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Use of B-Type Natriuretic Peptide in the Evaluation and Management of Acute Dyspnea

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ABSTRACT

BACKGROUND

B-type natriuretic peptide levels are higher in patients with congestive heart failure than in patients with dyspnea from other causes.

METHODS

We conducted a prospective, randomized, controlled study of 452 patients who presented to the emergency department with acute dyspnea: 225 patients were randomly assigned to a diagnostic strategy involving the measurement of B-type natriuretic peptide levels with the use of a rapid bedside assay, and 227 were assessed in a standard manner. The time to discharge and the total cost of treatment were the primary end points.

RESULTS

Base-line demographic and clinical characteristics were well matched between the two groups. The use of B-type natriuretic peptide levels reduced the need for hospitalization and intensive care; 75 percent of patients in the B-type natriuretic peptide group were hospitalized, as compared with 85 percent of patients in the control group (P=0.008), and 15 percent of those in the B-type natriuretic peptide group required intensive care, as compared with 24 percent of those in the control group (P=0.01). The median time to discharge was 8.0 days in the B-type natriuretic peptide group and 11.0 days in the control group (P=0.001). The mean total cost of treatment was $5,410 (95 percent confidence interval, $4,516 to $6,304) in the B-type natriuretic peptide group, as compared with $7,264 (95 percent confidence interval, $6,301 to $8,227) in the control group (P=0.006). The respective 30-day mortality rates were 10 percent and 12 percent (P=0.45).

CONCLUSIONS

Used in conjunction with other clinical information, rapid measurement of B-type natriuretic peptide in the emergency department improved the evaluation and treatment of patients with acute dyspnea and thereby reduced the time to discharge and the total cost of treatment.

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Heart failure is a major public health problem. Currently, more than 15 million patients have heart failure in North America and Europe, with nearly 1.5 million new cases every year.[1-5] Heart failure is the most frequent cause of hospitalization among people older than 65 years of age, and these hospitalizations are an important part of the enormous cost of the disease. Over the past decade, the rate of hospitalization for heart failure has increased by 159 percent.[3] It is estimated that in the United States in 2001, the direct cost of the care of patients with heart failure exceeded $24 billion.[3] Therefore, cost-effective management is of paramount importance. However, the rapid and accurate differentiation of heart failure from other causes of dyspnea remains a clinical challenge, especially in the emergency department.[4-10] After evaluating a patient's symptoms, conducting a physical examination, and performing electrocardiography and chest radiography, the clinician is often left with considerable diagnostic uncertainty, which results in misdiagnosis and delays the initiation of appropriate therapy.[7,10] In addition, the misdiagnosis of heart failure causes morbidity and increases the time to discharge and the cost of treatment, because the use of a treatment strategy for other conditions, such as chronic obstructive pulmonary disease, may be hazardous to patients with heart failure, and vice versa.[6,8,9]

Observational studies have suggested that, when used in conjunction with other clinical information, B-type natriuretic peptide levels may be useful in establishing or ruling out the diagnosis of heart failure in patients with acute dyspnea.[6,7,10-14] B-type natriuretic peptide is a 32-amino-acid polypeptide secreted by the cardiac ventricles in response to ventricular volume expansion and pressure overload.[15-17] The levels of B-type natriuretic peptide are elevated in patients with left ventricular dysfunction, and the levels correlate with both the severity of symptoms and the prognosis.[3,6,7,9-19] However, the clinical effect of this diagnostic test on the evaluation and treatment, outcome, and cost of treatment of patients with dyspnea is unknown. Therefore, we performed a randomized, controlled trial to test the hypothesis that a diagnostic strategy guided by the rapid measurement of B-type natriuretic peptide levels would improve the evaluation and care of patients with acute dyspnea who present to the emergency department and would thereby reduce the time to discharge and the total cost of treatment.

METHODS

SETTING AND STUDY POPULATION

The B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation (BASEL) Study was a prospective, randomized, controlled, single-blind study conducted in the emergency department of the University Hospital in Basel, Switzerland. Patients were evaluated in the emergency department by at least two physicians: a resident in internal medicine and an internal-medicine specialist. The study investigators were not directly involved in patient care in the emergency department, nor did they have any influence on the decision to discharge patients from the ward. The study was carried out according to the principles of the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all participating patients.

We screened 665 consecutive adults who presented to the emergency department between May 2001 and April 2002. Eligible patients were those who had acute dyspnea as the primary symptom, with no obvious traumatic cause of dyspnea. Patients with severe renal disease (defined by a serum creatinine level of more than 250 μmol per liter [2.8 mg per deciliter]), patients with cardiogenic shock, and patients who requested an early transfer to another hospital were excluded. There were no limitations to entry according to the time of day at which patients arrived in the emergency department or the availability of research staff.

