Preoperative B-type natriuretic peptide risk stratification: do postoperative indices add value?

Rodseth RN, MBChB, FCA, MMed
Perioperative Research Group, Department of Anaesthetics, University of KwaZulu-Natal, Durban; Outcomes Research Consortium, Cleveland, Ohio
Vasconcellos K, MBChB, FCA
Outcomes Research Consortium, Cleveland, Ohio; Department of Anaesthetics and Critical Care, King Edward V Hospital, Durban
Naidoo P, MBChB, FCPath(Chem)
National Health Laboratory Services; Department of Chemical Pathology, Nelson R Mandela School of Medicine, University of KwaZulu-Natal
Biccard BM, MBChB, FCA, PhD
Perioperative Research Group, Department of Anaesthetics, University of KwaZulu-Natal, Durban
Correspondence to: Reitze Rodseth, e-mail: reitzerodseth@gmail.com
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Abstract

Objectives: It is unclear if there is value in measuring postoperative B-type natriuretic peptide (BNP) in patients risk-stratified using preoperative BNP.

Design: Prospective observational study.

Setting and subjects: Patients undergoing vascular surgery at Inkosi Albert Luthuli Hospital, Durban.

Data on intraoperative risk predictors, i.e. the nature of the surgery, number of transfused red blood cell units and the duration of surgery, were collected. Preoperative and postoperative BNP, electrocardiographic and troponin I monitoring were performed. Multivariable analysis was conducted to identify independent predictors of adverse cardiac events and then tested using reclassification statistics.

Outcome measures: The composite of troponin elevation within the first three postoperative days and all-cause mortality within 30 days of surgery.

Results: In 149 eligible patients, the study outcome occurred in 27 patients and was independently predicted by red blood cell (RBC) transfusion [odds ratio (OR) 1.8, 95% confidence interval (CI):1.08-3.08] and postoperative ischaemia (OR 7.1, 95% CI: 2.78-18.2). Postoperative BNP was not statistically significantly associated with the outcome (OR 2.1, 95% CI: 0.81-5.45, p-value = 0.13). In patients who were risk stratified using preoperative BNP, postoperative ischaemia appropriately improved risk classification overall (a net reclassification improvement of 82.5%, p-value < 0.001).

Conclusion: RBC transfusion and postoperative ischaemia, but not postoperative BNP, were independent predictors of the composite outcome of all-cause mortality or postoperative troponin elevation. Postoperative ischaemia improved overall risk classification.

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Introduction

Myocardial infarction (MI) is the most common life-threatening complication after noncardiac surgery,[1,2] and 1 in 10 patients who suffer a perioperative MI die within 30 days of their surgery.[2,3] Identifying these at-risk patients may provide physicians with a window for intervention. Risk assessment should not only occur preoperatively, but should take place throughout the perioperative period. The revised cardiac risk index,[4] commonly used for preoperative risk stratification, is a static tool and is unable to reflect changes in perioperative risk.[5] By contrast, biomarkers are not static measurements and may be more suited to dynamic risk assessment.

B-type natriuretic peptide (BNP) is a hormone that is released from the myocardium in response to volume strain or myocardial ischaemia, and strongly predicts postoperative cardiovascular complications in both vascular and noncardiac surgery.[6,7] An individual patient data meta-analysis of 850 patients undergoing vascular surgery found that preoperative BNP was superior to the revised cardiac risk index, and its individual components, for preoperative risk stratification.[8,9] Preoperative BNP was subsequently compared to dynamic preoperative risk predictors, i.e. preoperative troponin, myocardial ischaemia monitoring and C-reactive protein, to determine the optimal tool for preoperative risk stratification.[10] Compared to these three

modalities, BNP was the only clinically useful predictor of postoperative events.

As preoperative BNP risk stratification becomes more commonly used, it raises questions as to the role of postoperative BNP measurement. Firstly, is postoperative BNP, drawn shortly after surgery, able to quantify changes in patient risk and subsequently improve preoperative BNP risk stratification? Secondly, how does postoperative BNP compare to other postoperative risk factors, such as postoperative myocardial ischaemia in identifying at-risk patients?

Patients undergoing vascular surgery were risk stratified in this prospective observational study, using preoperative BNP. Data on potential intraoperative risk predictors, i.e. the nature of the surgery, number of transfused red blood cell (RBC) units and the duration of the surgery, were collected. Postoperative BNP was measured and postoperative myocardial ischaemia monitored. The aim was to determine which independent intra- and postoperative factors could improve the identification of patients who would suffer MI within three days of surgery, or die within 30 days of undergoing surgery.

