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Hypertension and Serum C-Reactive Protein Levels in Pre-eclampsia

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Abstract

A case-control study was carried out in the Department of Obstetrics & Gynaecology of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, between January 2013 and June 2014, to see the association of hypertension and C-reactive protein (CRP) levels in pre-eclampsia patients. A total of 78 patients were enrolled in the study. Patients were divided into three groups: group-I included of 26 pregnant women with mild pre-eclampsia, while group-II had 26 pregnant women with severe pre-eclampsia and group-III had 26 women with normal pregnancy. Group-I and group-II were together considered as 'case', while group-III was considered as 'control'. We adopted a convenient sampling technique. For each patient, after a 10-minute of resting phase, blood pressure was measured following standard procedure. C-reactive protein (CRP) was measured from patients' serum based on latex particle-enhanced nephelometric immunoassay using CardioPhase® High Sensitivity CRP kit. The mean systolic BP was found 155.0±13.7 mmHg in group-I+group-II (case group) (i.e., mild and severe pre-eclampsia), while 108.46±0.8 mmHg in group III (control group). Similarly, the mean diastolic BP was found 102.31±9.7 mmHg in group-I+group-II and 68.46±7.8 mmHg in group-III. The differences were statistically significant (p=0.001). The mean CRP level was found 23.82±21.8 mg/L in group-I+group-II (case group) and 4.42±0.9 mg/L in group-III (control group). The difference was statistically significant (p=0.001). A positive significant correlation was found between systolic blood pressure and CRP level, as of Pearson's correlation coefficient r=0.439 (p=0.025) and r=0.434 (p=0.027) in mild and severe pre-eclampsia respectively. Similarly, a positive significant correlation was found between diastolic blood pressure and CRP level, as of Pearson's correlation coefficient r=0.446 (p=0.022) and r=0.440 (p=0.024) in mild and severe pre-eclampsia respectively.

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Introduction

Pre-eclampsia is a crucial concern in pregnancy as well as a major public health challenge in its maternal and child health (MCH) domain.[1] It is a hypertensive disorder of pregnancy that may be responsible for complications like maternal stroke, seizures, cerebral oedema, hepatic failure, renal failure, disseminated intravascular coagulation (DIC), or placental abruption, as well fetal and neonatal consequences like intrauterine growth restriction (IUGR), stillbirth, and severe prematurity due to premature termination of pregnancy for maternal indications.[1,2] However, diagnosis, screening and management of pre-eclampsia still remain controversial, as does the classification of its severity.[1,2] It is generally accepted that the onset of a new episode of hypertension during pregnancy (with persistent blood pressure ≥140/90 mm Hg) with the occurrence of substantial proteinuria (≥0.3 g/24h) after 20 weeks of gestation

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can be used as criteria for identifying pre-eclampsia.[1,3,4] Although some add oedema as a feature that usually occurs after the 20th gestational week and most frequently near term, oedema has been abandoned as a diagnostic criterion, as it is found in more than 80% of normal pregnant women.[4] According to the American College of Obstetricians and Gynecologists (ACOG), the diagnosis of hypertension in pregnancy is made by any one of the following criteria: i) a systolic blood pressure of ≥140 mmHg; ii) a diastolic blood pressure of ≥90 mmHg; iii) a rise of ≥30 mmHg in systolic blood pressure; iv) a rise of ≥15 mmHg in diastolic blood pressure.[5] However, those alterations in blood pressure should be observed on at least two different occasions at least 6 hours apart.

