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Study of Serum Copeptin Level in Preeclampsia

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Abstract: *Preeclampsia is apregnancy disorder associated with severe maternal, fetal and neonatal complications. It is characterized by increased blood pressure, proteinuria, increased peripheral vascular resistance and reduced organ perfusion.[1]Incidence of preeclampsia in India is around 10%.[2] It is diagnosed as BP of ≥140 mmHg systolic or ≥90 mmHg diastolic on two occasions atleast 4 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure and proteinuria; in absence of proteinuria, new onset of hypertension with other multisystem symptoms.[3]A case-control study was conducted in Dept. of Biochemistry in collaboration with Dept. of Obstetrics and Gynecology, RIMS, Imphal (Manipur) from September 2016 to August 2018. Blood samples were collected from 30 cases of preeclampsia and 30 normal pregnant women. Samples were analyzed for Copeptin, liver functionand kidney function test markers.Copeptin was measured by ELISA, rest byautoanalyser. Serum urea, creatinine, uric acid, sodium, bilirubin, AST, ALT were found higher among 13.33%, 6.67%, 70%, 63.34%, 3.3%, 43.3%, 66.7% cases respectively. Whereas, lower levels of serum potassium and protein were found among 56.67% and 70% cases respectively.Copeptinwas found to be more sensitive as compared to traditional biomarkers for preeclampsia. The current study aims to diagnose and predict outcome of preeclampsia with by comparing serum Copeptin levels in preeclamptic patients and normal pregnant women.*

Keywords: *LFT, KFT markers,Copeptin, preeclampsia*

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I. Introduction

Preeclampsia is a complex pregnancy disorder that has been associated with severe maternal, fetal and neonatal complications. It is characterized by increased blood pressure (BP), proteinuria, vasospasm, increased peripheral vascular resistance and reduced organ perfusion. Usually, it is associated with primigravida patients during the last trimester.[1] The incidence of preeclampsia in India is around 10% and around 2-5% in US.[2] It is diagnosed as BP of ≥140mmHg systolic or ≥90mmHg diastolic on two occasions atleast 4 hours apart after 20 weeks of gestation in a woman with previously normal blood pressure and proteinuria (≥300 mg per 24 hour urine collection or ≥+1 by dipstick method); in the absence of proteinuria, new onset of hypertension with other multisystem symptoms indicative of preeclampsia such as thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema or cerebral or visual symptoms.[3] Although age, parity, social status, race, genetic factors, twin gestation, hydatiform mole, obesity, smoking, hypolumbarlordosis, chronic hypertension, diabetes mellitus, chronic renal disease are among several risk factors identified for preeclampsia, the mechanism by which the disease develops is still not well understood.[4]It is known to cause immediate and long term maternal-fetal morbidities such as fetal growth restriction, maternal-fetal death and future adult neurological and cardiovascular diseases for mother and child.[5-10] Copeptin is a 39 amino acid long, glycosylated peptide.[11] Vasopressin is translated in 1:1 stoichiometric ratio with a small, inactive prosegment Copeptin.[12] Increased vasopressin may decrease kidney function and may increase blood pressure through the V1a and V2 receptors.[13] The study is thus planned to investigate the serum level of Copeptin in preeclampsia and to assess whether there is any correlation between Copeptin and pregnancy outcome in preeclampsia.

II. Materials and methods

A case control study was conducted in Department of Biochemistry in collaboration with Department of Obstetrics and Gynecology, Regional Institute of Medical Sciences, Imphal, Manipurfrom September 2016 to August 2018. A total 60 participants were included in this study.

Study Design: Case-control study

Study location: This was a tertiary care teaching hospital based study done in Department of Biochemistry in collaboration with Department of Obstetrics and Gynecology, RIMS, Imphal.

Study duration: September 2016 to August 2018.
Sample size: 60
Sample size calculation: m_1 (mean of control) = 0.54, m_2 (mean of case) = 0.92, u = 1.28, power = 90, v = 1.96, 5% level, S_1 (standard deviation of control) =0.25, S_2 (standard deviation of case) = 0.57

$$= \frac{(1.28+ 1.96)^2 (0.25+0.57)^2}{(0.54-0.92)^2}$$

= 28
So, taking round figures, No. of cases = 30 No. of controls =30 Total = 60
Subjects and selection method: The study population was drawn from 60 participants. Samples were collected for estimation of Copeptin, liver function test, kidney function test markers.
Inclusion criteria:
1. 30 diagnosed patients of preeclampsia (cases)
2. 30 healthy pregnant women (controls)

