American Journal of Epidemiology and Infectious Disease, 2016, Vol. 4, No. 6, 105-109
Available online at http://pubs.sciepub.com/ajeid/4/6/1

DOI:10.12691/ajeid-4-6-1

BNP as Predictor of Pediatric Severe Sepsis Fluid Responsiveness in Limited Resource Setting Country

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Abstract Fluid responsiveness is an important aspect in severe sepsis management, assessed by static and dynamic parameter tools. Unfortunately, they are not widely used in limited resource setting. Brain natriuretic peptide is cardiac hormone correlated with CVP measurement as one of the static parameter, but its associations with dynamic parameter has not studied yet. **Objective:** To investigate whether BNP might predict fluid responsiveness based on clinical and inferior vena cava index criteria. **Study Design:** A cross sectional study was conducted on 59 severe sepsis subjects aged 1–14 years who met the inclusion criteria enrolled through consecutive sampling during October 2013 to March 2014. Patients were given fluid resuscitation based on 2012 Surviving Sepsis Campaign. BNP measurements were performed at 0 and 1 hour after fluid resuscitation. Responder and non-responder groups were classified based on clinical and IVC index criteria. Ultrasound using M Mode was performed to calculate IVC index. Unpaired t test and receiver operating characteristic curves were generated for BNP to predict fluid responsiveness. **Results:** Baseline characteristics between responder and non-responder groups were almost similar. Initial BNP between groups using both criteria were not significantly different ($p>0.05$). The area under curve of BNP_0 was 0.04. The best cut off values of log BNP to predict fluid responsiveness was 1.9pg/mL. BNP ≤1.9 pg/mL has a sensitivity, specificity, negative predictive value and positive predictive value of each were 50%, 50%, 50%, 50%, respectively. **Conclusion:** BNP cannot reflect and accurately predict fluid responsiveness due to multifactorial factors of raising BNP and mostly subject were spontaneous breathing which more difficult to predict.

Keywords: *BNP, severe sepsis, fluid responsiveness*

Cite This Article: Nanan Sekarwana, Heda Melinda Nataprawira, Nur Melani Sari, Dadang Hudaya Somasetia, and Rahmat Budi Kuswiyanto, "BNP as Predictor of Pediatric Severe Sepsis Fluid Responsiveness in Limited Resource Setting Country." *American Journal of Epidemiology and Infectious Disease*, vol. 4, no. 6 (2016): 105-109. doi: 10.12691/ajeid-4-6-1.

1. Introduction

Sepsis was a leading cause of mortality in pediatric critically ill and a major health problem among children in both developing and industrialized countries. Improvement of treatment could have a substantial effect on survival and quality of life of all children, that including fluid resuscitation as the most important aspect of pediatric sepsis management. [1,2,3] Unfortunately, only 50% of critically ill patients will respond to volume expansion by significant increase of cardiac output. [4] Giving more fluid in this group might be deleterious, ineffective, and cause fluid overload. These emphasized the need for accurate determination of fluid responsiveness in pediatric severe sepsis. [5,6] Static and dynamic parameter tools are available to assess fluid responsiveness but they are not widely used in pediatric sepsis group particularly in limited resource setting.

Brain natriuretic peptide is a neurohormone released mostly from the cardiac ventricle in response to volume expansion and increased wall tension. A halflife of 20 minutes, changes in serum BNP level might rapidly reflect the effect of volume resuscitation on ventricular preload. [7] Brain natriuretic peptide is also a reliable biomarker for left ventricle dysfunction. Measurement of BNP is increasingly performed in adult patients especially as a tool in the management of heart failure for diagnosis, risk stratification, and monitoring response of therapy. [8,9] Brain natriuretic peptide level and its changes have good correlation with static parameter such as central venous pressure and global end diastolic volume index. [9] Decision to give fluid resuscitation in the presence of high plasma BNP level that suggest having cardiac dysfunction and absence of fluid responsiveness is challenging especially in physician face in daily basic in pediatric severe sepsis. [5] The study to assess cardiac dysfunction and fluid responsiveness in pediatric sepsis group was limited, even though studies in adult critical care with circulatory failure showed that sonographic evaluation of the inferior vena cava (IVC) diameter might be a good predictor of intravascular volume status. [10] Further investigation should be taken to confirm these findings especially in pediatric sepsis.

