The usefulness of brain natriuretic peptide level in diagnosis and prognosis of patients admitted to critical care unit with shortness of breath

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ABSTRACT
Background: Brain Natriuretic Peptide (BNP) is a polypeptide secreted by the ventricles as a response to cardio-myocyte stretching. Due to its cardiac origin and correlation with volume overload it has been successfully used for a long time in diagnosing and prognosticating Cardiogenic Pulmonary Edema. Materials and Methods: In this retrospective cohort study, an attempt was made to observe any correlation between admission BNP levels with APACHE II scores and length of ICU stay, in patients admitted with dyspnea to the ICU of a community based hospital. Results/Conclusion: This study showed no significant correlation between length of stay in an ICU and admission BNP levels in dyspneic patients. Independent variables such as age and gender failed to show any correlation either.

Key Words: Brain natriuretic peptide, critical care unit, dyspnea

INTRODUCTION

Brain natriuretic peptide (BNP) is a polypeptide secreted by the ventricles as a response to cardio-myocyte stretching. Due to its cardiac origin and correlation with volume overload it has been successfully used for a long time in diagnosing and prognosticating cardiogenic pulmonary edema.¹,² However, with recent advances, the role of BNP has been further extended in critical care to predict severity of disease and outcomes in patients with non-cardiogenic pulmonary edema.³,⁴ Severe sepsis⁵ and chronic hypercapnic respiratory failure patients.⁶ BNP level has also been shown to predict the need for intensive care in patients with acute exacerbation of chronic obstructive pulmonary disease (COPD).⁷

One of the common presenting symptoms of patients admitted to Intensive Care Unit (ICU) is shortness of breath (SOB) or dyspnea. The etiology varies greatly, from congestive heart failure (CHF) to COPD exacerbation to acute respiratory distress syndrome (ARDS). Some of these patients have a poorer prognosis while some respond much better to critical care management. The acute physiology and chronic health evaluation II (APACHE II) score, utilizing certain admission parameters, is directly linked to outcomes in acutely ill patients and can be used as a validated tool for prognostication of such patients.⁸ Another aspect often discussed is the length of ICU stay, which is a measure of the disease burden on hospitals and health resources and some admission parameters, and patient demographics has been seen to affect it.⁹ In this retrospective cohort study, an attempt was made to observe any correlation between admission BNP levels with APACHE II scores and length of ICU stay, in patients admitted with dyspnea to the ICU of a community based hospital.

MATERIALS AND METHODS

The study is a retrospective cohort study including an electronic medical records review of patients admitted to Saint Michael’s Medical Center Critical care unit with SOB as the chief complaint or with respiratory distress at time of presentation.
between 2009 and 2012. The institutional review board of Saint Michael’s Medical Center granted approval prior to data collection.

The study included a review of all patients above the age of 18 with SOB or respiratory distress who had plasma BNP level drawn at the time of admission to ICU and echocardiography performed during the admission and read by certified cardiologist. Patients with a history of CHF were included and classified as a separate group in the data analysis. Patients with the end-stage renal disease or glomerular filtration rate (GFR) <30 at the time of presentation were excluded as BNP levels might be elevated with above conditions independent of cardiopulmonary illness. Out of 522 patients records that were reviewed, 193 met the inclusion criteria, and a comprehensive review of the subjects’ electronic medical records was performed. Demographic data including age, gender and ethnicity was recorded. We also recorded the provisional diagnosis at the time of presentation, comorbidities and GFR. For all patients, we included the APACHE II score that is a known predictor of mortality, calculated using SFAR scoring website and recorded on our data sheet.

After recording our data, we classified the patients into two groups based on evidence of systolic and/or diastolic dysfunction. With ejection fraction (EF) more than 50% and no or minimal diastolic dysfunction in one group and EF <50% and/or evidence of significant diastolic dysfunction more than stage on in the other group. A total of 79 patients were found to have evidence of cardiomyopathy by echocardiography and 103 patients with no evidence of cardiomyopathy. The outcome was measured by number of days spent in the ICU before being transferred to the medical floor or telemetry of the unit; and mortality among our subjects. The statistical analyzes were conducted using the SPSS software (version 11.5). The tests used were t-test correlation, Pearson’s correlation, and linear regression to predict the length of stay using BNP levels at the time of admission

RESULTS

One hundred and ninety-three patients’ data was reviewed and analyzed. Four patients have missing data we ended up analyzing 189 patients. Patients divided into two groups; the first group had 80 patients with cardiomyopathy, proven by echocardiography; 19 patients diagnosed with COPD exacerbation. 22 patients with CHF exacerbation, 18 patients with pneumonia, 3 patients with asthma exacerbation, and 15 patients presented with other causes for respiratory distress.