A total of 452 patients were enrolled in the trial, and group assignment was accomplished with the use of a computer-generated randomization scheme in a 1:1 ratio without stratification. A total of 225 patients were randomly assigned to be evaluated with the use of a diagnostic strategy that included the rapid bedside measurement of B-type natriuretic peptide levels, and 227 were assigned to be evaluated with the use of the conventional diagnostic strategy. The B-type natriuretic peptide was not measured for clinical purposes by clinicians who treated patients in the control group, nor was it measured serially in either of the groups.

ROUTINE CLINICAL ASSESSMENT

All patients underwent an initial clinical assessment that, in general, included a clinical history taking, a physical examination, electrocardiography, pulse oximetry, blood tests, and chest radiography. Echocardiography and pulmonary-function tests

were strongly recommended on an outpatient basis for patients who were released from the emergency department, as well as for the patients who were admitted.

MEASUREMENT AND INTERPRETATION OF B-TYPE NATRIURETIC PEPTIDE LEVELS

During the initial evaluation, at the time of venipuncture for routine blood tests, a 5-ml specimen of venous blood was collected in tubes containing potassium EDTA. During a 15-minute period, B-type natriuretic peptide was measured with the use of a rapid fluorescence immunoassay (Biosite Diagnostics). The precision, analytic sensitivity, and stability of the system have been described previously.[14,18] In brief, the coefficient of variation within a given assay has been reported to be 9.5 percent, 12.0 percent, and 13.9 percent for levels of 28.8, 584.0, and 1180.0 pg per milliliter, respectively, and the coefficient of variation among assays is known to be 10.0 percent, 12.4 percent, and 14.8 percent, respectively.[14,18] The limit of analytic sensitivity was less than 5.0 pg per milliliter, with a measurable range of 0 to 1300 pg per milliliter.

In the group in which B-type natriuretic peptide levels were measured, diagnostic and therapeutic decisions were not based on the B-type natriuretic peptide levels alone; instead, this information was considered in the context of the other clinical information obtained and the physicians' clinical impressions, as previously described.[20] In brief, we used a B-type natriuretic peptide level of 100 pg per milliliter to separate dyspnea caused by heart failure from other causes of dyspnea.[3,6,7,9-13,20] In patients with a B-type natriuretic peptide level below 100 pg per milliliter, the diagnosis of heart failure was considered unlikely, and alternative causes of dyspnea had to be investigated. In patients with a B-type natriuretic peptide level of more than 500 pg per milliliter, heart failure was considered the most likely diagnosis, and rapid therapy with diuretics, nitroglycerin, angiotensin-converting–enzyme inhibitors, and morphine was recommended. For patients with B-type natriuretic peptide levels between 100 and 500 pg per milliliter, the protocol recommended the use of clinical judgment and possible further diagnostic testing to rule out stable baseline left ventricular dysfunction and other conditions as the real cause of acute dyspnea.[3,6,7,9-14,20] No formal adjustment was recommended regarding the B-type natriuretic peptide cutoff values in patients with mild chronic kidney disease. Patients in the control group were evaluated and treated according to the most recent clinical guidelines.[4,5]

END POINTS

The time to discharge and the cost of treatment were the primary end points of the study. Secondary end points included in-hospital and 30-day mortality. The time to discharge was defined as the interval from presentation at the emergency department to discharge. Patients who died in the hospital were excluded from the calculation of this end point. Since ratios of costs to charges have not been defined for the majority of services and departments at our institution, hospital charges were used as the most appropriate estimate of the true costs.[21,22] To avoid an imbalance owing to differences in reimbursement or charges associated with different types or classes of insurance, charges were standardized according to the actual rates for patients with general insurance who were living in Basel. The current reimbursement for the measurement of B-type natriuretic peptide in Switzerland ($47) was used. The time to treatment was defined as the interval from presentation to the initiation of the appropriate therapy — other than bed rest and supplemental oxygen — according to the final discharge diagnosis. This therapy included diuretics or vasodilators in patients with heart failure, anticoagulants in patients with pulmonary embolism, and inhaled bronchodilators or systemic corticosteroids in patients with an exacerbation of obstructive pulmonary disease. All end points were assessed in a blinded fashion by physicians who were not involved in patient care, with the use of all medical records pertaining to each patient.

