women hospitalized after 20 weeks of gestation with hypertension of 140/90 mmHg or higher on two occasions, at least 6 h apart, with proteinuria were included in the study.

Exclusion Criteria

Patients with known renal disease, diabetes and urinary tract infections were excluded from the study.

We studied the demographic profile, gestational age, blood pressure, sulphosalicylic acid test, dipstick test, urine protein-to-creatinine ratio and 24-h urine protein estimation of each patient. The procedure was explained, and consent was obtained from each patient. A first voided morning urine sample was obtained for sulphosalicylic acid test, dipstick test, urine protein and creatinine estimation and urine culture. Subsequent urine samples were collected for 24 h, including a next-day first-morning voided sample, which was obtained for the 24-h urine protein estimation.

Sulphosalicylic acid test was done by standard accepted methods and dipstick test with kits. Urine protein estimation was performed by the colorimetric method. Urine creatinine estimation was performed by the modified Jaffe's method using a standard autoanalyser. The sensitivity, specificity, and positive predictive and negative predictive values were determined for different protein-to-creatinine ratios. Receiver operating characteristic (ROC) curves were used for comparisons; values of greater than or equal to 300 mg/day were considered true positive for proteinuria, and values of less than 300 mg/day were considered true negative for proteinuria.

Results

A total of 764 subjects were recruited for the present study. Among them, 81 delivered before collection of the 24-h urine sample. The 24-h urine collection was incomplete for

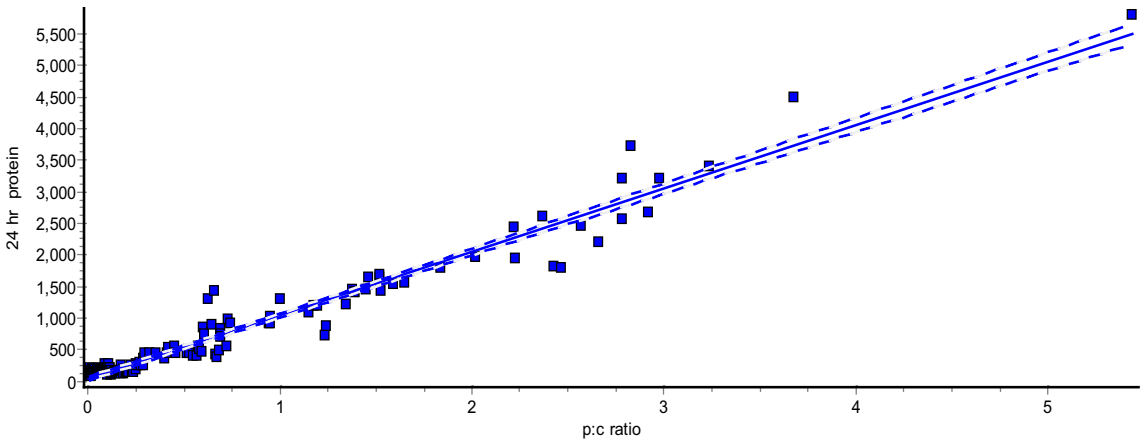

Fig. 1 Scattered diagram showing correlation between the spot urine protein-to-creatinine ratio (mg/mg) and the 24-h urine protein (mg/mg)

Table 1 Critical analysis of the proteinuria estimation method

Tests	Proteinuria	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Likely hood ratio	Area under curve (AUC)
Sulphosalicylic acid test	1 +	58.7	47.08	38.57	66.81	1.109	0.667
	2 +	44.2	88.09	75	66.84	3.817	0.667
Dipstick test	1 +	71.43	51.58	53.69	69.67	1.475	0.695
	2 +	49.1	87.37	75.34	68.6	3.88	0.695
Protein-to-creatinine ratio	0.285	100	99.65	99.56	100	2.83	0.995

66 subjects. Twenty-three subjects exhibited no continuity between the spot urine collection and 24-h urine collection, and 32 subjects had a urinary tract infection. Thus, 202 subjects were excluded from the study. Therefore, 562 subjects were studied and followed up to 6 weeks postnatally, and among them, 23 had chronic hypertension. Ultimately, 509 subjects were included in the study.

The ages of subjects ranged from 18 years to 39 years, with the majority, in the age group of 21–30 years. The mean age was 25.09 years.

