Impact of elevated probnp on clinical outcomes

The impact of elevated proBNP on clinical outcomes in non-cardiac vascular procedures

Introduction

N-terminal prohormone Brain Natriuretic Peptide (NT-proBNP) is a prohormone attached to an inactive 76 amino acid N-terminal protein. [1] It is cleaved to release Brain Natriuretic Peptide in response to excessive stretching, secondary to increased intravascular pressure in the ventricles of the heart. [2] Both BNP and proBNP play an important role in fluid and blood pressure regulation and act by both modifying cardiac load and stimulating vascular remodelling. [3-5] Furthermore, BNP and proBNP act on the kidneys by increasing the excretion of sodium in order to induce diuresis. [6]

To the everyday clinician, what usually comes to mind when thinking about BNP is its use as a marker in patients with heart failure. Important information regarding factors such as a patient's left ventricular ejection fraction can be gained from the measurement of pro-BNP. High levels of NT-proBNP are also associated with left ventricular failure following cardiac repair of congenital heart disease as well as atherosclerosis and atrial fibrillation. [7] [8, 9] Though levels of BNP are typically used in practice, both BNP and NT-proBNP have been shown to have equal diagnostic value for conditions such as heart failure and left ventricular systolic dysfunction. [6]

When evaluating non-cardiac patients pre-operatively, it is important to risk-stratify those at risk of cardiac events. [10] In many cases, physical activity of

the patient may be a poor estimation of overall cardiovascular risk, necessitating other means of risk determination. [11]

The application of BNP/NT-proBNP as a marker for post-operative outcomes in vascular patients has become of increasing interest in recent years. [12] It may be suggested that extra consideration should be put in place preoperatively for patients with elevated levels of NT-proBNP due to its use as a prognostic marker with respect to cardiovascular complications. [12, 13] Many studies suggest a powerful link between high preoperative levels of NT-proBNP/BNP and post-operative cardiovascular events. [2, 14, 15] Both the European Society of Cardiology and the European Society of Anaesthesiology have acknowledged this evidence and have recommended the consideration of measuring NT-proBNP levels preoperatively in high risk non-cardiac surgery patients. [12]

Peripheral vascular disease is highly prevalent and contributes to large scale morbidity and mortality daily. [16] An elevated pro-BNP level has been shown to be more common in patients with peripheral arterial disease than in control groups. [5] These high BNP levels are associated with reduced functional capacity as well as mortality in such patients. [17, 18]

Endovascular procedures involving lower limbs are oftentimes necessary in cases such as critical limb ischaemia. [19] Patients undergoing such procedures with a high pre-operative NT-proBNP have been shown to have a higher risk of late cardiovascular events when compared to patients with normal levels of NT-proBNP. [4, 20]

In observation of the role of BNP and proBNP levels as markers of prognosis in the vascular system, it is not surprising that these markers have an effect on the carotid vessels. High levels of BNP have implications on the carotid system including carotid arterial stiffness and carotid axis occlusion. [21, 22] In carotid endarterectomy (CEA) NT-proBNP is considered to be a reliable predictor of early post-operative cardiac complications. [23] Furthermore, major adverse cardiovascular events are associated with elevated levels of BNP at the time of endovascular intervention. [24]

Abdominal Aortic Aneurysm (AAA) is a potentially fatal and relatively common condition. [25] It is defined as a pathological permanent dilation of the aorta over 3cm or over 50% its original diameter. [25, 26] In the event of a ruptured AAA, approximately 80% of patients die. [27] As AAA is often asymptomatic, screening measures have been adopted in order to identify and monitor those at risk. Elective repair may be indicated when an AAA measures > 5. 5cm [26] . An endovascular approach for aneurysm repair (EVAR) is adopted in the presence of favourable anatomy. In the absence of such favourable anatomy, an open surgical repair (OSR) is performed. Approximately 4-6% of patients die from this procedure [26, 28] .

During OSR, high pressures caused by clamping as well as increased myocardial wall stress, elevate BNP levels and directly contribute to adverse cardiovascular events during surgery. [29] Furthermore, BNP levels have superior sensitivity and specificity (88% and 89% respectively) for adverse

outcomes following AAA repair than other non-invasive tests such as dobutamine and dipyridamole stress echocardiography. [29]

It has been suggested that patients may be risk stratified according to their NT-proBNP levels. NT-proBNP levels exceeding 300pg/ml are associated with peri-operative development of MACE and NT-proBNP levels below this level are unlikely to result in MACE. [2] This value will be used as a cut-off point in order to distinguish those with elevated NT-proBNP from those with non-elevated NT-proBNP.

Objectives:

We aim to assess the impact of an elevated pre-operative level of NT-proBNP on the clinical outcomes of patients undergoing non-cardiac vascular surgery procedures.