Point of care ultrasound (POCUS) to determine diameter, collapsibility index, and distensibility index of inferior vena cava (IVC) were non-invasive techniques that reflect central venous pressure as surrogate marker of adequacy of fluid resuscitation and volume status. [11] The use of respiratory IVC diameter variation is very popular because it is very easy to record, and needs a short learning curve, even for non-cardiologist residents or physicians.

The objective of this study was to determine whether initial BNP is associated with fluid responsiveness in pediatric severe sepsis based on clinical parameter and IVC collapsibility or distensibility index.

2. Methods

2.1. Study Population

A cross sectional study was conducted in October 2013–March 2014 in Pediatric Emergency. This study was reviewed and approved by the Health Research Ethics Committee. Informed consent was obtained from parents or their guardians. We included children aged 1–14 years who met severe sepsis or septic shock criteria based on the International Pediatric Sepsis Definition Conference 2005, given normal saline fluid resuscitation at least 20 mL/kg body weight, and had good nutritional status based on WHO Child Growth Standards (WCGS) 2006 or WHO reference 2007. [12,13] Sepsis was defined as the systemic response to infection manifested by two or more of the following conditions: 1) temperature>38.5° C or <36°C, 2) heart rate of >2 SD of age, 3) respiratory rate >2 SD of age, 4) white blood cell count more than upper limit of age and below limit of age or the presence of >10% of band. Severe sepsis was sepsis with one of these conditions: cardiovascular dysfunction or acute respiratory distress syndrome (ARDS) or more than two organs dysfunction. Septic shock was defined as sepsis with evidence of perfusion abnormalities including lactic acidosis, decreased peripheral pulses, mottle or cool extremities, prolonged capillary refill, oliguria (urine output< 1 mL/kg body weight/hour), or acute alteration of mental status. [12] Subjects with cold shock were identified as those having cold, clammy extremities, poor capillary refill, weak pulses, and narrow pulse pressure. Those with warm shock had warm skin, flash capillary refill, bounding pulses, and a wide pulse pressure. [14] The exclusion criteria of this study were 1) subject who had administered fluid resuscitation prior to the study enrollment, 2) pre-existing congenital heart disease, chronic renal failure, chronic liver failure based on clinical assessment, and 3) taking medications including angiotensin converting enzyme (ACE) inhibitors, beta blockers, diuretics, and nesiritide. Fluid resuscitation was given within 15–20 minutes, repeated until shock state was resolved or clinical sign of fluid overload appear.

2.2. Clinical, Sonograph, and BNP Measurement

Subject characteristics of groups were recorded. Heart rate, systolic blood pressure, diastolic blood pressure, capillary refill time, shock index, inotropic and vasoactive supports were measured before (T_0) and after fluid resuscitation (T_1). Collapsibility IVC index (cIVC) was determined in spontaneous breathing subject meanwhile mechanical ventilated subjects used distensibility index (dIVC) which were taken before and 5 minutes after fluid resuscitation. The Ax SYM® method micro particle enzyme immunoassay (MEIA) was performed to measure the level of BNP before fluid resuscitation (BNP_o) and within 1 hour (BNP_1) afterwards from the plasma supernatan. Δ BNP was calculated as BNP_1 minus BNP_0. Range of sensitivity was from 10–5,000 pg/mL. Whole blood was collected in vacutainer tube containing ethylene diamine tetraacid (EDTA), centrifuged, and the plasma supernatant was stored at -80°C. Fluid responder group was defined by clinical criteria and IVC criteria, and non-responder group didn’t fulfill both criteria. Clinical criteria was defined as 10% increment of systolic or mean blood pressure from the base line meanwhile IVC criteria took cut off point ≥20.5% [15].

