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Serum N-Terminal Pro B-Type Natriuretic Peptide is associated with maternal complication in pregnancy with severe preeclampsia

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ABSTRACT

Background: Hypertension is the second most common cause of maternal death in the world. Predicting the occurrence of preeclampsia (PE) complications is needed to optimize management. Brain natriuretic peptide (BNP) is a polypeptide, secreted by cardiac ventricular myocytes. Research linking N-Terminal Pro B-Type Natriuretic Peptide (NT-proBNP) levels with maternal complications has never been conducted in Indonesia. The aim of the study is to evaluate plasma NT-proBNP levels in pregnant women with pre-eclampsia and normotension and to find a relationship between NT-proBNP levels and maternal complications incidence.

Methods: This cross sectional study was conducted on thirty women with severe preeclampsia with gestational age >20 weeks who attended and underwent labor at Dr. Kariadi Hospital Semarang during study period. Patients with a history of chronic disease, underweight or obese, history of heart disease and consumption of heart drugs were excluded. Serum NT-proBNP was taken prior labor. Correlation between NT-proBNP serum levels and physical characteristics as well as complications was performed using the Mann-Whitney and Spearman correlation test.

Results: NT-proBNP serum levels were significantly higher in the severe preeclampsia group, especially early-onset compared to the normotensive group ($p<0.05$). Increased serum NT-proBNP levels are associated with several maternal complications, especially HELLP syndrome, pulmonary edema, retinopathy and renal impairment.

Conclusions: Increased serum NT-proBNP levels are associated with severe preeclampsia and several maternal complications.

Keywords: preeclampsia, NT-proBNP, maternal complications.
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BACKGROUNDS

Hypertensive disorders in pregnancy cause about 30% of maternal deaths.[1] According to World Health Organization, hypertension accounts for 14% of global maternal mortality and global second most common cause of maternal mortality.[2] Preeclampsia is a serious medical problem with high complexity. Severe preeclampsia can lead to life-threatening maternal complications including eclamptic seizures, HELLP syndrome, placental abruption, acute cardiovascular complications and pulmonary edema.

Predicting the occurrence of preeclampsia complications is needed to optimize proper management, thus preventing maternal and infant morbidity and mortality. Various biomarkers are increased in preeclamptic women, including Corin, LDH, leptin, PAPP-A, inhibin and activin A, cystatin C, beta 2 microglobulins, beta-trace protein, sFlt-1/PGF ratio, BNP and NT-proBNP.[3-10] Although there are various potential markers for preeclampsia, the reliability of these markers for predicting the severity and complication of preeclampsia was inconsistent between studies.

Brain natriuretic peptide (BNP) is a polypeptide, secreted as N-Terminal pro BNP (NT-proBNP) by cardiac ventricular myocytes in response to excessive myocardial stretch and further broken down into active BNP hormones and biologically inactive NT-proBNP.[11,12] NT-proBNP levels are found to be higher in preeclampsia due to an increase in afterload that coincides with a pre-existing excessive volume increase and a decrease in NT-proBNP metabolic clearance due to renal impairment.

There has not been any research linking NT-proBNP levels with maternal complications in Indonesia. This study will evaluate plasma NT-proBNP levels in preeclampsia and normotension women and evaluate the correlation between plasma NT-proBNP levels and maternal complications.

METHODS

Research subject

Thirty women with ≥20 weeks of gestation who visited, referred or underwent labor at Dr. Kariadi Hospital with severe preeclampsia based on 2016 PNPK

Table 1. Sample characteristics

Variable	Normotensive		Severe PE		p†
	n	%	n	%	
Maternal age					
< 20	0	0.0	2	6.7	
20 – 35	22	73.3	17	56.7	<0.001*
> 35	8	26.7	11	36.7	
Gravidity					
Nulliparous	15	50.0	8	26.7	<0.001*
Multiparous	15	50.0	22	73.3	
Gestational age					
≤ 34 weeks	2	6.7	8	26.7	<0.001*
> 34 weeks	28	93.3	22	73.3	
Maternal Morbidity					
Yes	5	16.7	11	36.7	<0.001*
No	25	83.3	19	63.3	
Delivery					
CS	18	60.0	18	60.0	<0.001*
Non-CS	12	40.0	12	40.0	
Placental abruption					
Yes	0	0.0	0	0.0	<0.001*
No	30	100	30	100	
Eclampsia					
Yes	0	0.0	1	3.3	<0.001*
No	30	100	29	96.7	
Pulmonary edema					
Yes	0	0.0	2	6.7	<0.001*
No	30	100	28	93.3	
CHF					
Yes	0	0.0	2	6.7	<0.001*
No	30	100	28	93.3	
Retinopathy					
Yes	0	0.0	4	13.3	<0.001*
No	30	100	26	86.7	
Cerebrovacsular accident					
Yes	0	0.0	1	3.3	<0.001*
No	30	100	29	96.7	
Renal disfunction					
Yes	0	0.0	4	13.3	<0.001*
No	30	100	26	86.7	

