B-Type Natriuretic Peptide is Predictive of Postoperative Events in Orthopedic Surgery

Humberto Villacorta Junior[1], Isabela Simões de Castro[2], Marise Godinho[2], Camila Mattos[2], Rogério Visconti[2], Maurício Saud[2], Mônica Novais[2], Cláudia Murad[2], Fernanda Nogueira[2]

Universidade Federal Fluminense[1], Niterói; Instituto Nacional de Traumatologia e Ortopedia[2], Rio de Janeiro, RJ - Brazil

Abstract

Background: Clinical assessment is not always sufficient to predict postoperative (PO) cardiac complications. B-type natriuretic peptide (BNP) has an important prognostic value in patients with heart failure. Its value as a predictor of events in orthopedic surgeries has not yet been tested.

Objective: To assess the value of BNP in predicting cardiac complications in the PO period of orthopedic surgeries.

Methods: A total of 208 patients undergoing surgical treatment of femur fracture and hip or knee arthroplasty were prospectively evaluated. Of these, 149 (71.6%) were women and the mean age was 72.6 ± 8.8 years. In the preoperative period, the patients underwent conventional clinical assessment and their surgical risk was estimated according to the American Society of Anesthesiologists' (ASA) classification. BNP was determined in the preoperative period, and its ability to predict PO cardiac events (death; acute myocardial infarction; unstable angina; atrial fibrillation; ventricular tachycardia; or heart failure) was analyzed using multivariate logistic regression analysis.

Results: Seventeen patients (8.0%) experienced cardiac events. Median BNP was significantly higher in these patients in comparison to those without cardiac events (93 [interquartile range 73-424] *vs* 26.6 [13.2-53.1], p = 0.0001). BNP was the main independent predictor of events (p = 0.01). The ASA classification was not an independent predictor. Analysis of the ROC curve demonstrated that for a cut-off point of 60 pg/ml, BNP showed sensitivity of 76.0% and specificity of 79.0% in the prediction of events, with an area under the curve of 83.0%.

Conclusion: BNP is an independent predictor of PO cardiac events in orthopedic surgeries. (Arq Bras Cardiol 2010;95(6):743-748)

Keywords: Orthopedics; orthopedic procedures; postoperative care; natriuretic peptide, B-type.

Introduction

Patients undergoing non-cardiac surgeries may experience cardiac events such as acute myocardial infarction and acute pulmonary edema as postoperative complications[1,2]. The identification of patients at risk for these events is important, and clinical assessment alone is not always sufficient. In selected patients, this assessment is usually complemented by non-invasive methods for the analysis of ischemia and cardiac function. However, these methods involve costs, so it is necessary to identify the patients who might be left without this assessment.

B-type natriuretic peptide (BNP) is a marker of cardiac dysfunction and myocardial ischemia of great prognostic value in patients with heart failure and acute coronary syndromes[3-5]. Its value in detecting patients at risk for postoperative cardiac complications in orthopedic surgery has not been determined.

The objective of this study was to evaluate the value of BNP in the prediction of postoperative cardiac events in patients undergoing orthopedic surgeries.

Methods

Population

A total of 208 patients undergoing elective surgical treatment of femur fracture, or hip or knee arthroplasty were prospectively included in the period from March 2006 to January 2007.

All patients gave written informed consent and the study was approved by the institutional ethics committee under number 075, in December 15, 2004. Data were collected during preoperative visits and from prospective analysis of the medical records. In the preoperative period, the surgical risk was established using the criteria of the American Society of Anesthesiologists (ASA). The criteria of this classification are well known and patients are classified in ASA I, II, III, IV, V or VI risk status.

Mailing address: Humberto Villacorta Junior •
Rua Marquês do Paraná, 303 - 24033-900 - Niterói, RJ - Brazil
Email: hvillacorta@cardiol.br
Manuscript received March 9th, 2010; revised manuscript received May 6th, 2010; accepted May 24, 2010.

In 58 cases (27.8%), preoperative transthoracic echocardiography was performed using a Toshiba Nemio 30 ultrasound scanner, with a 2.5 MHz electronic transducer, and left ventricular ejection fraction (LVEF) was determined using the Teichholz method.