C-reactive protein (CRP) is a plasma protein associated with acute inflammatory responses. In the past decades, scientists showed interest to find out if CRP correlates with the pathogenesis of pre-eclampsia, as elevation in serum CRP have been associated with risk of cardiovascular disease.[6-8] To connect an inflammatory marker like CRP (which is elevated in response to stress, tissue injury and other inflammatory stimuli) with hypertension in pregnancy and related endothelial dysfunction that leads to vascular dysfunction and suboptimal placental development is critical. Moreover, maternal systemic inflammation might also be a response to ischaemia of the placenta, due to suboptimal placentation. Those all perceived as pathophysiological changes in pre-eclampsia.[9] Therefore, involving CRP as an inflammatory biomarker in early pregnancy might be helpful for early identification of pregnant women at risk for pre-eclampsia[6,10] and a priority to implement preventive measure from public health perspective.[11] CRP level was found higher in women with pre-eclampsia in comparison with normal pregnancy.[6,8] Besides, ethnic variation in CRP levels was also observed.[7] However, the functional role of CRP in pre-eclampsia still remains enigmatic. Therefore, we proposed this study to examine maternal CRP levels, as marker of low-grade inflammation in early pregnancy to predict pre-eclampsia and its severity as well as to see the association of hypertension and C-reactive protein (CRP) levels in Bangladeshi women with pre-eclampsia.

Methods

This case-control study was carried out in the Department of Obstetrics & Gynaecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh, between January 2013 and June 2014. A total of 78 patients were enrolled in the study. A total of 78 patients were enrolled in the study. Patients were divided into three groups: group-I included of 26 pregnant women with mild pre-eclampsia, while group-II had 26 pregnant women with severe pre-eclampsia and group-III had 26 women with normal pregnancy. Group-I and group-II were together considered as 'case', while group-III was considered as 'control'. We adopted a convenient sampling technique.

Inclusion criteria:

For mild pre-eclampsia case: Pregnant women having 20-40 weeks of gestation with hypertension (BP >140/90 mmHg but <160/110 mmHg on two occasions, at least 6 hours apart) with proteinuria >3 mg/day but <5 g/day.

For severe pre-eclampsia case: Pregnant women of 20-40 weeks of gestation having one or more of the following manifestations:

1) Systolic blood pressure >160 mmHg and diastolic blood pressure >110 mmHg on 2 occasions, at least 6 hours apart;
2) Proteinuria of ≥5 g/24h or ≥3 g on two random urine samples collected at least 4 hours apart;

3) Oliguria (<500 ml in 24 hours);
4) Cerebral or visual disturbance;
5) Epigastric or right upper quadrant pain;
6) Pulmonary oedema or cyanosis;
7) Impaired liver function;
8) Thrombocytopenia (platelet count <100000/mm3); and
9) Fetal growth restriction.

For control: Apparently healthy normotensive women having 32-40 weeks of pregnancy

Exclusion criteria: Patients with a history of diabetes mellitus, chronic renal disease, hepatic disease, chronic hypertension or cardiovascular disease, systemic infection, systemic lupus erythematosus, or any haemorrhagic disorder or psychiatric illness.

After collecting demographic data and clinical history and performing physical examination, a 10-minute of resting phase was given to each patient. Then, blood pressure was measured following standard procedure. Korotkoff phase-I (first beat heard) and phase-V (disappearance of sound) were used to determine systolic (SBP) and diastolic blood pressure (DBP) respectively. When DBP was found 90 mmHg or more, it was confirmed on two occasions at least 6 hours apart. Then 3 ml of venous blood was drawn from each patient with proper aseptic precautions. The blood was transferred into a clean dry test tube and taken to the laboratory. Blood was allowed stand still for about 30 minutes to clot. Clot was then separated and was centrifuged at 3000 rpm for 5 minutes. The separated serum was carefully drawn by micropipette and was stored in micro centrifuge tube at -70oC until the test was done. Quantitative measurement of C-reactive protein (CRP) was done from patients' serum based on latex particle-enhanced nephelometric immunoassay (PENIA) using CardioPhase® High Sensitivity CRP (hsCRP) kit (made by Siemens Medical Solutions USA, Inc.) in the Department of Biochemistry & Molecular Biology of the same hospital.