Notes: † Saphiro-wilk test, *abnormal data distribution

severe preeclampsia criteria and thirty normotensive counterparts were recruited for study. Severe preeclampsia is defined as the presence of one of the following symptoms or signs : 1) Hypertension: SBP of ≥ 160 mmHg or ≥ DBP of 110 mmHg, on two examinations at least 15 minutes apart in the same arms; 2) Thrombocytopenia: platelet count < 100,000/microliter); 3) Renal failure: serum creatinine concentration greater than 1.1 mg/dL or an increase of the serum creatinine concentration in the absence of another renal disease; 4) Hepatic failure: elevated transaminase concentrations (to twice average concentration), and/or upper quadrant or epigastric pain; 5) Pulmonary edema; 6) Neurologic symptoms: stroke, headache, visual disturbance; 7) Uteroplacental circulatory disturbance: Oligohidramnion, Fetal Growth Restriction (FGR), absent or reserved end-diastolic velocity (ARDV). Patient with history of chronic diseases (e.g. chronic hypertension, heart disease, lung disease, kidney disease, liver disease, hyperthyroidism, diabetes, and autoimmune disorder), body mass index >30 or <18.5, had history of peripartum cardiomyopathy, heart valve disease, and

severe electrocardiographic abnormalities and currently taking heart medication were excluded from the study.

Data collection

Venous blood samples were taken prior delivery, induction or cesarean section in both groups. Complete blood count, Liver Function Test (LFT), Kidney Function Test, LDH, NT-proBNP were performed. NT-proBNP plasma measurements were carried out using the Roche CARDIAC proBNP kit using the Cobas h232 instrument in heparin-treated venous blood at the Prodia laboratory. Patient history, physical examination findings, biochemical examination results, maternal outcomes and other associated complications were recorded. All patients were followed for 48 hours. Any maternal or other cardiovascular complications occurred within 48 hours were also recorded.

Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 20. Saphiro-Wilk tests were used to analyze normality of data distribution. Categorical data are described as percentages and continuous data are described as mean ± SD or median (range). Student-t test (for normally distributed data) or Mann Whitney test (for not normally distributed data) was used for variable comparison. Relationship between NT- proBNP and various parameters such as parity, gestational age, systolic and diastolic blood pressure, signs and symptoms of impending, and PE appearance were determined statistically using the ANOVA/Kruskal Wallis/Mann Whitney test. Correlation between NT-proBNP levels and parameters such as age and blood test results between the two groups was determined statistically using Pearson's correlation for normally distributed data and Spearman's correlation for not normally distributed data.

RESULTS

Baseline Characteristic

We included were 30 pregnant women with severe preeclampsia and 30 normotensive women who met the study criteria. Sample characteristics were presented in table 1.

Table 2. Comparison of NT-proBNP level based on maternal age

Maternal age	Mean ± SD	Median (min-max)	Normality	p
< 20	348.00 ± 362.04	348 (92 – 604)	–	0.610§
20 – 35	384.79 ± 524.15	78 (40 – 2640)	0.000	
> 35	241.37 ± 324.22	79 (40 – 1065)	0.000	

Notes : § Kruskal wallis

Table 3. Comparison of NT-proBNP level based on gravidity

Gravidity	Mean ± SD	Median (min-max)	Normality	p
Nulliparous	344.70 ± 605.01	92 (40 – 2640)	0.000	0.562‡
Multiparous	228.68 ± 343.79	79 (40 – 1584)	0.000	

Notes : ‡Mann whitney

Table 4. Comparison of NT-proBNP level based on blood pressure

BP	Mean ± SD	Median (min – max)	Normality	p
Normotension	103.10 ± 149.39	58 (40 – 824)	0.000	0.001‡*
Severe PE	443.20 ± 590.63	124 (40 – 2640)	0.000	