BNP determination

BNP was determined by immunofluorescence, using the Triage method (Biosite Inc, San Diego, CA, USA), point-of-care system. Blood was drawn on the day of surgery or up to 48 hours earlier. Five ml were drawn, and the analysis was carried out in whole blood within four hours of collection. For the analysis of BNP variation with surgery, its levels were also determined 24 h after surgery.

Outcome measures

The patients were followed up during hospitalization (median of 5 days, interquartile range = 4-8) by the study investigators and were evaluated for the presence of postoperative cardiac complications. The following events were considered outcome measures: acute myocardial infarction (AMI); unstable angina; acute pulmonary edema; heart failure; acute atrial fibrillation; sustained ventricular tachycardia; or cardiac death.

Electrocardiographic assessment and chest radiography were obtained from all patients in the pre and postoperative periods. Serial determination of myocardial necrosis markers and echocardiography were additionally performed for patients with chest pain, shortness of breath, sudden hemodynamic changes or supraventricular or ventricular arrhythmias in the postoperative period. Cardiac death was defined as death from cardiac causes during hospitalization. AMI was defined as an elevation of myocardial necrosis markers by two times above the upper limits of normal associated with suggestive symptoms or new Q waves in the electrocardiogram (ECG). Acute pulmonary edema was diagnosed by means of clinical examination and chest radiography; cardiac arrhythmias were diagnosed using electrocardiography.

The first event was considered an outcome measure, with no double counting of events for the same patient.

Statistical analysis

Categorical variables were expressed as absolute number and percentage and analyzed by the chi square test or by the Fischer's exact test, when appropriate. Continuous variables were expressed as mean and standard deviation. BNP values were expressed as median and interquartile range because they were non-normally distributed. Continuous variables were analyzed using the Student's t test, except for BNP, which was analyzed by the Mann-Whitney test because it was non-normally distributed.

The independent variables analyzed were age; gender; previous AMI; history of angina; previous surgical or percutaneous myocardial revascularization; previous heart failure; atrial fibrillation; significant changes on resting electrocardiogram (pathological Q waves; left bundle branch block; left ventricular overload; ST-segment or T-wave changes; atrial fibrillation and frequent premature ventricular complexes); enlarged heart on chest radiography; LVEF on echocardiography; creatinine; hemoglobin; cigarette smoking; chronic obstructive pulmonary disease (COPD); previous stroke; use of drugs (betablockers, angiotensin-converting enzyme inhibitors); ASA classification; systemic hypertension; dyslipidemia; diabetes mellitus; and family history of CAD.

In the univariate analysis, variables with $p < 0.10$ were included in the multivariate logistic regression model in order to determine the variables independently related to the postoperative outcome measures. The variables BNP and age were dichotomized in the multivariate model, being included as BNP values > 60 pg/ml and age > 70 years. Ejection fraction was not included in the multivariate analysis because it was only available in less then one third of the cases.

Results

Table 1 shows the baseline characteristics of the population as a whole. Sixty-two patients (29.8%) were receiving betablockers, 102 (49.0%) were receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blocker and 73 (35.0%) were taking diuretics. Resting ECG was normal in 120 patients (57.7%); 42 (20.0%) showed Q waves suggestive of previous AMI; left bundle branch block occurred in 11 (5.2%); left ventricular overload in 9 (4.3%); ST-segment or T wave abnormalities occurred in 10 (4.8%); atrial fibrillation in 7 (3.3%); and frequent premature ventricular complexes in 5 (2.5%).

No significant variation was found between preoperative and postoperative BNP levels, with medians and interquartile ranges of 27.9 (13.3-65) *vs* 23.5 (13.2-63.5), respectively, $p = 0.34$. Seventeen (8.0%) patients experienced cardiac events. Preoperative median BNP levels were significantly higher in patients who experienced cardiac events in comparison to those who did not (93 [interquartile range 73-424] *vs* 26.6 [13.2-53.1], $p = 0.0001$), as shown in Figure 1. The characteristics of patients with and without outcome measures are shown in Table 2.