Collapsibility/distensibility IVC index was calculated from diameter respiratory variation obtained with the SonoSite (SonoSite Inc, Bothell, Wash) M-turbo using the P21 5-1 MHz phased array transducer**.** All the investigators underwent 2 hours of focused sonograph training by pediatric cardiologist before study initiation. The measurement was taken at upstream of supra hepatic vein joining with the IVC with M mode-IVC sub-costal longitudinal view before and 5 minutes after the fluid resuscitation. Distensibility IVC index was calculated as follows: (max diameter during inspiration–minimum diameter during expiration)/minimum diameter during expiration. Collapsibility IVC index (cIVC) was calculated as follows: (max diameter during expiration–minimum diameter during inspiration)/minimum diameter during inspiration). [16] After the measurement, fluid resuscitation and the use of vasoactive agent were instituted according to Surviving Sepsis Campaign 2012 [17].

2.3. Statistical Analysis

Continuous variables were expressed as mean and standard deviation, or median and range as appropriate. Categorical data were expressed as proportion. If data were normally distributed, the comparisons were perfomed using student t test, otherwise Mann Whitney test was used. Chi square was used to analyze categorical data. We did logistic transformation due to skewness of BNP values. Diagnostic performance of BNP_0 in predicting the fluid responsiveness was evaluated using receiver operating characteristic (ROC) curve, allowing the determination of the optimal threshold value and the corresponding sensitivity, specificity, positive and negative predictive values. The ability for BNP_0 to discriminate between responder and non-responder groups was determined by the area under the ROC curve (AUC). All statistical analysis was conducted using SPSS 17 for Windows software. $P<0.05$ with two tailed test was considered to be statistically significant.

The study has been approved by the Research and Ethics Committee of the Universitas Padjadjaran Medical School, Indonesia, and written both subjects and parental consents were obtained.

3. Results

3.1. Subject Enrollment and Baseline Characteristic

During the study period a total of 59 subjects were included. Based on clinical criteria, 26/59 subjects were classified as responder. Both of responder and non-responder groups were mostly boys and the average age between groups were not significantly different. It consisted of cold shock [n=38], warm shock, [n=8], and severe sepsis [n=13]. There were significant different between group on systolic blood pressure and shock index after fluid resuscitation. The non-responder group had lower blood pressure and higher shock index than responder group (Table 1).

IVC was only measured in 21/59 subjects due to discontinuous availability of the bedside USG (sonosite M Turbo) during the study period. Table 1 showed that most subjects in the responder group had severe sepsis (P=0.026) while in the non-responder group mostly had cold shock (0.026). These results were different with the second criteria (Table 2) where cold shock dominated both responder and non-responder group (P=0.133). Systolic blood pressure and shock index after initial fluid bolus between groups were significantly different using two criteria (P=0.00 vs P=0.012). Most of the study subjects were not on mechanical ventilation (53/59). At baseline BNP_0, $BNP_{1,}$ and Δ BNP were not different between groups using clinical criteria (P=0.119; P=0.71; P=0.247) (Table 3) and either the IVC criteria (P=0.209; P=0.655; P=0.92) respectively in Table 4.

3.2. BNP and Fluid Responsiveness

The area under the curve (AUC) of plasma BNP was 0.04. The best cut off values of log BNP to predict fluid responsiveness was 1.9 pg/mL. A plasma BNP lower than 1.9 has a sensitivity of 50%, a specificity 50% and a negative predictive value of 50% and a positive predictive value 50%.

Table 1. Subject Characteristics Based on Clinical Criteria

	Responder (n=26)	Non-responder (n=33)	P value
Boys	16	20	0.578
Age (months)	54.3±41.5	55.91±43.6	0.645
Severe Sepsis	13	0	
Warm shock	3	5	0.026*
Cold shock	10	28	
Heart rate			
To(x/minute)	143±14.7	150±8	0.072
T1(x/minute)	129±13.7	138±27	0.067
Systolic blood pressure*			
To (mmHg)	66.4±9.9	64.7±11.8	0.460
T1 (mmHg	78.8±10.8	60.3±11.8	0.000**
Capillary refill time (second)	3.1±0.9	3.2±0.6	0.843
Inotrope-Vasoactive Index	13.1±16.8	22.1±20	0.06
Shock index	1.92±0.3	2.16±0.4	0.012**
Mechanical Ventilated	1	5	0.05

*Ten non-responder subjects developed lower BP after fluid resuscitation
** unpaired t tes.