All clinical information of the patients was obtained through preformed structured questionnaire in the patient data sheet. Once all necessary data was obtained and checked for completeness, data was compiled, coded and analyzed using Statistical Package for Social Science (SPSS) version 16.0 for Windows. Simple descriptive analysis was adopted, as mean±SD (standard deviation) was considered for numerical data. Comparison between two groups was done using unpaired Student's t-test. A p-value <0.05 was considered statistically significant.

Ethical clearance was obtained from the Institutional Review Board of Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh.

Results

A total of 78 patients were enrolled in the study. Comparing blood pressure of the study patients. The mean systolic BP was found 155.0±13.7 mmHg in group-I+group-II (case group) (i.e., mild and severe preeclampsia), while 108.46±0.8 mmHg in group III (control group). Similarly, the mean diastolic BP was found 102.31±9.7 mmHg in group-I+group-II and 68.46±7.8 mmHg in group-III. The differences were statistically significant (p=0.001). The mean CRP level was found 23.82±21.8 mg/L in group-I+group-II (case group) and 4.42±0.9 mg/L in group-III (control group). The difference was statistically significant (p=0.001) (Table-I). A positive significant correlation was found between systolic blood pressure and CRP level, as Pearson's correlation coefficient showed r=0.439 (p=0.025) and r=0.434 (p=0.027) in mild and severe pre-eclampsia respectively (Fig. 1). Similarly, a positive significant correlation was found between

diastolic blood pressure and CRP level, as Pearson's correlation coefficient showed r=0.446 (p=0.022) and r=0.440 (p=0.024) in mild and severe pre-eclampsia respectively (Fig. 2).

Table-I: Blood pressure and CRP levels of the study patients with and without pre-eclampsia (N=78)

Variables	Group-I+Group-II (Mild+Severe PE) Case (n=52) Mean±SD	Group-III Control (n=26) Mean±SD	t-value	p-value
Systolic BP (mm of Hg)	155.0±13.7 (140-190)	108.46±10.8 (90-120)	15.11	0.001^S
Diastolic BP (mm of Hg)	102:31±9.7 (90-120)	68.46±7.8 (60-80)	17.28	0.001^S
C-Reactive Protein (mg/L)	23.82±21.8 (3.94-78.1)	4:42±0.9 (3.71-6.9)	4.52	0.001^S

Figures in the parentheses indicate range; p-value reached from unpaired Student's t-test; S=significant.

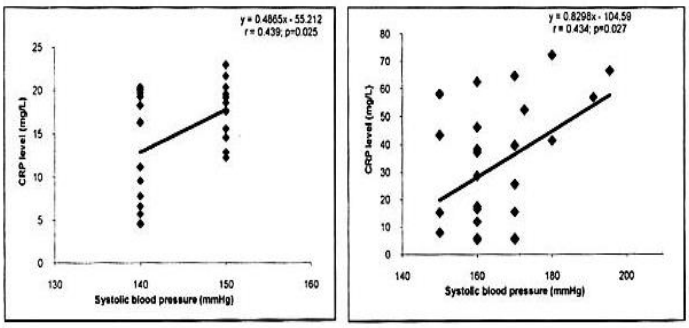

Fig. 1: The scatter diagram showing positive association between systolic blood pressure (SBP) and CRP level in mild and severe pre-eclampsia.

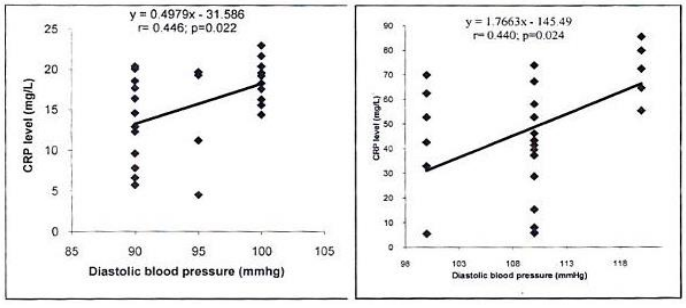

Fig. 2: The scatter diagram showing positive association between diastolic blood pressure (DBP) and CRP level in mild and severe pre-eclampsia.