Method

A prospective observational study was undertaken at Inkosi Albert Luthuli Central Hospital, KwaZulu-Natal, to determine the predictors of all-cause mortality in patients undergoing vascular surgery. The study was funded through a three-year, self-initiated research grant from the Medical Research Council of South Africa. Ethics approval was granted by the Ethics Committee of the Nelson R Mandela School of Medicine (ethics number BF068/07), and the study was registered with the South African National Clinical Trials Register (DOH-27-0810-3320).

All elective patients undergoing vascular surgery between 19 February 2008 and 15 March 2011 were eligible for recruitment. This data set was previously used to compare preoperative BNP with the revised cardiac risk index,[11] and to compare preoperative BNP with dynamic preoperative risk predictors, i.e. preoperative troponin, myocardial ischaemia monitoring and C-reactive protein.[10] Patients for whom a pre- and postoperative BNP measurement was noted, as well as those who underwent postoperative electrocardiographic (ECG) ischaemia monitoring, were eligible for this substudy.

Data collection

Once signed informed consent was obtained, the following was performed:

- Preoperative BNP within 24 hours preceding surgery.
- Postoperative BNP within 24 hours after surgery.
- Continuous blinded postoperative ECG (Holter) monitoring for the first 24 hours postoperatively.
- Troponin I daily for the first three postoperative days.

Data were collected on patient demographics, the presence of revised cardiac risk index factors,[4] as well as intraoperative variables, i.e. surgery type, number of transfused RBC units and the duration of the surgery. Aorto-iliac surgery, i.e. all surgery on the aorta or on the iliac arteries, excluding endovascular surgery, was defined as high-risk vascular surgery. Intraoperative blood pressure and heart rate data were not collected. On completion of the study, all Holter data were analysed in a blinded fashion using the previously described methodology.[7] For this study, postoperative ischaemia was defined as any episode of ST-segment depression > 1 mV from baseline lasting ≥ 10 minutes in duration.

Biomarker assays

All samples were centrifuged and analysed on receipt using the ADVIA Centaur Xp, utilising chemiluminescent technology. The analytical range for BNP is 0.58-1445 pmol/ml (2.01-5 000 pg/ml), with a coefficient of variation of 3.5% and 3.8% at 500 pmol/l (1 730.1 pg/ml) and 131 pmol/l (453.3 pg/ml), respectively. The analytical range for troponin I is 0.006-50 ng/ml, with a coefficient of variation of 11.5% and 8.7% at 0.61 ng/ml and 5.45 ng/ml, respectively.

Study outcome

The primary study outcome was defined as a composite of all-cause mortality within 30 days of surgery or troponin elevation above the upper reference limit of 0.1 ng/ml within the first three postoperative days.[10,12]

Statistical analyses

All categorical data were analysed using descriptive statistics, and presented as percentages and 95% confidence interval (CI) where appropriate. Categorical data were analysed using the Fisher's exact test or Pearson's chi-square test, where appropriate. All continuous data were analysed using descriptive statistics and presented as mean standard deviation (SD) when the distribution was normal, and median interquartile range (IQR) with a non-Gaussian distribution, and compared using Independent Samples' t-test or Mann-Whitney U-test, respectively.

A receiver-operating characteristic (ROC) curve was used to determine the optimal discriminatory point preoperative BNP. The optimal discriminatory point is that point which maximises diagnostic accuracy for the study outcome: in this case, all-cause mortality or postoperative troponin elevation. This point was determined using the minimum distance technique on the ROC curve.[13] This was then used to preoperatively stratify patients as high or low risk. Predictive intra-variables were identified by conducting univariate analysis to identify variables with a p-value < 0.1 for the study outcome. This was repeated for postoperative BNP and postoperative ischaemia. Only these variables were entered into the multivariate regression to minimise bias associated with the estimate of risk.[14] Backward stepwise logistic regression was used for the multivariate analysis, based on likelihood ratios, with entry and removal probabilities set at 0.05 and 0.1, respectively.

The ROC curve was used to determine optimal discriminatory points for independent variables and then category-free net

reclassification was applied to determine if they significantly improved on preoperative BNP risk stratification. Category-free net reclassification ensures that results are independent of the clinical risk stratification tool used during the study, so allowing for objective comparisons with potential future risk predictors.[15] The overall effect of the reclassification is described by the change in net reclassification, where a positive change reflects an improvement in risk stratification. Net reclassification is the difference between the proportion of patients correctly and incorrectly reclassified according to the study outcome.[10,16] SPSS® 19.0 for Windows® (2012) and Microsoft Office® Excel® 2007 were used for data analysis.