In the multivariate analysis, preoperative BNP was the main predictor of events ($p = 0.01$), followed by age ($p = 0.042$). Previous AMI ($p = 0.05$) showed a borderline value, as shown in Table 3. The ASA classification was not an independent predictor. The analysis of the ROC curve (Figure 2) demonstrated that for a cut-off point of 60 pg/ml, BNP showed sensitivity of 76.0% and specificity of 79.0% to predict events, with an area under the curve of 83.0%. Table 4 shows the sensitivity and specificity for several BNP cut-off points.

Although pulmonary thromboembolism and fat embolism were not considered outcome measures of the study, it is worthy pointing out that they did not occur in this case series.

Discussion

In the present study, BNP levels determined up to 48 hours prior to surgery were the main independent predictor of postoperative cardiac events, proving superior to conventional clinical parameters and to the ASA classification. The cut-off point of 60 pg/ml showed good accuracy in the detection of cardiac events, with an area under the curve of 83.0%.

Table 1 - **Baseline characteristics of the overall population and according to the ASA classification**

Characteristics	Values
Age (years)	72.6 ± 8.8
Male gender	59 (28.3%)
Previous myocardial infarction	64 (30.7%)
History of angina pectoris	24 (11.5%)
Surgical or percutaneous myocardial revascularization	52 (25.0%)
Previous heart failure	48 (23.0%)
Cigarette smoking	17 (8.2%)
Hypertension	122 (58.0%)
Diabetes mellitus	62 (29.8%)
Dyslipidemia	85 (40.8%)
Family history of CAD	58 (27.8%)
Chronic obstructive pulmonary disease	18 (8.6%)
Previous stroke	12 (5.7%)
Abnormal resting electrocardiogram	84 (40.3%)
Enlarged heart on chest teleradiography	23 (11.0%)
Ejection fraction on echocardiography (%)*	66 ± 12.5
Creatinine (mg/dl)	0.97 ± 1.03
Hemoglobin (mg/dl)	12.6 ± 2.0
B-type natriuretic peptide (pg/ml) **	27.9 (13.3 - 65.0)
American Society of Anesthesiology classification	2.08 ± 0.4

*CAD - coronary artery disease; * available in 58 patients; **median and interquartile range.*

Table 2 - **Univariate analysis of the variables related to postoperative cardiac outcome measures**

Variable	With cardiac events n = 17	Without cardiac events n = 191	p value
Age (years)	67 ± 7.3	78 ± 6.2	0.001
Male gender	6 (35.2%)	53 (27.7%)	0.68
Previous myocardial infarction	10 (58.0%)	54 (28.0%)	0.019
History of angina	5 (29.4%)	19 (9.9%)	0.06
Surgical or percutaneous MR	9 (53.0%)	43 (22.5%)	0.018
Previous heart failure	9 (53.0%)	39 (20.4%)	0.01
Cigarette smoking	3 (17.6%)	14 (7.3%)	0.29
Hypertension	14 (82.3%)	108 (56.5%)	0.06
Diabetes mellitus	6 (35.2%)	56 (29.3%)	0.78
Dyslipidemia	8 (47%)	77 (40.3%)	0.76
Family history of CAD	6 (35.3%)	52 (27.2%)	0.64
Chronic obstructive pulmonary disease	2 (11.7%)	16 (8.3%)	0.89
Previous stroke	2 (11.7%)	10 (5.2%)	0.51
Abnormal resting electrocardiogram	11 (64.7%)	73 (38.2%)	0.06
Ejection fraction on echocardiogram (%)*	63.3 ± 10	66.4 ± 12.9	0.48
Creatinine (mg/dl)	1.0 ± 0.42	0.98 ± 1.0	0.86
Hemoglobin (mg/dl)	12.5 ± 2	12.5 ± 1.7	0.68
B-type natriuretic peptide (pg/ml)**	93 (73.5 - 424)	26.6 (13.25 - 53.1)	0.0001
ASA classification	2.37 ± 0.5	2.05 ± 0.4	0.003
Betablockers	4 (23.5%)	58 (30.3%)	0.55
ACEI or ARB	8 (47.0%)	94 (49.2%)	0.86
Diuretics	6 (35.3%)	67 (35.0%)	0.98
Statins	9 (52.9%)	96 (50.2%)	0.83