Table 2. Subject Characteristics Based on IVC criteria

	Responder (n=26)	Non-responder (n=33)	P value
Boys	8	6	0.626
Age (months)	52.5±46	76.1±45.8	0.035
Severe Sepsis	5	0	0.133
Warm shock	1	1	
Cold shock	7	7	
Heart rate			
To(x/minute)	141.2±16.2	143±10.8	0.78
T1(x/minute)	129±14.6	130±26.7	0.78
Systolic blood pressure*			
To (mmHg)	61.9±11,1	63.7±7.4	0.6
T1 (mmHg	73±65.9	59.4±14.7	0.003**
Capillary refill time (second)	2.8±0.9	3.4±1.1	0.26
Inotrope-Vasoactive Index	14.23±15.2	20.1±10	0.415
Shock index	1.7±0.3	2.2±0.4	0.005**
Mechanical Ventilated	1	5	0.05

*Five non-responder subjects developed lower BP after fluid resuscitation
** unpaired t test.

Table 3. Mean BNP Based on Clinical Criteria

	Responder	Non-responder	P value
BNP0	1.68	1.98	0.119
BNP1	2.12	2.45	0.71
ΔBNP	1.818	2.03	0.247

Table 4. Mean BNP based on IVC index Criteria

	Responder	Non-responder	P value
BNP0	1.56	1.98	0.209
BNP1	2.15	2.29	0.655
ΔBNP	2.02	2.03	0.92

4. Discussion

Dynamic parameter was superior over static parameters in predicting fluid responsiveness and the evidence indicates that these dynamic parameters should be utilized when fluid expansion is required in the critically ill. Somehow in pediatric group, due to limited resources and only a few studies had been carried on assessing fluid responsiveness, it was scarcely used especially in resource limited setting. [18,19] In patients undergoing positive pressure ventilation, heart lung interactions can be used to reliably identify fluid responsiveness. Most dynamic parameters can be measured by using widely available devices for continuous beat-to-beat cardiac output monitoring. Distensibility and collapsibility index of vena cava inferior (IVC) was one of these tools, but the technique clearly dependent on the availability of the necessary equipment and echocardiography expertise. [20] Inferior vena cava diameter measurements might also assist in ongoing resuscitation by providing means to measure central venous pressure (CVP) non-invasively. Implied that the dIVC can be used as a measure of intravascular volume in response to resuscitation. A small collapsed IVC indicates hypovolemia and warrants for further fluid resuscitation [21].

In this study, initial plasma BNP of two groups using two criteria were not significantly different, this result was dissimilar with Muller et al. who studied BNP compared to CVP in predicting fluid responsiveness in critically ill adult. [22] Muller et al. found that initial BNP was lower in the responder group but fluid resuscitation did not increase plasma BNP so did BNP failed to predict fluid responsiveness. It was the same as our results that showed the initial plasma BNP and its changes did not predict fluid responsiveness accurately based on both criteria. This study was in line with other preliminary study comparing BNP, central venous pressure, and transcutaneous aortic Doppler. [23] Neither BNP or CVP correlated with the increase in stroke volume. [23] Both of them were static parameter which were inferior than dynamic parameter. As previously reported, CVP was a poor predictor of fluid responsiveness although a low value of CVP (-7mmHg) had a high specificity for predicting fluid responsiveness. Fluid responsiveness is a dynamic process, so if BNP is considered to be cardiac preload, BNP should share the same limitation with other static parameters.