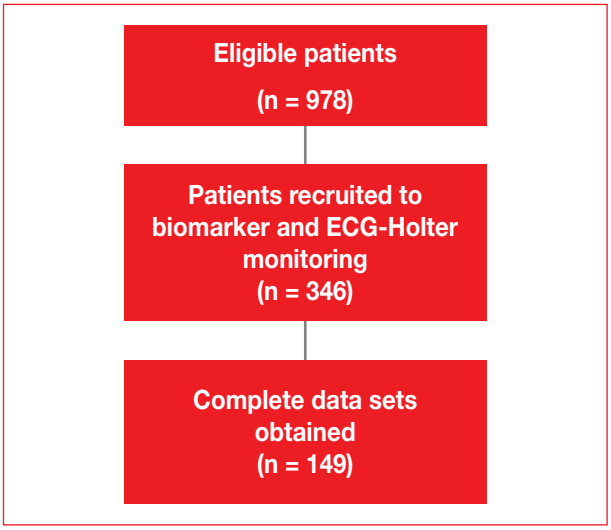
Results

Over the three-year study period, 978 eligible patients were identified, of which 346 consented to perioperative biomarker and Holter monitoring. A limited number of Holter monitors were available for the study, and only 305 patients had postoperative Holter monitoring. Complete data sets were available for 149 patients, of which 27 (10 deaths and 17 postoperative troponin elevations) suffered the study outcome (see Figure 1). Patient baseline characteristics, together with their preoperative BNP risk classification, are shown in Table I. The majority of patients underwent peripheral bypass surgery (n = 72, 48%), with aorto-iliac surgery (n = 29, 20%). Carotid interventions (n = 28, 19%) were the next most common.

The results of ROC analysis revealed that the optimal preoperative BNP threshold for the predictor of the study outcome was 38 pg/ml, and so patients with a measurement ≥ 38 pg/ml were categorised as high risk. Postoperatively, the optimal BNP threshold was 60 pg/ml, and hence patients with a measurement ≥ 60 pg/ml were categorised as high risk. The results of the univariate analysis for all intra- and postoperative variables are shown in Table II.

Based upon the results of the univariate analysis, transfused RBC units, optimal postoperative BNP value and postoperative ischaemia were entered into the multivariable regression. Only transfused RBC units (OR 1.8, 95% CI: 1.08-3.08, p-value = 0.02), and postoperative ischaemia (OR 7.1, 95% CI: 2.78-18.2, p-value < 0.001) were independently associated with the composite outcome. Optimal post-operative BNP was not statistically significantly associated with the outcome (OR 2.1, 95% CI: 0.81-5.45, p-value = 0.13).

Using reclassification statistics, tests were conducted to determine if transfused RBC units or postoperative ischaemia could significantly improve preoperative BNP risk stratification. Reclassification using transfused RBC units improved overall risk classification, but significantly worsened classification in patients who had an adverse event, thus adding no clinically useful information. Postoperative ischaemia significantly improved overall risk classification and reclassification in patients who suffered the study outcome of death or postoperative troponin elevation. This was also true for those who did not suffer this outcome



ECG: electrocardiographic

Figure 1: Flow diagram describing the recruitment of patients into the study

Table I: Baseline patient characteristics stratified by the study outcome of all-cause mortality or postoperative troponin elevation

Variables*	All patients (n = 149)	Patients with study outcome (n = 27)	Patients without study outcome (n = 122)	p-value
Age, years	59.2 ± 12.17	64.2 ± 12.3	58.0 ± 11.9	0.02
Male	110 (73.8)	15 (55.5)	98 (77.9)	0.03
Aorto-iliac surgery	29 (19.5)	10 (37)	19 (15.6)	0.02
RCRI class				
Low (RCRI 0)	62 (41.6)	10 (37)	52 (42.6)	0.67
Intermediate (RCRI 1 or 2)	75 (50.3)	13 (48.1)	62 (50.8)	0.83
High (RCRI ≥ 3)	12 (8.1)	4 (14.8)	8 (6.6)	0.23
RCRI components				
Coronary artery disease	55 (36.9)	16 (59.3)	39 (32)	0.01
Diabetes mellitus	55 (36.9)	13 (48.1)	42 (33.1)	0.19
Congestive heart failure	2 (1.3)	0	2 (1.6)	1.0
Cerebrovascular disease	36 (24.2)	4 (14.8)	32 (26.2)	0.32
Creatinine ≥ 2 mg/dl	2 (1.3)	0	2 (1.6)	1.0
Preoperative BNP (pg/ml)	91.8 (11.76-73.53)	123.2 (37.39-209)	84.8 (39.6-130)	0.53
BNP above optimal cut-point (≥ 38 pg/ml)	65 (43.6)	21 (77.8)	44 (36.1)	< 0.01