*ASA - American Society of Anesthesiology; ARB - angiotensin receptor blocker; CAD - coronary artery disease; ACEI - angiotensin-converting enzyme inhibitor; MR - myocardial revascularization. *available in 58 patients; **median and interquartile range.*

The utility of the natriuretic peptides BNP and N-terminal pro-BNP fraction (NT-proBNP) in predicting postoperative cardiac events has been reported in the past years both in studies including several types of non-cardiac surgery and in specific surgeries. In all of them, these markers stood out as the only independent predictor or one of the main independent predictors of the postoperative risk[6-10]. Dernellis and Panaretou analyzed the preoperative value of BNP in risk prediction in 1,590 patients undergoing different types of non-cardiac surgery[6]. The clinical variables independently associated with events were LVEF and previous AMI. When BNP was added to the model, these variables lost significance, and BNP > 189 pg/ml was the only independent predictor in the final model. The cut-off point value in that study was three times higher than the one found in the present study. This can be explained by the fact that they studied a population more severely ill than ours in relation to baseline characteristics, with higher prevalences of previous AMI, surgical or percutaneous myocardial revascularization and heart failure.

In another study, BNP was able to predict the mid-term mortality (median follow-up of 654 days) after major non-cardiac surgeries[8]. BNP cut-off point > 35 pg/ml showed sensitivity of 70.0% and specificity of 68.0%. The study population showed baseline characteristics similar to those of the present study, and the cut-off point obtained was closer to that found in our study. Similarly to BNP, NT-proBNP was able to predict cardiac complications in patients undergoing surgical treatment of abdominal aortic aneurysm[7]; in high-risk patients undergoing several types of non-cardiac surgeries[10]; and in the prediction of the incidence of atrial fibrillation following thoracic surgery for the treatment of lung cancer[9]. Our study corroborates previous findings in a specific population of patients undergoing orthopedic surgery. However, taking into consideration the data reported in the literature, natriuretic peptides seem to be good predictors of cardiac events in any type of non-cardiac surgery.

In the present study, we did not find a significant variation between preoperative and postoperative BNP levels. This finding differs from that observed in Schutt et al's study,[10]

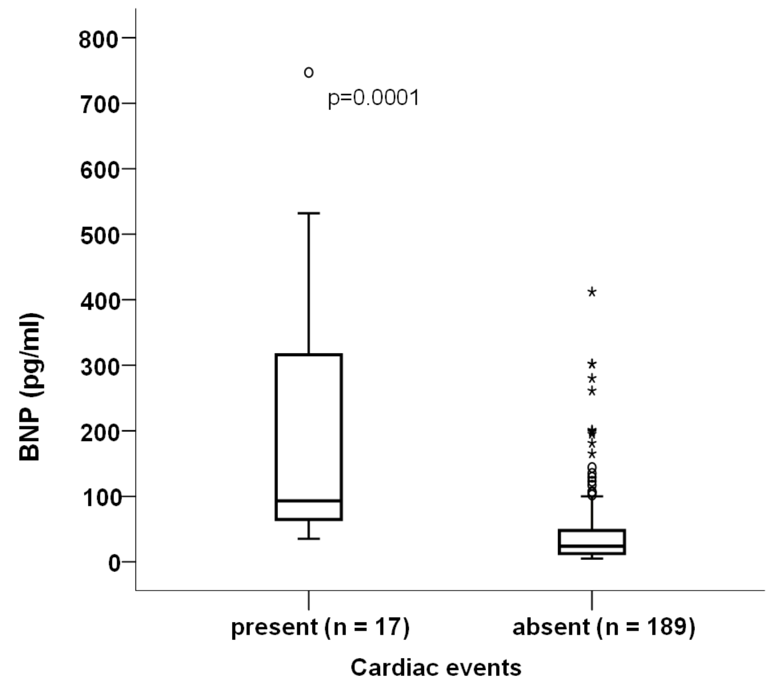

Figure 1 - B-type natriuretic peptide values according to the presence or absence of postoperative cardiac outcome measures.