Notes : *Significant (p < 0,05); ‡ Mann whitney

Table 5. Comparison of NT-proBNP level based on severe PE onset

Severe PE	Mean ± SD	Median (min – max)	Normality	p
Early Onset	673.50 ± 486.86	544 (92 – 1584)	0.662	0.021‡*
Late Onset	359.45 ± 612.51	96 (40 – 2640)	0.000	

Notes: *Significant (p < 0.05); ‡ Mann whitney

Serum NT-proBNP Level

The mean serum NT-proBNP levels were found to be higher in mothers aged 20-35 years (384.79 ± 524.15) compared to aged <20 years (348.00 ± 362.04) and >35 years (241.37 ± 324.22). Based on Kruskal Wallis analysis, the mean difference in NT-proBNP serum levels was insignificant (p=0.61) (Table 2).

NT-proBNP level was higher in nullipara (344.70 ± 605.01) than multipara (228.68 ± 343.79). This difference was not statistically significant with p = 0.562 (Table 3). Higher NT-proBNP serum levels were found at ≤34 weeks of gestation (560.60 ± 492.00) compared to >34 weeks (215.66 ± 436.32). Based on Mann-Whitney analysis, we found a statistically significant difference (p=0.003) in both groups .

Higher level of NT-proBNP also observes in severe PE rather then in normotension patients (Table 4). The NT-proBNP levels in early-onset severe PE were significantly higher than late-onset severe PE (p=0.021). The mean NT-proBNP levels in early-onset severe PE were 673.50 ± 486.86 and at late-onset severe PE were 359.45±612.51 (p=0.021) (Table 5).

Comparison between NT-proBNP level and maternal complications

Maternal complications were only found in the preeclampsia group. The serum NT-proBNP level was higher in patients with maternal complications. Based on the Mann-Whitney analysis, there were significant differences between the serum levels of NT-proBNP in associated complications of PE such as HELLP syndrome, pulmonary edema, retinopathy and renal dysfunction (p <0.05) (Table 6).

DISCUSSION

The demographic parameters of the patients in the two groups were similar. We found advanced maternal age and young age have higher PE incidence. However, no significant correlation was found between NT-proBNP levels and maternal age (p>0.05). Our finding was similar

Table 6. Comparison of serum NT-proBNP level and maternal complications

Complication	Mean ± SD	Median (min – max)	Normality	p
HELLP				
Yes	1084.3 ± 490.29	1065 (604 – 1584)	0.935	0.008‡*
No	230.46 ± 421.31	78 (40 – 2640)	0.000	
Eclampsia				
Yes	887.00 ± 0.00	887 (887 – 887)	–	0.151‡
No	262.75 ± 457.04	79 (40 – 2640)	0.000	
Pulmonary edema				
Yes	1131.5 ± 270.82	1131.5 (940 – 1323)	–	0.027‡*
No	243.55 ± 437.32	78.5 (40 – 2640)	0.000	
CHF				
Yes	499.50 ± 622.96	499.5 (59 – 940)	–	0.503‡
No	265.34 ± 458.92	84.5 (40 – 2640)	0.000	
Retinopathy				
Yes	788.75 ± 550.12	602 (367 – 1584)	0.209	0.008‡*
No	236.32 ± 435.92	78 (40 – 2640)	0.000	
Cerebrovacsular accident				
Yes	2640.0 ± 0.00	2640 (2640 – 2640)	–	0.083‡
No	233.03 ± 342.45	79 (40 – 1584)	0.000	
Renal disfunction				
Yes	1417.5 ± 920.27	1235.5 (559 – 2640)	0.660	0.002‡*
No	191.41 ± 281.09	78 (40 – 1323)	0.000	

Notes: * Significant (p<0.05); ‡ Mann-Whitney U test

with Tyas et al. study which reported that advanced maternal age (>35 years) is an independent risk factor for the occurrence of poor maternal and fetal outcomes in preeclampsia patients.[13]