Exclusion criteria:
1. Chronic hypertension
2. Diabetes mellitus
3. Multiple pregnancy
4. Renal disease
5. Pregnancy induced hypertension
6. Smokers
7. Alcoholics

Procedure methodology:
Written informed consent was obtained from all the participants. A brief clinical history was taken from all cases.
Blood samples for estimation of serum Copeptin, LFT, KFT parameters were drawn from cases as well as from controls. Copeptin levels were estimated by ELISA.Serum urea by enzymatic kinetic method, creatinine by colorimetric method, electrolytes by Ion Selective Electrodes method, total bilirubin by colorimetric method, AST, ALT by UV method, uric acid by enzymatic colorimetric method and total protein by biuret method with help of autoanalyser.

Statistical analysis:
Data was analysed using SPSS version 20 (SPSS Inc., Chicago, IL). Analysis was performed by using t-test. For comparison of the mean values ANOVA test was used. P<0.05 was considered significant.

III. Results

Fig. 1 shows that maximum no. i.e. 10 (33.3%) of cases are in the age group of 35-40 years and above. Among controls most of them i.e. 8 (26.67%) belong to >25-30 years age group.

Fig. 1: Age distribution between case and control groups

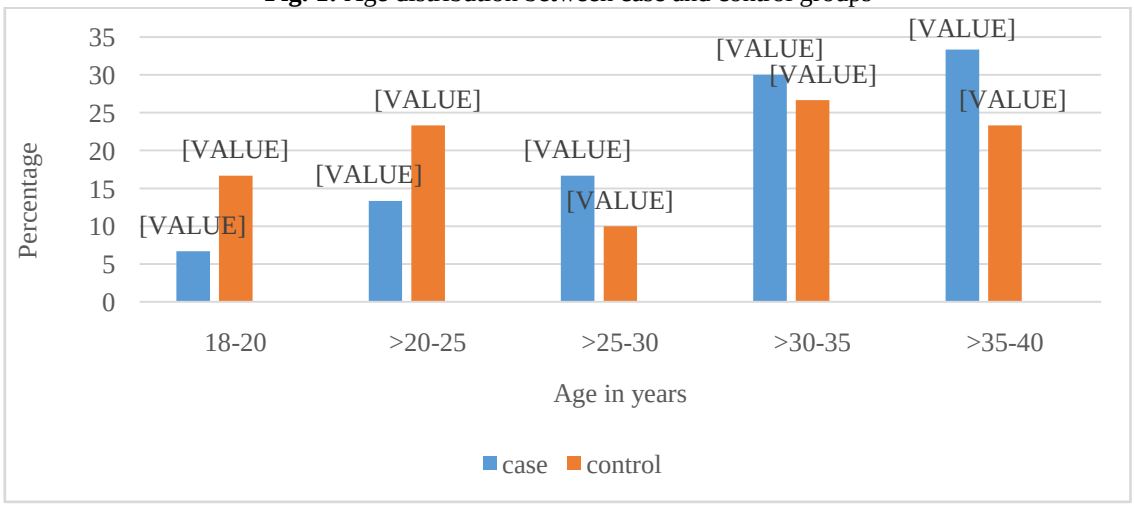

Figure 2 shows dwelling wise distribution of the respondents. It is evident that 40% cases belong to rural areas where as 60% belong to urban areas.

Fig. 2: Bar diagram showing distribution of the respondents by their site of dwelling

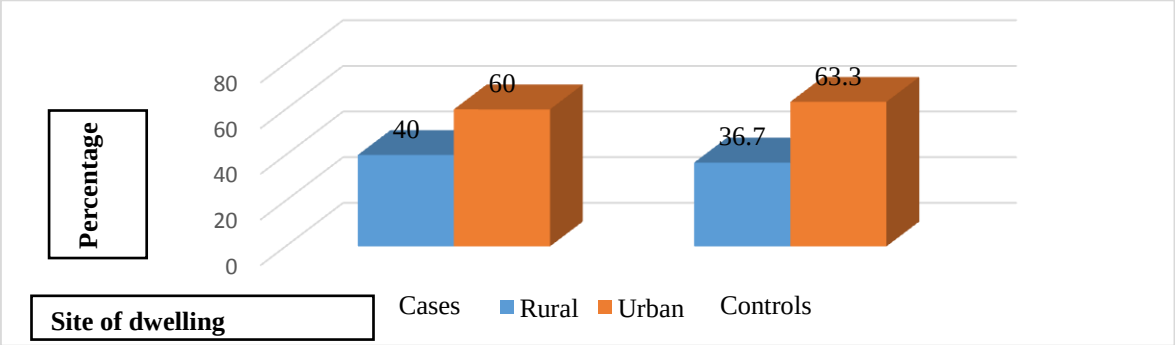

Table 1 shows that mean systolic blood pressure among cases and controls were 149.33 and 110.60 mmHg respectively.Whereas, mean diastolic blood pressure among cases and controls were 86.87 and 69.8 mmHg respectively.