Table 3 - **Independent predictors related to the postoperative cardiac outcome measures**

Variable	Odds ratio	95% confidence interval	p value
BNP > 60 pg/ml	3.58	1.74 - 4.06	0.011
Age > 70 years	2.50	1.44 - 4.33	0.042
Previous myocardial infarction	1.48	1.00 - 2.20	0.050

in which 89.0% of the patients presented with increased postoperative NT-proBNP as determined within three days of the surgery, even in the absence of clinically detectable HF. The authors hypothesize that this may have been related to the excess of fluid administered during surgery, but they could not prove this notion in their study.

In the present study, BNP levels were not only predictive of mortality or heart failure, but also of postoperative AMI and angina. This finding corroborates the idea that BNP is a good marker not only of myocardial dysfunction, but also of myocardial ischemia, as previously demonstrated[11,12].

In patients with chest pain who seek the emergency room, it has been described that BNP levels increase even before the elevation of myocardial necrosis markers[11]. Also, in patients with stable CAD, BNP predicts induced ischemia in stress tests[12].

Therefore, our data suggest that high BNP levels in asymptomatic patients could indicate silent ischemia, and the test could be useful to detect patients eligible for the investigation of myocardial ischemia by means of imaging methods in the preoperative period of non-cardiac surgeries.

In this study, a relevant finding was the fact that the ASA classification could not detect postoperative events. Although this classification is widely used, it is known to have limitations. Its subjectivity results in considerable interobserver variation[13-15]. In a Spanish study, a questionnaire containing 10 hypothetical cases was handed out to 333 physicians among residents, anesthesiologists, and chiefs of service. Considerable interobserver disagreement was observed[13]. For this reason, cardiologists have chosen to use the Goldman classification.

Limitations

Echocardiography was performed in only 58 cases, thus limiting the comparison of BNP with echocardiographic information. However, the main objective of this study was to test the performance of BNP in comparison to conventional parameters of the medical history and physical examination. Thus, we conclude that our findings suggest that BNP could help select patients who need additional tests such as echocardiography or myocardial scintigraphy for a better definition of the postoperative cardiac risk. Also, despite the small number of patients undergoing echocardiography, no significant difference was found between the LVEF of patients with or without outcome measures.

Another limitation is that other surgical risk scores, such as Goldman or Lee classification, were not used. However, the ASA classification is the most widely used score in clinical practice in Brazil.

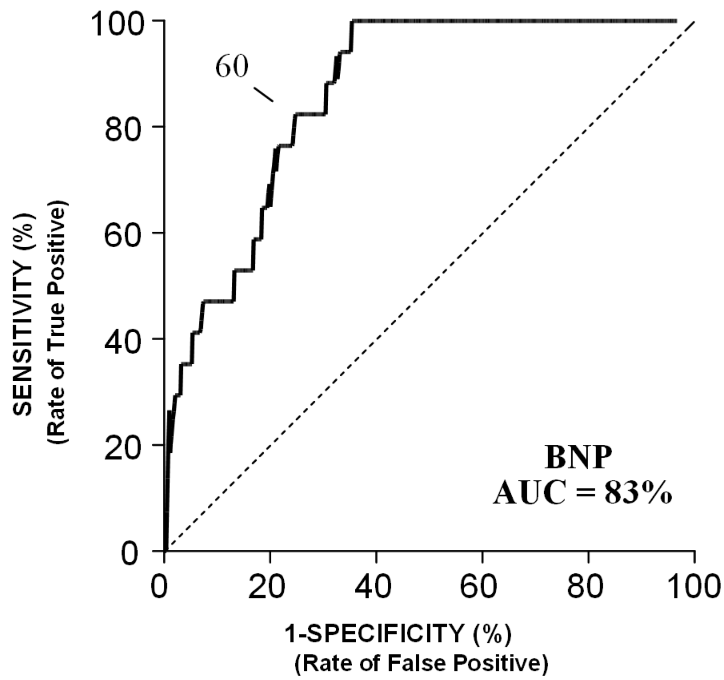

Figure 2 - BNP performance in the prediction of cardiac outcome measures using the ROC curve. The value of 60 pg/ml identifies the cut-off point with the best sensitivity and specificity. AUC- area under the curve.