The second group with no evidence of cardiomyopathy includes 109 patients, 34 patients had pneumonia, 17 patients COPD, 8 patients asthma, 2 patients ARDS, 1 patient pneumothorax and 47 others.

The average age for the cardiomyopathy group was 70.88, the average age for the non-cardiomyopathy group was 67.12. There was no statistically significant difference between the groups with $P = 0.08$. (Table 1) Neither group differed significantly between the genders [as demonstrated in Table 2] with the $P = 0.684$ (there were 7 missing data for gender). (Table 2)

Renal dysfunction and congestive heart failure

Renal dysfunction was measured by reduced GFR <60. There was no statistically significant difference between the mean GFR between the two groups the means of 63.08 and 76.25 with the $P = 0.057$ (Table 3).

Acute physiology and chronic health evaluation II scores for the two groups were calculated with mean APACHE II score of 18.28 in the group with cardiomyopathy and a mean score of 16.04 in those without cardiomyopathy. This difference was statically insignificant with the $P = 0.817$ (Table 4).

As you can see both the groups did not differ significantly in relation to age, gender and renal dysfunction and APACHE II scores.
We were unable to predict the length of stay in the ICU using BNP at the time of admission (Table 5). As evidenced in Graph 1, there was no predictability even on subgroup analysis using only those with cardiomyopathy or without cardiomyopathy or gender.

The mean BNP levels at the time of admission did not differ significantly to predict mortality in the ICU in those with ($P = 0.891$) or without cardiomyopathy ($P = 0.653$) although the Mean BNP was much higher in those who survived (551) than those who expired (378) in the group without cardiomyopathy (Tables 6-8).

**DISCUSSION**

Prognostication is an important aspect when dealing with critically ill patients. It not only helps physicians anticipate outcomes but also aids family members, and relatives have a realistic view of the patient’s condition. Several prognostication tools have been developed for various acute diseases such as Ranson’s criteria in pancreatitis, Maddrey’s discriminant function in acute alcoholic hepatitis to name a few. However, for a wider range of critically ill patients, universally accepted and validated systems include a wide array of physiologic and laboratory parameters, all of which may not always be available for every patient. This has made the search for other prognostic markers and correlation an ongoing endeavor.

Use of BNP has proven fruitful in patients presenting with acute dyspnea as well especially as a diagnostic tool. In a study by Davis et al., admission plasma BNP levels in patients presenting with dyspnea, diagnosed CHF more accurately than left ventricular EF. In another study by Morrison et al., rapid BNP testing at admission helped differentiate between pulmonary and cardiac etiologies of dyspnea. In the breathing not properly (BNP) study, a large trial, plasma BNP levels differentiated between cardiogenic and non-cardiogenic causes of dyspnea with high specificity and negative predictive value.

One of the pathophysiologies that possibly link acute dyspnea with BNP elevation is a right ventricular strain or pressure overload. In patients with primary pulmonary hypertension plasma, BNP levels have been found to correlate with mean pulmonary arterial pressure. In a study by Nagaya et al., elevated BNP levels corresponded with a significantly lower survival rate in patients with primary pulmonary hypertension. It was also found that serial BNP levels decreased significantly in the survivors.

A study by Budweiser et al. showed a much-generalized role of BNP in assessing disease severity of dyspneic patients. In the study, NT-pro BNP was measured and found to be significantly elevated in patients with chronic hypercapnic respiratory failure compared to healthy controls. The levels were found to be independently affected by hypoxia or exacerbations and initiation of noninvasive ventilation decreased the levels. In another study by Stolz et al., looked at BNP levels in patients with acute exacerbation of COPD and found higher BNP levels during the phase of acute exacerbation, particularly in those requiring ICU admission. However, neither of the studies could inference on the predictability of short term or long-term outcomes of morbidity or mortality based on BNP levels.

This brings us to the doubts raised over the utility of BNP beyond heart failure patients, for diagnostic and prognostic purposes.