Table 1: Relation between systolic and diastolic blood pressure among cases and controls

Blood pressure	Cases (mean ± SD)	Controls (mean ± SD)	t-test
Systolic	149.33 ± 7.0	110.60 ± 3.9	Value=26.4 p<0.05
Diastolic	86.87 ± 5.0	69.8 ± 5.4	Value=12.5 p<0.05

Table 2 shows that 43.3% and 66.7% cases have shown higher levels of AST and ALT respectively. 70% of cases have shown lower protein level.

Table 2: Distribution of LFT Parameters

Parameters	High	Normal	Low
Total bilirubin	1 (3.3%)	29 (96.7%)	-
AST	13 (43.3%)	17 (56.7%)	-
ALT	20 (66.7%)	10 (33.3%)	-
Total protein	-	9 (30%)	21 (70%)

Table 3 shows that only 13.33% and 6.67% cases have shown higher serum Urea and Creatinine level respectively. 63.34% cases have shown higher Sodium whereas, 56.67% cases have shown lower Potassium level.

Table 3: Distribution of KFT Parameters

Parameters	High	Normal	Low
Urea	4 (13.33%)	25 (83.34%)	1 (3.34%)
Creatinine	2 (6.67%)	28 (93.33%)	-
Uric acid	21 (70%)	9 (30%)	-
Na^+	19 (63.34%)	10 (33.33%0	1 (3.33%)
K^+	1 (3.33%)	12 (40%)	17 (56.67%)

Table 4 shows that among cases the value of serum Copeptin was significantly higher than controls, mean values were 66.1 and 6.33 pmol/L among the cases and controls respectively.

Table 4: Relation between Copeptin level among cases and controls

Cases/Controls	Copeptin (pmol/L) Mean ± SD	Students t-test
Cases	66.1 ± 15.84	Value = 22.85 Df-58 P<0.05
Controls (normal range: 1-12 pmol/L)	6.33 ± 1.90	

Table 5 shows that all the babies were normal in case of normal Copeptin level but in case of high Copeptin level low birth weight was found in 11 cases and dead in 9 cases. The findings were found to be statistically significant.

Table 5: Relation between Copeptin level among cases and controls according to outcome

Outcome	High Copetin level	Normal level	Fischer exact test
Death	9 (100)	0 (0.0)	Chi-square value = 30
Low birth weight	11 (100.0)	0 (0.0)	P = 0.0001
Healthy	10 (25.0)	30 (75.0)	
Total	30 (100.0)	30 9100.0)	

Table 6 shows that serum Copeptin level was positively correlated with blood pressure. All the liver function test parameters were positively correlated with Copeptin level except serum protein level; whereas, all kidney function test parameters were positively correlated except serum potassium level, which was found to be negatively correlated.

Table 6: Correlation of markers with Copeptin

Parameters	r value
SBP	0.891
DBP	0.794
Urea	0.770
Creatinine	0.831
Uric acid	0.778
Na^+	0.619
K^+	-0.671
TB	0.547
AST	0.836
ALT	0.712
Total protein	-0.692