Table 4 - **Sensitivity and specificity to predict outcome measures according to different BNP cut-off points**

BNP (pg/ml)	Sensitivity (%)	Specificity (%)
20	100	45
40	88	67
60	76	79
80	53	85
100	47	89
200	35	96

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

This study was funded by CNPq.

Study Association

This study is not associated with any post-graduation program.

References

1. Mangano DT. Perioperative cardiac morbidity. Anesthesiology. 1990; 72 (1): 153-84.
2. Mangano DT, Goldman L. Current concepts: preoperative assessment of patients with known or suspected coronary disease. N Engl J Med. 1995; 333 (26): 1750-6.
3. Villacorta H, Duarte A, Duarte NM, Carrano A, Mesquita ET, Dohmann HJF, et al. Valor do peptideo natriurético do tipo B no diagnóstico da insuficiência cardíaca congestiva em pacientes atendidos com dispnéia na unidade de emergência. Arq Bras Cardiol. 2002; 79 (6): 564-8.
4. Dokainish H, Zoghbi WA, Lakkis NM, Ambriz E, Patel R, Quinones MA, et al. Incremental predictive power of B-type natriuretic peptide and tissue Doppler echocardiography in the prognosis of patients with congestive heart failure. J Am Coll Cardiol. 2005; 45 (8): 1223-6.
5. de Lemos JA, Morrow DA, Bentley JH, Omland T, Sabatini MS, McCabe CH, et al. The prognostic value B-type natriuretic peptide in patients with acute coronary syndromes. N Engl J Med. 2001; 345 (14): 1014-21.
6. Dernellis J, Panaretou M. Assessment of cardiac risk before non-cardiac surgery: brain natriuretic peptide in 1590 patients. Heart. 2006; 92 (11): 1645-50.
7. Feringa HHH, Bax JJ, Elhendy A, de Jonge R, Lindemans J, Schouten O, et al. Association of plasma N-terminal pro-B-type natriuretic peptide with postoperative cardiac events in patients undergoing surgery for abdominal aortic aneurysm or leg bypass. Am J Cardiol. 2006; 98 (1): 111-5.
8. Cuthbertson BH, Amiri AR, Croal BL, Rajagopalan S, Brittenden J, Hillis GS.

Utility of B-type natriuretic peptide in predicting medium-term mortality in patients undergoing major non-cardiac surgery. Am J Cardiol. 2007; 100 (8): 1310-3.

9. Cardinale D, Colombo A, Sandri MT, Lamantia G, Colombo N, Civelli M, et al. Increased perioperative N-terminal pro-B-type natriuretic peptide levels predict atrial fibrillation after thoracic surgery for lung cancer. Circulation. 2007; 115 (11): 1339-44.

10. Schutt RC, Cevik C, Phy MP. Plasma N-terminal prohormone brain natriuretic peptide as a marker for postoperative cardiac events in high-risk patients undergoing noncardiac surgery. Am J Cardiol. 2009; 104 (1): 137-40.

11. Bassan R, Potsch A, Maisel A, Tura B, Villacorta H, Nogueira MV, et al. B-type natriuretic peptide: a novel early blood marker of acute myocardial infarction in patients with chest pain and no ST-segment elevation. Eur Heart J. 2005; 26 (3): 234-40.

12. Bibbins-Domingo K, Ansari M, Schiler NB, Massie B, Whooley MA. B-type natriuretic peptide and ischemia in patients with stable coronary disease: data from the Heart and Soul Study. Circulation. 2003; 108 (24): 2987-92.

13. Castillo J, Canet J, Gomar C, Hervás C. Imprecise status allocation by users of the American Society of Anesthesiologists classification system: survey of Catalan anesthesiologists. Rev Esp Anestesiol Reanim. 2007; 54 (7): 394-8.

14. Mak PH, Campbell RC, Irving MG. The ASA physical status classification: interobserver consistency. Anaesth Intensive Care. 2002; 30 (5): 633-40.

15. Conners MS, Tonnessen BH, Sternbergh WC, Carter G, Yoselevitz M, Money SR. Does ASA classification impact success rates of endovascular aneurysm repairs? Ann Vasc Surg. 2002; 16 (5): 550-5.