A higher number of multiparous pregnancies were found in the severe PE group compared to normotensive group. These findings differ from studies conducted by Kumari et al. study who reported a higher number of nulliparous women in pre-eclampsia group.[10] Furthermore, we found that serum NT-proBNP levels were higher in nulliparous patients than in multiparous patients, but this correlation was not statistically significant. Nulliparous has been known as risk factor for preeclampsia. Bdolah et al. reported that a relatively anti-angiogenic state characterizes nulliparous women in their circulation during late third trimester and altered angiogenic profile in nulliparous women may be a potential molecular mechanism that explains the epidemiological link between excess PE and nulliparity.[14]

In this study, serum NT-proBNP levels were found significantly higher in PE group, especially in early-onset PE compared to late-onset PE (p=0.021). This finding is consistent with previous studies which reported a significant increase in serum NT-proBNP levels in the PE and severe PE groups compared with the control group.[10] Seong et al. also found an increase in NT-proBNP levels in severe PE patients compared to mild PE patients (1766.43 pg/mL versus 214.97 pg/mL).[16] Furthermore, other studies reported a higher serum BNP levels during postpartum period in preeclamptic patients than in normotensive patients and this increase persisted for 3-6 months after delivery.

Increment of serum NT-proBNP levels is likely due to preeclampsia's pathophysiology and the biological mechanism of action of BNP. Research shows that BNP increases natriuresis and decreases vascular resistance, while preeclampsia characterized by generalized vasoconstriction. It is suspected that the increase of BNP level in preeclampsia patients is a mechanism to reverse the cardiovascular changes that arise from the preeclampsia syndrome.[15] However, further research is needed to determine the exact role of BNP in preeclampsia.

In this study we found several maternal complications in preeclampsia patients that were not found in normotensive patients, including HELLP syndrome in 3 cases (10%), eclampsia and cerebrovascular disorders in 1 case (3.3%), pulmonary edema and congestive heart failure in 2 cases (6.7%), and retinopathy and renal dysfunction in 4 cases (13.3%). Analysis of NT-proBNP serum levels showed a significant correlation with the incidence of HELLP syndrome, pulmonary edema, retinopathy and renal dysfunction. Several women even have more than one complication. Similar results were also obtained from Kumari et al. who reported 31 complications in 19 women with preeclampsia, with partial HELLP syndrome and preeclampsia was the most common complication and had a significant correlation with increased NT-proBNP levels.[13]

In this study we did not assess the

predictive value of complications with serum NT- proBNP levels. Previous studies reported that NT-proBNP levels above 500 pg/mL had a good positive predictive value (83.38%) and below 100 pg/mL had a good negative predictive value (92.85%) for PE related complications. In accordance with the findings in previous studies, our study found that majority of PE patient with complications had NT-proBNP serum levels >500 pg/mL. In hypertensive diseases of pregnancy, increased levels of NT-proBNP in preeclampsia are associated with increased cardiac filling pressures and diastolic dysfunction. Increased levels of NT-proBNP in pregnant women with known cardiac disease may lead to earlier diagnosis of impending heart failure. Similarly, elevated levels of NT-proBNP assist with the diagnosis of peripartum cardiomyopathy.[15,17]

There are several limitations in this study, including: the relatively small number of samples, inconsistent timing NT-proBNP test (before the patient undergoes labor, induction or cesarean section) and the absence of long-term monitoring of maternal and fetal outcomes. However, this study shows that NT-proBNP is a useful marker to predict PE complications. Early management and referral to higher health services for women with elevated NT-proBNP levels are expected to prevent complications and reduce maternal morbidity and mortality, which are still relatively high in Indonesia.

CONCLUSION

Serum NT-proBNP levels were higher in severe preeclampsia group than in normotensive group. Serum NT-proBNP levels were higher in early-onset compared to late-onset preeclampsia. Increased serum NT-proBNP levels were associated with several maternal complications in the severe preeclampsia group compared to normotensive group.

CONFLICT OF INTEREST

The authors do not have financial relationships with any organizations that might have an interest in the submitted work. They have no other relationships or activities that could influence or appear to have influenced the submitted work.

ETHICAL CONSIDERATION

All subjects were asked to give written consent prior study. This study has been approved Ethical Committee Faculty of Medicine, Universitas Udayana with ethical clearance reference number: No.565/EC/KEPK-RSDK/2020. All study procedure in accordance to.

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AUTHOR CONTRIBUTION

All author contribute equally on writing the original draft and agree to final version of the manuscript for publication.