STATISTICAL ANALYSIS

The statistical analyses were performed with the use of the SPSS/PC software package (version 11.0, SPSS). A P value of less than 0.05 was considered to indicate statistical significance. All data were analyzed according to the intention-to-treat principle. Comparisons were made with the use of the t-test, the Mann–Whitney U test, Fisher's exact test, or the chi-square test, as appropriate. All hypothesis testing was two-tailed. The trial was designed to enroll 222 patients in each group. This number provided the study with a power of 80 percent to detect a reduction in the time to discharge from 10.0 to 8.0 days (20 percent) with the use of the diagnostic strategy guided by measurement of the B-type natriuretic peptide level. Assumptions included the

Table 1. Base-Line Characteristics of the Patients.

Characteristic	B-Type Natriuretic Peptide Group (N=225)	Control Group (N=227)
Age — yr		
Mean	70.3	70.8
95% Confidence interval	68.2–72.4	68.9–72.7
Range	19–97	21–96
Sex — no. (%)		
Male	132 (59)	130 (57)
Female	93 (41)	97 (43)
Smoking status — no. (%)		
Never smoked	101 (45)	114 (50)
Current smoker	64 (28)	45 (20)
Previous smoker	60 (27)	68 (30)
Medical history — no. (%)		
Coronary artery disease	113 (50)	112 (49)
Arterial hypertension	113 (50)	124 (55)
Diabetes mellitus	47 (21)	56 (25)
Chronic obstructive pulmonary disease	75 (33)	65 (29)
Asthma	17 (8)	12 (5)
Pneumonia	30 (13)	28 (12)
Pulmonary embolism	18 (8)	13 (6)
Other pulmonary or pleural disease	20 (9)	26 (11)
Any pulmonary disease	119 (53)	107 (47)
Depressive disorder	15 (7)	21 (9)
Stroke or peripheral vascular disease	40 (18)	49 (22)
Chronic kidney disease	56 (25)	56 (25)
Deep-vein thrombosis	19 (8)	22 (10)
Symptoms — no. (%)		
Shortness of breath*		
While walking up a slight incline	32 (14)	33 (15)
While walking on level ground	125 (56)	132 (58)
At rest	66 (29)	58 (26)
Paroxysmal nocturnal dyspnea	79 (35)	87 (38)
Nocturia	60 (27)	76 (33)
Chest pain	76 (34)	78 (34)
Coughing	101 (45)	123 (54)
Expectoration	72 (32)	87 (38)
Fever	59 (26)	50 (22)
Systolic blood pressure — mm Hg		
Mean	146	145
95% Confidence interval	142–150	141–149
Diastolic blood pressure — mm Hg		
Mean	85	86
95% Confidence interval	83–87	83–89
Heart rate — beats/min		
Mean	96	99
95% Confidence interval	93–99	96–103
Temperature — °C		
Mean	37.6	37.4
95% Confidence interval	37.2–38.1	37.2–37.5

Table 1. (Continued.)

Characteristic	B-Type Natriuretic Peptide Group (N=225)	Control Group (N=227)
Signs — no. (%)		
Tachypnea (>20 breaths/min)	106 (47)	104 (46)
Elevated jugular venous pressure	32 (14)	32 (14)
Hepatojugular reflux	25 (11)	24 (11)
Rales	103 (46)	104 (46)
Wheezing	55 (24)	45 (20)
Hyperresonant percussion	22 (10)	17 (7)
Dullness	20 (9)	26 (11)
S_3 gallop	4 (2)	2 (1)
Cyanosis	14 (6)	19 (8)
Lower-extremity edema	73 (32)	83 (37)
Hemoglobin — g/dl		
Mean	13.5	13.4
95% Confidence interval	13.3–13.8	13.0–13.8
Serum creatinine — μmol/liter†		
Mean	113	116
95% Confidence interval	105–121	109–123
Serum albumin — g/liter		
Mean	34	33
95% Confidence interval	33–34	32–34
Medications — no. (%)		
Beta-blockers	51 (23)	57 (25)
Diuretics	118 (52)	103 (45)
Nitrates	32 (14)	30 (13)
ACE inhibitors‡	91 (40)	86 (38)
Digoxin	21 (9)	24 (11)
Aspirin	73 (32)	74 (33)
Amiodarone	19 (8)	18 (8)
Calcium-channel blockers	26 (12)	37 (16)
Inhaled bronchodilators	47 (21)	37 (16)
Inhaled corticosteroids	34 (15)	27 (12)
Oral corticosteroids	36 (16)	24 (11)
Anticoagulants	56 (25)	51 (22)

* Four patients in the B-type natriuretic peptide group and two patients in the control group had shortness of breath only while walking up a steep incline.
† To convert values for creatinine to milligrams per deciliter, divide by 88.4.
‡ ACE denotes angiotensin-converting–enzyme inhibitor or angiotensin-receptor blocker.

use of a two-tailed test, a 5 percent level of significance, and a standard deviation of 7.5 days in both groups.