Discussion

Our study revealed that the mean CRP levels were 23.82±21.8 mg/L in group-I+group-II (case group) and 4.42±0.9 mg/L in group-III (control group). The difference was statistically significant (P=0.001). Moreover, the mean CRP levels were observed 12.13±6.1mg/L and 35.51±25.5mg/L in group-I (mild pre-eclampsia) and in group-II (severe pre-eclampsia) respectively. The difference was statistically significant between two groups (P=0.001). Serum CRP levels in mild and severe pre-eclampsia were markedly higher compared to normal pregnant women. Similar observations were reported by Mirzaie *et al.* as they found CRP levels 14.28±11.62 mg/L in mild pre-eclampsia, 34±25.27 mg/L in severe pre-eclampsia and 3.42±5.48 mg/L in normal pregnancy.[12] On the other hand, Ustün *et al.* reported that the mean serum CRP was 52.1 mg/L (range was 9.3-187 mg/L) in mild pre-eclampsia, while 74.1 mg/L (range was 4.0-272 mg/L) in severe preeclampsia and 3.7 mg/L (range was 3.1-43.5 mg/L) in normal pregnancy.[13] However, those values were found to be higher than our findings. In contrast, Gandevani *et al.* observed that the mean hs-CRP levels were in mild 7.2±2.2 mg/L and 9.4±3.9 mg/L in mild and severe PE; those values were significantly higher than the normal group 2.5±2.7 mg/L.[14] However, their CRP levels were lower than the findings of the current study.

This study showed a positive significant correlation between systolic blood pressure (SBP) and CRP level. The values of Pearson's correlation coefficient were r=0.439 (p=0.025) and r=0.434 (p=0.027) in mild and severe pre-eclampsia respectively. Similarly, Mirzaie et al. found a positive correlation between serum levels of CRP and systolic blood pressure.[12] We also observed a positive significant correlation

between diastolic blood pressure (DBP) and CRP level. The values of Pearson's correlation coefficient were r=0.446 (p=0.022) and r=0.440 (p=0.024) in mild and severe pre-eclampsia respectively. Mirzaie *et al.* also found a positive correlation between serum levels of CRP and diastolic blood pressure.[12] Ustün *et al.* also found a significant correlation between mean arterial pressure and CRP (r=0.515, p=0.001) in women with pre-eclampsia.[13] Another study done by Kumru *et al.* also showed a strong positive correlation between serum hs-CRP level and diastolic blood pressure (r=0.9, p=0.05) in pre-eclampsia patients.[15] According to the study results of de Jonge *et al.,* C-reactive protein levels were not associated with SBP and DBP patterns throughout pregnancy; however, trimester-specific multivariate linear regression models showed that as compared to low C-reactive protein levels (<5.0 mg/l), elevated levels (≥20.0 mg/l) were associated with maternal SBP and DBP.[10]

Our study has several limitations. A small sample from a single-centre trial may not be able to present the true picture of the country. All other causes of elevated CRP (e.g., cardiovascular disease, rheumatological disease or any systemic inflammation) were not properly evaluated in this study due to time and budget constraint. Hence, our study hardly clarify whether the elevated CRP level is a cause or a consequence of pre-eclampsia.

Conclusion

Our data suggests a significant rise of CRP levels in pre-eclampsia patients. Moreover, a positive significant correlation is also evident between their blood pressure (both systolic and diastolic) and CRP levels. To conclude, hypertension in pre-eclampsia is often driven by inflammation, and CRP serves as a valuable biomarker, indicating both the ongoing inflammatory process and its potential severity, making it important for diagnosis, monitoring, and understanding the disease's mechanisms.

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