Initial plasma BNP was similar to those reported in previous studies in pediatric septic patients which stated BNP in severe sepsis group was higher than sepsis and healthy controls but the BNP level in this research was lower. [26,27] A research in Turkey reported BNP level was 384±1191 pg/mL while the U.S. study had a median BNP 115 (26–2960) pg/mL. [26,27] The difference was due to the limited study subject, sepsis severity, and timing of BNP measurement. There was no previous study in pediatric sepsis group assessed fluid responsiveness based on brain natriuretic peptide. Significant increment of brain natriuretic peptide will appear in excessive volume expansion which in turn damages the endothelial glycocalyx, and this is followed by a rapid shift of intravascular fluid into the interstitial space, leading to a marked increase in extra vascular lung water (EVLW) and tissue edema. [5] Indeed, in a cohort of patients with sepsis, Zhang and colleagues demonstrated a strong correlation between the net fluid balance, the increase in brain natriuretic peptide, and global end diastolic volume as static parameters. [8,9]

This study used IVC index as a dynamic parameter of fluid responsiveness. cIVC moderately predicted fluid responsiveness in spontaneously breathing patients with acute circulatory failure but there was no united threshold cIVC in spontaneous breathing subjects even in adult sepsis group the cIVC index threshold ≥40% needed cautious use. In patients with a low cIVC value (<40%), fluid responsiveness cannot be excluded, while patients with cIVC above 40% are more likely to respond to fluid challenge. [16] The 40% cut off value is in accordance with recent studies in adult population, cIVC value below 40% cannot exclude fluid responsiveness while patients with cIVC above 40% are more likely to respond to fluid challenge (responder group).[16] More limited studies were found in pediatric population, only one study conducted by Khalid et.al that used cut off point in 20.5% to predict fluid responsiveness. This study used the same value due to unavailability cut off point cIVC index in spontaneous breathing pediatric sepsis group.

Subject populations were mostly spontaneous breathing patients whom fluid responsiveness were more difficult to assess. Spontaneous inspiratory effort increases intra-abdominal pressure which could exaggerate the preload response that affected fluid responsiveness. [20] Determination of fluid responsiveness using the dynamic evaluation methods has good accuracy than static measurements. [24] However, an important limitation of these methods is those indexes and measurements were validated for specific groups of patients under sedation and volume controlled mechanical ventilation, with no respiratory effort and no arrhythmias. A single study performed with healthy patients under spontaneous breathing also failed to establish a relationship between CVP baseline value and fluid responsiveness. Fluid responsiveness in spontaneous breathing was not correlated with CVP, pulmonary arterial wedge pressure, and ventricular end-diastolic volumes measurement. [24] Moreover, dynamic indices were not valid in spontaneously breathing patients since this research was dominated with spontaneous breathing subjects, it was more difficult to predict fluid responsiveness and thus highlight the need for additional studies especially in pediatric severe sepsis group. No previous studies in pediatric sepsis group assessed fluid responsiveness based on BNP.

Fluid responsiveness was also influenced by cardiac performance as described by Frank Starling curve. Hartemink et al. suggested that an increased circulating NT-pro BNP plasma level was an independent marker of greater systolic cardiac dysfunction, irrespective of filling status, and is a better predictor of fluid non responsiveness in septic than non-septic group of critically ill patients. [28] A significant increase of BNP percentage after fluid challenge irrespective of initial value may indicate that cardiac contractility is impaired and the LV dilated, indicating a strategy away from fluid resuscitation and toward inotropic use. [29] We did not performed measurement of cardiac dysfunction in early study, it might be better if we correlated fluid responsiveness with cardiac dysfunction in early presentation. There might be a correlation with fluid responsiveness in cardiac dysfunction group. We used a weak threshold to divide the subject population by clinical judgement based on 10% increment of systolic or mean arterial blood pressure and un-validated threshold of IVC in children. We should use more reliable tools to define fluid responsiveness.

The strength of the study was one of the few studies which had larger subjects assessing fluid responsiveness in pediatric severe sepsis using IVC index with threshold 20.5% as responder group and BNP changes as predictor fluid responsiveness. Limitation of this study wws discontinuity of assessment tool of fluid responsiveness and we did not perform other fluid status measurement as cardiac index or CVP to validate the results. We did not perform cardiac function and mostly subject were spontaneous breathing which fluid responsiveness was more difficult to predict.

5. Conclusion

Brain natriuretic peptide in this study group could not reflect and did not accurately predict fluid responsiveness. Further study is needed to validate the threshold of collapsibility IVC index in spontaneous breathing pediatric severe sepsis group.

Conflict of Interest Statement

No competing interest to declare.

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