IV. Discussion

This study was conducted to estimate serum copeptin levels in preeclamptic patients and normal pregnant women. And also it was aimed to compare the findings with other established parameters such as serum sodium, potassium, urea, creatinine, total bilirubin, aspartate transaminase, alanine transaminase, total protein and uric acid in the study cases. Maximum number of preeclamptic cases were in the age group of 35 years and above. This finding was supported by the study conducted by Chan TF et al.[14] They found out that the incidence of preeclampsia and eclampsia in 20-24 year age group was the lowest. They concluded that advanced maternal age was associated with increased risk of preeclampsia. When age was compared with copeptin level, both were found to be positively correlated and finding was statistically significant ($p<0.05$). From the region wise distribution it can be seen that 60% cases belonged to urban area. According to a study done by Middendorp DV et al[15] they found that incidence of preeclampsia were higher in urban areas. They also found that BMI and heart rate were independently related to a high systolic BP while urban residence and BMI were independently related to diastolic BP. They also added that urban residence, high education, high collar job were positively related to raised BP. They explained that increased BMI compared to the rural dwellers, number of women with a family history of hypertension, though another unknown factor might have contributed to the difference in diastolic BP. SBP, DBP were significantly higher among the cases. A study by Tabassum H et al[16] among Riyadh population has shown that the SBP, DBP were higher compared to control group and the mean values were 167.0 mmHg, 98.51 mmHg respectively. In the present study when the basic demographic features like SBP and DBP were compared to serum copeptin levels, it was found that all were positively correlated with copeptin and the findings were statistically significant.Serum urea levels in the study were normal in 83.34% cases followed by higher levels seen in 13.33% cases. Serum creatinine levels were normal in 93.33% cases followed by higher levels seen in 6.67% cases. Serum uric acid was higher in 70% cases followed by normal in 30% cases. When all the parameters were compared between preeclamptic and normal pregnant women, findings were found to be significantly raised in cases than controls. This study was in agreement with a study described by Israa A and Jumaah M[17] who opined that serum urea, creatinine, serum uric acid in preeclamptic groups were elevated significantly as compared to normotensive pregnant group. They concluded that it is important to assess renal function tests especially serum uric acid for all pregnant women having high blood pressure as it is the first change and denote for affecting renal function in preeclamptic cases. In our study when all the parameters were compared with copeptin level, it was seen that all the kidney function markers were positively correlated with serum copeptin level.In our study, serum sodium levels were high in 63.34% cases followed by normal levels seen in 33.33% of the cases. Low value was seen in 3.33% cases. Serum potassium levels were low in 56.67% cases followed by normal levels seen in 40% cases. In a study by Tabassum H et al[16]