RESULTS

A total of 452 patients were enrolled. The base-line characteristics were well matched between the study groups (Table 1). The mean age was 71 years. In both groups, slightly more than 40 percent of the patients were women. The medical history included coronary artery disease in 50 percent of patients, hypertension in 52 percent, chronic obstructive pulmonary disease in 31 percent, any pulmonary disease in 50 percent, and diabetes in 23 percent.

The median time from presentation at the emergency department to the initiation of the appropriate therapy according to the final discharge diagnosis was 90 minutes in the control group and 63 minutes in the B-type natriuretic peptide group

(P=0.03) (Table 2). The use of B-type natriuretic peptide levels significantly reduced the need for hospitalization and intensive care: 75 percent of patients in the B-type natriuretic peptide group were hospitalized, as compared with 85 percent of those in the control group (P=0.008), and 15 percent of patients in the B-type natriuretic peptide group required intensive care, as compared with 24 percent of those in the control group (P=0.01).

There was a considerable range in the time to discharge, reflecting the variety of diseases responsible for acute dyspnea. As shown in Figure 1, the time to discharge was significantly shorter in the B-type natriuretic peptide group (median, 8.0 days) than in the control group (median, 11.0 days; P=0.001). This difference translated into a significant difference in the mean total cost of treatment: $7,264 in the control group, as compared with $5,410 in the B-type natriuretic peptide group (P=0.006). Twenty-one patients (9 percent) in the control group died in the hospital, as compared with 13 patients in the B-type natriuretic peptide group (6 percent, P=0.19).

Heart failure was the final discharge diagnosis in 45 percent of patients in the B-type natriuretic peptide group and 51 percent of patients in the control group (P=0.2). Exacerbation of obstructive pulmonary disease was more commonly the cause of acute dyspnea in the B-type natriuretic peptide group than in the control group (23 percent vs. 11 percent, P=0.001). The treating physician indicated that two causes contributed to the acute dyspnea in 11 patients (5 percent) in the B-type natriuretic peptide group and in 10 patients (4 percent) in the control group (P=0.81).

Clinical 30-day follow-up data were available for all patients. The rates of readmission and mortality within 30 days after discharge were similarly low in the two groups (Table 2). The 30-day mortality rate was 10 percent in the B-type natriuretic peptide group and 12 percent in the control group. Among patients who were not initially admitted, rates of secondary admission were 5 percent in the B-type natriuretic peptide group (3 of 56 patients) and 9 percent in the control group (3 of 34 patients, P=0.67), and the respective 30-day mortality rates were 4 percent (2 deaths) and 3 percent (1 death) (P=1.00).

Table 2. End Points.*

End Point	B-Type Natriuretic Peptide Group (N=225)	Control Group (N=227)	P Value
Time to treatment — min			0.03†
Median	63	90	
Interquartile range	16–153	20–205	
Time to discharge — days			0.001†
Median	8.0	11.0	
Interquartile range	1.0–16.0	5.0–18.0	
Hospitalization — no. (%)	169 (75)	193 (85)	0.008
Admission to intensive care — no. (%)	33 (15)	54 (24)	0.01
Cost of intensive care — $			0.07
Median	874	1,516	
95% Confidence interval	423–1,324	989–2,043	
Total treatment cost — $			0.006
Median	5,410	7,264	
95% Confidence interval	4,516–6,304	6,301–8,227	
In-hospital mortality — no. (%)	13 (6)	21 (9)	0.21‡
30-day mortality — no. (%)	22 (10)	28 (12)	0.45‡
30-day readmission rate — no. (%)	26 (12)	23 (10)	0.63

* The time to treatment was defined as the interval from presentation at the emergency department to the initiation of the appropriate therapy according to the final discharge diagnosis.
† The Mann–Whitney U test was used.
‡ Fisher's exact test was used.