Labour was induced in 408 subjects by various acceptable methods. Of the 509 subjects, 306 (60.1%) had term deliveries, and 203 (39.9%) had preterm deliveries. The subjects included 472 singleton pregnancies, while 31 had twins and 6 had triplets. Five subjects had a single foetal demise. Of the 547 babies from the 509 pregnancies, 383 (70.30%) had a low birth weight of < 2500 g. One hundred and sixty-four (29.70%) newborns were transferred to the neonatal intensive care unit. Furthermore, 21 newborns expired in the neonatal intensive care unit. The incidence of prematurity was 41%, while the incidence of intrauterine growth retardation was 15.38%.

For significant proteinuria, sulphosalicylic acid test with 1 + proteinuria has sensitivity, specificity, positive predictive value and negative predictive value of 59, 48, 39 and 67%, whereas with 2 + has sensitivity, specificity,PPV and NPV of 44, 88, 75 and 67%, respectively. Dipstick test with 1 + proteinuria has sensitivity, specificity, positive predictive value, negative predictive value of 71, 52, 54 and 70%, whereas 2 + has sensitivity, specificity,PPV and NPV of 49, 87, 75 and 69%, respectively.

An excellent correlation coefficient (r) = 0.93 existed with 95% confidence interval between spot urine protein-to-creatinine ratio (mg/mg) and 24-h urine protein (mg/day) as calculated by Pearson's method (Fig. 1). Coefficient of determination (r^2) is 0.86 ($p < 0.0001$).

The area under the receiver operating characteristic (ROC) curve is 0.995(95% confidence interval). The cut-off value of 0.285 has sensitivity, specificity, positive predictive value and negative predictive value of 100%, 99.65%, 99.56% and 100%, respectively (Table 1).

Discussion

This study consisting of 509 out of 764 (255 subjects excludedo due to various reasons) subjects revealed a p value of < 0.0001 (two-tailed), which is considered extremely significant, and an excellent correlation coefficient ($r = 0.9778$), (with a 95% confidence interval of 0.9700–0.9836,) for the spot urine protein-to-creatinine ratio (mg/mg) and 24-h urine protein (mg/day) was calculated by Pearson's method (Table 2).

Table 2 Correlation coefficient between the spot urine protein-to-creatinine ratio (mg/mg) and the 24-h urine protein (mg/day) calculated by Pearson's method

Number of subjects	p value (two-tailed)	95% confidence interval	Correlation coefficient (r)	Coefficient of determination (r^2)
509	< 0.0009	0.9700–0.9836	0.9778	0.9561

The cut-off value of 0.285 results in a sensitivity of 100%, specificity of 99.02%, positive predictive value of 99%, and negative predictive value of 100%, with a 67% likelihood ratio.

In the study by Leanos-Miranda et al. [4], the cut-off value was ≥ 0.3 with a 98.2% sensitivity, 98.8% specificity, 97.2% positive predictive value and 99.2% negative predictive value. The present study results were comparable with results of various previous studies [5–11].

Conclusion

The level of urinary protein excretion has considerable clinical implications for the course of pregnancy and the perinatal and maternal outcomes. Therefore, early detection of even minor degrees of proteinuria is important.

Dipstick analysis as a screening procedure for proteinuria lacks reliability and has a high rate of false positives. For years, the 24-h urine collection method has been the gold standard for the quantification of proteinuria in the management of women with pre-eclampsia. However, this method is cumbersome, subject to collection errors, requires good patient compliance and results in a delayed diagnosis. The value of the protein-to-creatinine ratio in a single urine sample is potentially more accurate because it avoids collection errors and yields more physiologically relevant information.

The protein-to-creatinine ratio is a superior diagnostic tool for predicting significant proteinuria. The cut-off value for the spot urine protein-to-creatinine ratio is 0.285 mg protein/mg creatinine. A level below this is not associated with significant proteinuria, and further testing is unnecessary. This method for the quantification of proteinuria when properly interpreted, can provide valuable information for clinical purposes and is a satisfactory substitute for 24-h protein estimation.

Limitations

This study was limited to hospitalized, non-ambulatory patients. Since protein excretion is affected by postural changes, the ambulatory status of the subjects (i.e. patients that are allowed to stand versus those confined to a supine position) may be a confounding factor in the quantitation of proteinuria.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interests.

Ethics Approval This study with reference number IEC No. SEC/2011/1/1 and dated 24 February 2011 has been approved by Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India-605006, research committee and institute ethics subcommittee (human studies) on 13 January 2011.

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