opined that reduction in serum potassium and raised sodium might have possible role to play in the etiopathogenesis of preeclampsia. Sodium and potassium might act as predisposing factors or as risk factors especially in predisposed individuals, rather than major causative factors. Pregnancy induced hypertension might be an early sign of abnormality in the transport of sodium and potassium across the vascular smooth muscle cell membrane, which is responsible for regulation of blood pressure. They added that hypernatremia in the case group could be due to sodium retention. Sodium retention, by means of release of digitalis like factor, potassium deficit or hypokalemia inhibit sodium pump of arterial and arteriolar vascular smooth muscle cells, thereby increasing the sodium concentration and decreasing the potassium concentration in the intracellular fluid. When serum sodium and potassium were compared to serum copeptin levels in the present study, both the markers showed that sodium was positively correlated (r=0.883) and the findings were statistically significant ($p<0.05$) whereas, potassium was negatively correlated with copeptin and it was statistically significant. $p<0.05$ and r = - 0.697.Serum total bilirubin levels in this study were normal in 96.7% cases followed by higher levels seen in 3.33% cases. Serum AST levels were normal in 56.7% cases followed by higher levels seen in 43.3% cases whereas ALT levels were higher in 66.7% cases followed by normal in 33.3% cases. When all the parameters were compared between preeclamptic and normal pregnant women, it was found to be significantly raised in cases than controls. The finding of this study was similar to that described by Munazza B et al[18] who opined that raised levels of serum bilirubin and liver enzymes like ALT, AST and alkaline phosphatase were seen in preeclamptic cases. In the present study when all the markers were compared with serum copeptin level, they were found to be positively correlated.Serum protein levels were found lower than the normal range in 70% cases and normal in 30% cases in the present study. This is again in agreement with the findings of Muzammil S et al.[19]Their study showed that serum concentrations of total protein, albumin and A/G ratio were significantly reduced in preeclampsia, while these changes were not related to age, parity and mean arterial blood pressure. They concluded that the considerable changes in serum proteins that occur in preeclampsia could be a result of heavy proteinuria. Their observation also concluded that total proteins, albumin and globulin were inversely proportional to the blood pressure and urine albumin except A:G ratio in preeclamptic women. When serum protein was compared with serum copeptin level both the markers were found to be negatively correlated and statistically significant. The r value was -0.767, p value was <0.05.Serum copeptin levels were estimated in both cases and controls. In healthy individuals, the range varies from 1-12 pmol/L. In this study none of the cases had values in the normal range. The mean copeptin level among the cases was 66.1 pmol/L and standard deviation was 15.84 pmol/L. Among the controls mean value was 6.33 pmol/L whereas, standard deviation was 1.90 pmol/L. Our findings are in accordance with the results of Tuten A et al.[20] In their study, while comparing serum copeptin levels among early onset controls and preeclamptic cases, they found that the mean values of the marker were 0.54 ng/ml and 0.92 ng/ml respectively. Mean values of the marker in late onset controls and cases were 1.15 ng/ml and 1.65 ng/ml respectively. Raised values were statistically significant in early onset cases and controls only. They also found that maternal serum copeptin levels were positively correlated with gestational age, systolic and diastolic blood pressure. But levels did not correlate with maternal age, BMI, birth weight, uterine and umbilical artery doppler values in both early onset and late onset preeclampsia.They explained that early onset preeclampsia is primarily considered a foetal disorder, typically associated with placental dysfunction, a reduction in placental volume, intrauterine growth restriction, abnormal uterine and umbilical artery doppler evaluation, low birth weight, multi organ dysfunction, perinatal death and adverse maternal and neonatal outcomes. By contrast, late onset precclampsia is considered a maternal disorder, resulting from maternal constitutional disorder, associated with a normal placenta, larger placental volume, normal foetal growth, normal uterine and umbilical artery doppler evaluation, normal birth weight and more favourable maternal and neonatal outcomes. Increased placental estrogen production stimulates hepatic corticosteroid binding globulin production, eventually depleting levels of cortisol thereby activating HPA axis and increasing serum levels of free cortisol. They also concluded that positively correlated copeptin and gestational age signified that it was reflecting increased individual stress levels during pregnancy.In a study by Yeung EH et al,[21] analysis of blood samples were done before randomization (before 21 weeks and 6 days of gestation) and twice during follow up between gestational weeks 26 and 29 and at approximately 36 weeks. They found the mean baseline copeptin level among controls was 3.8 pmol/L whereas in case of all preeclamptic cases the mean value was 5.1 pmol/L. They opined that higher copeptin concentrations, measured before recognition of clinical disease, were associated with increased preeclampsia risk. Levels of copeptin increased across gestation regardless of preeclampsia case status but differed more markedly by case status closer to the time of diagnosis. Copeptin was not associated with gestational diabetes mellitus or gestational hypertension apart from preeclampsia, suggesting that it was specific to development of preeclampsia. They also observed that women with gestational hypertension (those who avoid kidney damage despite elevated blood pressure) do not overly secrete vasopressin above and beyond that of normal pregnancy which confirms the differences in pathophysiology of the 2 conditions. Among women in later who were diagnosed to be preeclamptic, copeptin might serve as an early marker of the possible effect on renal function. It is seen that the patients who had high copeptin levels majority had poor pregnancy outcome. In only 33.33% cases, patients had delivered healthy

babies, whereas rest were of either low birth weight (36.66%) or dead (30%). It was also observed that the patients who had delivered normal babies, copeptin values were <60 pmol/L. Patients who had copeptin values >60 pmol/L had the worse outcome. Our findings were also supported by the work carried out by Akinlade KS et al.[22] They concluded that there was significant negative correlation between maternal serum copeptin and some foetal/neonatal outcome. They also concluded that there was elevated maternal copeptin level in preeclampsia, which increased with severity. Furthermore, copeptin level in third trimester could predict preeclampsia and elevation was associated with adverse perinatal outcome.

V. Conclusion

The results of this study shows that copeptin level was more than the normal range, that is, 1-12 pmol/L in all the cases. The increase in copeptin levels among cases and controls was correlated with the markers of kidney and liver functions. The study demonstrates that copeptin could effectively help in diagnosis of the preeclampsia cases for effective treatment as well as it might predict the pregnancy outcome. In fact it was observed that copeptin levels had better sensitivity than markers of liver and kidney functions.As the study pattern is a case control study, the future pattern of copeptin levels among the patients in the follow up period could not be ascertained. If follow ups could be done, this could have helped to understand how long the copeptin levels remain high in the post natal period. Also the patients were selected as diagnosed cases of preeclampsia when they had been hospitalized with acute symptoms after 20 weeks of gestation. But those who were prone to preeclampsia and were in early trimesters (<20 weeks), were left out. The efficiency of copeptin in diagnosing such cases could be a matter of interest for future researchers.Nevertheless it may be concluded that serum copeptin can be used as a diagnostic marker in addition to conventional biomarkers like serum urea, creatinine, electrolytes, total bilirubin, AST, ALT, serum protein and uric acid.

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