*: Categorical variables are presented as number (%), age as mean standard deviation, preoperative BNP as median interquartile range

BNP: B-type natriuretic peptide, CVA: cerebrovascular accident, RCRI: revised cardiac risk index

Table II: Intra- and postoperative predictors of all-cause mortality or postoperative troponin elevation

Variables	OR (95% CI)	p-value
Operative variables		
Type of surgery (aorto-iliac versus other)	3.2 (1.27–8.02)	0.14
Duration of surgery (per minute of surgery)	1.0 (1–1.0)	0.44
RBC transfusion (≥ 1 units transfused)	1.7 (1.09–2.58)	0.02*
ECG Holter monitoring		
Postoperative ischaemia (≥ 1 episode of 10 minutes)	1.1 (1.05–1.16)	0.01*
Mean heart rate	1.0 (0.97–1.03)	0.92
Maximum heart rate	1.0 (0.98–1.02)	0.81
Cumulative heart rate > 100 bpm	1.0 (0.99–1.00)	0.33
BNP		
Optimal postoperative (> 60 pg/ml)	2.9 (1.2–6.9)	0.02*
Absolute change	1.01 (1–1.02)	0.12
Percentage change	1.03 (0.98–1.09)	0.23

*Variables with P < 0.1 and included in multivariable analysis
CI: confidence interval, BNP: B-type natriuretic peptide, bpm: beats per minute, ECG: electrocardiographic, OR: odds ratio, RBC: red blood cells

(Table III). In high-risk patients with elevated preoperative BNP, exposure to postoperative ischaemia improved risk stratification in patients with and without an event (Table IV).

Discussion

The role of preoperative B-type natriuretic peptide

In this study, preoperative BNP was able to identify patients who, if they received blood transfusion or experienced postoperative ischaemia, were at an extremely high risk of all-cause mortality or postoperative troponin elevation. Multiple studies and meta-analysis have demonstrated that BNP is perhaps the most powerful preoperative predictor of adverse cardiac events. It consistently outperforms traditional clinical risk predictors.[4] By using preoperative BNP, physicians are able to identify vulnerable patients and focus their intra- and postoperative interventions on this subset of cases.

Intra- and postoperative risk predictors

Risk factor identification only has clinical value if the identified risk predictors can be modified. In this study, intraoperative blood transfusion and postoperative ischaemia were found to be risk predictors that were strongly associated with adverse postoperative events. It is likely that intraoperative blood transfusion is a surrogate maker for surgery complexity and that it represents the magnitude of the surgical insult.[17,18] If this view is correct, it is not greatly modifiable. Surgical pathology largely dictates which procedure a patient will require, but it is possible to modify this by choosing to perform techniques that are associated with less surgical insult or by deferring surgery altogether. It is also possible that a component of the adverse events associated with intraoperative blood transfusion relates to the transfusion of the blood itself.[19] This risk component may be modified by minimising intraoperative blood loss and avoiding the use of blood stored for >14 days.

By contrast, postoperative myocardial ischaemia seems to hold the potential to be a more modifiable predictor. Postoperative myocardial ischaemia occurs more commonly and for a longer time period than both pre- and intraoperative myocardial ischaemia,[20-24] and ST-segment depression has been identified in up to 20% of vascular surgical patients.[25] Furthermore, postoperative myocardial ischaemia (> 10 minutes) independently predicts troponin elevation (OR 3.88, 95% CI: 2.03-8.74, p-value < 0.0001),[25] and correlation has been shown with troponin and ischaemic

Table III: Results of reclassifying patients for the outcome of all-cause mortality or postoperative troponin elevation using red blood cell transfusion and postoperative ischaemia

	Reclassification change in patients without an event		Reclassification change in patients with an event		Overall net reclassification change	
	Proportion	p-value	Proportion	p-value	Proportion	p-value
RBC transfusion (≥ 1 unit)	+ 60.7%	< 0.001	- 25.9%	< 0.001*	+ 34.7%	0.04
Postoperative ischaemia	+ 63.9%	< 0.001	+ 18.5%	0.007	+ 82.5%	< 0.001