We aim to compare patients with an elevated plasma NT-proBNP to those who did not have an elevated NT-proBNP, following procedures for peripheral vascular disease, carotid stenosis and aortic aneurysm repair.

Primary endpoints:

To compare patients who had elevated plasma NT-proBNP with those who did not have elevated plasma NT-proBNP, regarding

- 30-day Major Adverse Cardiac Events (MACE) (cardiac arrest, myocardial infarction, and pulmonary oedema)
- 30-day mortality
- All cause 6-month mortality

Secondary Endpoints:

- Length of Intensive Care Unit stay and hospital stay
- Peri-operative morbidity (renal failure, dialysis, respiratory complications and wound complications).
- Procedure specific complications
    - Aneurysm Repair
        - Technical success
        - Sustained clinical success
        - Bowel ischaemia
        - Lower limb embolisation
    - Carotid Endarterectomy
        - Stroke
        - Sustained clinical success
    - Peripheral Revascularisations
        - Haemodynamic success
        - Binary restenosis
        - Sustained clinical success
        - Amputation free survival
- Freedom from secondary intervention

Research Question

The purpose of this study is to postulate whether or not elevated pre-operative NT-proBNP levels is associated with adverse cardiovascular outcomes following non-cardiac vascular surgery.

Methods

Study design and setting

The study was retrospective in design, using quantitative data. It was designed to assess the clinical and technical outcomes of patients who underwent non-cardiac vascular surgery and to compare these outcomes in patients with elevated plasma NT-proBNP to patients that did not have elevated NT-proBNP. The SVS Reporting standards were used to guide this effort [30, 31] .

The study was a clinical audit of all patients who underwent non-cardiac vascular surgery procedures from 2002 to 2016 at a tertiary referral vascular surgery centre.

In this study, elevated NT-proBNP will be defined as NT-proBNP >/= to 300pg/ml and non-elevated proBNP will be defined as proBNP < 300pg/ml.

Patient population

Inclusion criteria:

Patients were included if they underwent a non-cardiac vascular surgery and had a preoperative NT-proBNP analysis performed.

Exclusion criteria:

Patients were excluded if any of the following conditions existed:

1. Incorrectly collected samples.
2. Emergency vascular intervention.

3. No documented NT-proBNP analysis performed or documented on the system.

To adjust for confounding factors, demographics such as CVD risk factors, clinical presentation and perioperative outcomes among patients with elevated NT-proBNP and those who did not have elevated NT-proBNP were compared.

Outcome variables and endpoints

Outcome variables were defined according to the SVS reporting guidelines. [30, 31]

The primary endpoint was to compare patients with elevated NT-proBNP with those who did not have elevated NT-proBNP regarding 30-day Major Adverse Cardiac Events (MACE) (cardiac arrest, myocardial infarction, and pulmonary oedema), 30-day mortality and all cause 6-month mortality.

The secondary end-point of this study was post-operative morbidity. This was considered if the patient sustained a clinical complication (length of intensive care unit stay and hospital stay, renal failure, dialysis, respiratory complications and wound complications) or procedure related complications (abdominal aneurysm repair, carotid endarterectomy repair, peripheral revascularisation complications and requirement of secondary intervention as detailed in the SVS reporting standards) [30, 31]

In order to limit confounding variables that may influence the outcomes, all revascularisation procedures were performed by the same surgeon, and the patient groups were evenly matched.

Data collection and statistical analysis

Demographic data as well as data regarding clinical presentation and vascular laboratory results were retrieved retrospectively from Vascubase 5. 2, a prospectively collated vascular database, at our vascular centre.

Where data were unavailable on the Vascubase system, the patient’s clinical notes were used to extract such data. Both pre-operative and post-operative NT-proBNP levels were recorded and entered into Statistical Package for the Social Sciences (SPSS) (IBM Corp, Armonk New York, USA). Both parametric and non-Parametric testing was used to assed the impact of elevated NT-proBNP on outcomes.

For categorical variables, Pearson’s Chi-square, Likelihood Ratio, and Fisher Exact tests were utilised.

Non-categorical variables were assessed via One Way ANOVA testing, provided they were normally distributed.

Homogeneity of results was also noted. The p-value was reported via ANOVA testing if it exceeded 0. 05, while it was reported by the Kruskal Wallis test if it was less than 0. 05.

When data was skewed, alternative Non-parametric Kruskal Wallis testing was implemented.

Ethical considerations

As this is a retrospective clinical audit, patient’s participating in this study have already given consent for biochemical testing, imaging and interventions that yielded the data used for this study.

Data that was collected in this study will be coded and stored on password protected computers and password protected electronic case reports.

This data will only be accessible to those listed as the co-investigators and the principle investigators in this study. Ethical approval was granted by the Galway University Hospital Ethics Committee, appendix 1.