REFERENCES

1. Adu-Bonsaffoh K, Obed SA, Seffah JD. Maternal outcomes of hypertensive disorders in pregnancy at Korle Bu Teaching Hospital, Ghana. Int J Gynaecol Obstet. 2014;127(3):238–42.
2. Wibowo N, Irwinda R, Frisdiantiny E, Karkata MK, Mose JC, Chalid MT, et al. National guidelines for the diagnosis and management of preeclampsia. Jakarta: POGI HKFM; 2016. p. 6–8.
3. Zhou Y, Wu Q. Role of corin and atrial natriuretic peptide in preeclampsia. Placenta. 2013;34(2):89–94.
4. Dave A, Maru L, Jain A. LDH (Lactate Dehydrogenase): a biochemical marker for the prediction of adverse outcomes in pre-eclampsia and eclampsia. J Obstet Gynaecol India. 2016;66(1):23–9.
5. Mumtaz F, Memon AR, Yousfani S, Tahir SM, Khushk I, Memon M, et al. Role of serum leptin level as a marker of severity of preeclampsia. J Ayub Med Coll Abbottabad. 2008;20(1):13–5.
6. Spencer K, Cowans NJ, Chefetz I, Tal J, Meiri H. First-trimester maternal serum PP- 13, PAPP-A and second-trimester uterine artery Doppler pulsatility index as markers of pre-eclampsia. Ultrasound Obstet Gynecol. 2007;29(2):128–34.
7. Spencer K, Cowans NJ, Nicolaides KH. Maternal serum inhibin-A and activin-A levels in the first trimester of pregnancies developing pre-eclampsia. Ultrasound Obstet Gynecol. 2008;32(5):622–6.
8. Kristensen K, Wide-Swensson D, Cshmidt C, Blirup-Jensen S, Lindström V, Strevens H, et al. Cystatin C, beta-2-microglobulin and beta-trace protein in pre-eclampsia. Acta Obstet Gynecol Csand. 2007;86(8):921–6.
9. Stepan H, Herraiz I, Cshlembach D, Verlohren S, Brennecke S, Chantraine, et al. Implementation of the sFlt-1/PlGF ratio for prediction and diagnosis of pre-eclampsia in singleton pregnancy: implications for clinical practice. Ultrasound Obstet Gynecol. 2015;45:241–6.
10. Kumari S, Gupta M, Vardhan H, Saini V, Gupta SK. NT-proBNP: A biochemical marker of maternal complications in pre-eclampsia. J Clin Diagnostic Res. 2017;11(11):QC12–6.
11. Weber M, Hamm C. Role of B-type natriuretic peptide (BNP) and NT-proBNP in clinical routine. Heart. 2006;92(6):843–9.
12. Fazlinezhad A, Rezaeian MK, Yousefzadeh H, Ghaffarzadegan K, Khajedaluee M. Plasma Brain Natriuretic Peptide (BNP) as an indicator of left ventricular function, early outcome and mechanical complications after acute myocardial infarction. Clin Med Insights Cardiol. 2011;5:77–83.
13. Tyas BD, Lestari P, Akbar MI. Maternal Perinatal Outcomes Related to Advanced Maternal Age in Preeclampsia Pregnant Women. Journal of Family & Reproductive Health. 2019;13(4):191.
14. Bdolah Y, Elchalal U, Natanson-Yaron S, Yechiam H, Bdolah-Abram T, Greenfield C, Goldman-Wohl D, Milwidsky A, Rana S, Karumanchi SA, Yagel S. Relationship between nulliparity and preeclampsia may be explained by altered circulating soluble fms-like tyrosine kinase 1. Hypertension in pregnancy. 2014;33(2):250-9.
15. Yamada T, Koyama T, Furuta I, Takeda M, Nishida R, Yamada T, Morikawa M, Minakami H. Effects of caesarean section on serum levels of NT—pro BNP. Clinical endocrinology. 2013;78(3):460-5.
16. Seong WJ, Kim CS, Hong DG, Koo TB, Park IS. Amino-terminal pro-brain natriuretic peptide levels in hypertensive disorders complicating pregnancy. Hypertens Pregnancy. 2011;30(3):287-94.
17. Rafik Hamad R, Larsson A, Pernow J, et al. Assessment of left ventricular structure and function in preeclampsia by echocardiography and cardiovascular biomarkers. J Hypertens. 2009;27:2257–64.