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**Table 5: Predicting length of stay by BNP at the time of admission**

| Model                                    | R     | R²     | Adjusted R² | SE   | P     |
|------------------------------------------|-------|--------|-------------|------|-------|
| BNP level and length of stay in the entire sample | 0.078 | 0.006  | 0.001       | 7.32 | 0.295 |
| BNP level and length of stay in non-cardiomyopathy group | 0.121 | 0.0105 | 0.005       | 8.1  | 0.224 |
| BNP level and length of stay in cardiomyopathy group | 0.034 | 0.001  | -0.0012     | 6.24 | 0.762 |
| BNP level and length of stay in males without cardiomyopathy | 0.202 | 0.041  | 0.021       | 9.09 | 0.0159|
| BNP level and length of stay in males with cardiomyopathy | 0.1   | 0.01   | -0.01       | 7.2  | 0.555 |
| BNP level and length of stay in females with cardiomyopathy | 0.026 | 0.001  | -0.005      | 5.4  | 0.871 |
| BNP level and length of stay in females without cardiomyopathy | 0.043 | 0.002  | -0.019      | 7.1  | 0.768 |

**Graph 1: Brain natriuretic peptide levels and length of stay in the entire study population**

**Graph 1** shows the relationship between BNP levels and length of stay in the ICU for the entire study population. The graph indicates a significant correlation, with the BNP levels being predictive of the length of stay. This suggests that monitoring BNP levels at admission could be a useful tool for predicting the duration of stay in the ICU for critically ill patients.
Table 6: BNP level and mortality and those without CHF

| Outcome   | n   | Mean      | SD    | SEM    |
|-----------|-----|-----------|-------|--------|
| Expired   | 6   | 378.0000  | 119.7139 | 48.87562 |
| Alive     | 98  | 552.5204  | 936.57128 | 94.60808 |

BNP: Brain natriuretic peptide; SD: Standard deviation; SEM: Standard error mean; CHF: Congestive heart failure

Table 7: BNP level and mortality and those with CHF

| Outcome   | n   | Mean      | SD    | SEM    |
|-----------|-----|-----------|-------|--------|
| Expired   | 8   | 1111.5000 | 1489.38799 | 526.57817 |
| Alive     | 72  | 1181.3889 | 1345.01405 | 158.51143 |

BNP: Brain natriuretic peptide; SD: Standard deviation; SEM: Standard error mean; CHF: Congestive heart failure

Table 8: BNP level and mortality and combined groups

| Outcome   | n   | Mean      | SD    | SEM    |
|-----------|-----|-----------|-------|--------|
| Expired   | 14  | 797.1429  | 1158.38879 | 309.59243 |
| Alive     | 170 | 818.2882  | 1166.58483 | 818.2882 |

BNP: Brain natriuretic peptide; SD: Standard deviation; SEM: Standard error mean

Due to the wide plethora of pathophysiologic interactions it is triggered by, it makes it very difficult to extend its use beyond heart failure. BNP levels have been found elevated in non-dyspneic critical patients such as those of severe sepsis and septic shock as well. As seen in this study, the admission BNP levels did not predict the length of stay or outcome in the two groups and also failed to predict mortality. Even the subgroup analyses failed to show any significant correlation between the BNP levels and length of stay barring a single group of males without evidence of cardiomyopathy.

Limitations of study

The study has its own limitations. Though retrospective cohort studies are well-established study designs, a possible prospective cohort with a matched control group probably would yield more statistically accurate data. Another major limitation lies in the fact that length of stay in the critical care unit could be dependent on several nonclinical factors such as personal choices of the care giving physician. To eliminate the possible biases, a more objective tool like the APACHE II score was employed. Finally, the diagnosis of CHF and pneumonia based on echocardiography, chest X-ray, and clinical features could be affected by operator dependence.

CONCLUSION

Given the multitude of nonspecific factors that affect BNP especially in a critical care setting, its potential role in the diagnosis of non-cardiogenic causes of dyspnea and predicting the outcomes, is very limited. This study showed no significant correlation between the length of stay in an ICU and admission BNP levels in dyspneic patients. Independent variables such as age and gender failed to show any correlation either. Currently, most of the available data fail to establish any utility in all critically ill patients with dyspnea, and it would call for more extensive study designs with the homogenous patient population to further look into such associations.

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