DISCUSSION

This randomized, controlled trial examined the effect of the measurement of B-type natriuretic peptide levels in the emergency diagnosis of patients with acute dyspnea. The use of B-type natriuretic peptide levels in conjunction with other clinical information reduced the time to the initiation of the

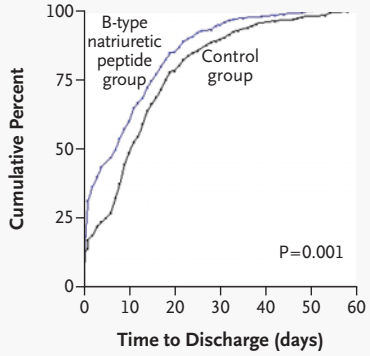

Figure 1. Cumulative Frequency Distribution Curve for the Time to Discharge of Patients in the B-Type Natriuretic Peptide Group as Compared with Those in the Control Group.

most appropriate therapy, the need for hospitalization and intensive care, the time to discharge, and the total cost of treatment. Given the morbidity associated with acute dyspnea and the cost associated with heart failure, chronic obstructive pulmonary disease, and other disorders that cause dyspnea,[1-5,8,9,14] B-type natriuretic peptide testing is likely to be of value in the treatment of patients with acute dyspnea. The mean total cost of treatment in this study was similar to the expenditures in the United States. In 1997, an estimated $5,501 was spent for every hospital-discharge diagnosis of heart failure.[3]

B-type natriuretic peptide testing reduced the total cost of treatment by 26 percent. This finding is supported by a retrospective analysis of the cost effectiveness of the use of B-type natriuretic peptide levels in screening for left ventricular systolic dysfunction in the general population, which also showed a 26 percent reduction in cost.[23]

Our findings extend the conclusions of observational studies in which the use of the measurement of B-type natriuretic peptide levels was validated by comparison with a retrospectively adjudicated diagnosis of heart failure by independent cardiologists.[3,6,7,9-14] In the largest of these studies — the Breathing Not Properly Multinational Study — B-type natriuretic peptide levels by themselves were more accurate than any historical or physical finding or laboratory value in identifying heart failure as the cause of dyspnea. The diagnostic accuracy of B-type natriuretic peptide at a cutoff value of 100 pg per milliliter was 83 percent, with a sensitivity of 90 percent and a specificity of 76 percent.[6,7]

In our study, exacerbation of obstructive pulmonary disease was more often the cause of acute dyspnea in the B-type natriuretic peptide group than in the control group. This finding corresponds well with a recent observation that exacerbation of chronic obstructive pulmonary disease frequently escapes recognition in the emergency department[24] and is also in agreement with the high negative predictive value of the B-type natriuretic peptide level for the diagnosis of heart failure. B-type natriuretic peptide levels below 100 pg per milliliter in a patient with acute dyspnea make the diagnosis of heart failure very unlikely and apparently help clinicians focus on the most common alternative diagnosis. Obstructive pulmonary disease was present in one third of our patients and may well have gone unrecognized as the cause of acute dyspnea in a considerable number of patients in the control group. Our findings, along with those of other investigators, provide support for the inclusion of the measurement of natriuretic peptides in the recent European guidelines for the diagnosis of heart failure.[5]

A particular strength of our study is that the study population was highly representative of the elderly population of patients with heart failure in clinical practice.[1-3] The mean age was 71 years, nearly half the patients were women, and coexisting conditions were common. The rapid and accurate differentiation of heart failure from other causes of acute dyspnea in such patients is often difficult, although essential for cost-effective management. The symptoms and signs of heart failure are neither sensitive nor specific and considerably overlap those of pulmonary disease.[4-7,13] The approach to the emergency diagnosis of acute dyspnea has been fundamentally unchanged for decades and has been complemented by electrocardiography, chest radiography, and echocardiography for the assessment of left ventricular function. Unfortunately, these methods have important limitations.[25-27]

The clinical experience with B-type natriuretic peptide testing is limited. Our interpretation of the test results was based on the data available when the study protocol was devised. Further studies should help to optimize the use of B-type natriuretic peptide measurements in clinical practice. The use of normal values corrected for age and sex may represent a clinically significant advance, since the levels of B-type natriuretic peptide increase with age and are higher in women than in men.[28] Moreover, a heart-failure diagnosis nomogram has been developed.[8] In patients with severe renal disease, B-type natriuretic peptide levels are increased. The mean B-type natriuretic peptide level in patients with a noncardiac cause of dyspnea and an estimated glomerular filtration rate of less than 60 ml per minute per 1.73 m^2 of body-surface area was nearly 300 pg per milliliter in the Breathing Not Properly Multinational Study.[29] Therefore, higher cutoff values need to be identified for this important patient population.

In conclusion, we found that when used in conjunction with other clinical information, rapid measurement of B-type natriuretic peptide levels in the emergency department improves the care of patients with acute dyspnea and thereby reduces the time to discharge and the total cost of treatment.

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