*: Significantly worse reclassification of patients with an event
RBC: red blood cells

Table IV: Results of reclassifying high-risk patients with B-type natriuretic peptide for the outcome of all-cause mortality or postoperative troponin elevation using ischaemia monitoring

Cohort	Reclassification change in patients without an event		Reclassification change in patients with an event		Overall net reclassification change	
	Proportion	p-value	Proportion	p-value	Proportion	p-value
Postoperative ischaemia	+ 63.6%	< 0.001	+ 33.3%	< 0.001	+ 97%	< 0.001

duration (r = 0.83) and peak troponin and cumulative ischaemic time (r = 0.78).[22]

Manipulation of postoperative heart rate and haemoglobin concentration may prevent or modify the frequency and severity of these events. Many studies report an association between perioperative heart rate elevation and myocardial ischaemia.[26,27] However, the absolute heart rate has not been able to discriminate between vascular patients who sustain an acute myocardial infarction and those who do not.[22] Neither the duration nor the frequency of tachycardia in patients presenting for peripheral vascular surgery has been shown to identify patients at risk of silent myocardial ischaemia.[24] Our univariate analysis is consistent with these data.

This study has identified both an intra- and postoperative risk factor, independently predicting all-cause mortality or postoperative troponin elevation. In a process that is similar to that used in preoperative risk stratification algorithms,[28] these intra- and postoperative independent risk factors may allow physicians to focus resources on patients who stand to benefit the most from them.

The role of postoperative B-type natriuretic peptide

Natriuretic peptides (NP), such as BNP or N-terminal pro-B natriuretic peptide are primarily released by cardiac myocytes in response to ventricular wall stretch.[29,30] It has been suggested that NP elevations are a marker of "pancardiac" injury, reflecting cardiac damage that is caused by multiple pathophysiological processes.[31] In many ways, NP can be thought to reflect a patient's current "cardiac age". A high preoperative NP identifies an "older heart" with less physiological reserve, which is at greater risk of an adverse event. As preoperative NP measurement has become more common, it has become clear that it is one of the strongest and most consistent predictors of postoperative cardiac complications.[6,7] This predictive success, together with the discovery that myocardial ischaemia is able to trigger NP release,[32] has led to hope that postoperative NP elevations could further identify patients who are at risk of adverse cardiac events.[33]

Studies that have examined the short term (≤ 6 months)[34,35] predictive ability of postoperative NP, found that it is not an independent predictor of an adverse cardiac event. These results are echoed in our study. By contrast, in the majority of studies in which patients were followed for ≥ 1 year, it was found that postoperative NP independently predicted adverse outcomes, i.e. all-cause mortality, cardiac mortality, nonfatal myocardial infarction or coronary revascularisation.[36-38]

The perioperative period is characterised by rapid haemodynamic changes and fluid shifts, all of which increase ventricular wall stress. While there is no doubt that myocardial ischaemia contributes to postoperative NP elevation, it is likely that perioperative haemodynamic changes are an important trigger for perioperative NP secretion, and not myocardial ischaemia alone. In a seminal paper by Alter et al, in which the authors demonstrated cardiac myocyte stretch to be the predominant trigger for BNP release, they noted that "the diagnostic use of BNP should primarily be directed to assess ventricular wall stress".[30]

Limitations

This study is limited by its observational nature, as well as the low number of complete data sets that were available for analysis. The cohort presented in this study does not represent a significantly biased sample as the excluded patients or drop-out cohort did not have a significant incidence of the primary outcome (17.1%, p = 0.81). There were only 27 events in the cohort, and the inclusion of three variables in the multivariable analysis may have resulted in over-fitting of the risk prediction model, thus limiting the accuracy of the point estimate. Monitoring postoperative ischaemia can be very challenging. In this cohort, significant interference on the recorded tracing or lead disconnection was noted in 30 of the 305 patients (10%) who received postoperative ECG monitoring, and in 40 cases (13%), ST-segment depression was present at baseline. Only modified V2 and V5 were used for ST-segment analysis. While this may have decreased the sensitivity in detecting myocardial ischaemia, the combination of these two leads has been reported to be as high as 90%.[23] As a result of these limitations, these data should be interpreted with caution.

Declarations

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Conclusion

RBC transfusion and postoperative ischaemia, but not postoperative BNP, are independent predictors of the composite outcome of all-cause mortality or postoperative troponin elevation. In the risk stratification of patients with preoperative BNP, postoperative ischaemia improved the overall risk classification and reclassification in patients with and without this outcome.

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