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International Journal of Current Research
Vol. 8, Issue, 09, pp.39399-39402, September, 2016

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

EFFECT OF SPINAL-EPIDURAL ANESTHESIA ON BRAIN NATRIURETIC PEPTIDE (BNP) IN PATIENTS WITH ISCHEMIC DILATED CARDIOMYOPATHY UNDERGOING PERIPHERAL VASCULAR SURGERY

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ARTICLE INFO

Article History:
Received 25th June, 2016
Received in revised form
10th July, 2016
Accepted 18th August, 2016
Published online 30th September, 2016

Key words:
Brain Natriuretic Peptide,
Cardiomyopathy,
Combined Spinal Epidural.

ABSTRACT

Background: Neuroaxial anesthesia for patients with cardiac disease is still a matter of debate. BNP has been added as a cardiac biomarker in response to stress. Spinal-epidural anesthesia seems to full fill some criteria of therapeutic intervention in cardiac patients. For this, in a group of patients with impaired left ventricular function, we test whether epidural –spinal anesthesia has an effect on BNP as well as testing the predictability of postoperative BNP for outcome.
Methods : the authors conducted this study on 24 lower extremity vascular surgery patients with ischemic dilated cardiomyopathy (EF <40 %) under combined spinal epidural anesthesia (CSE). The primary end point was the effect of CSE on postoperative BNP and its predictability for the outcome, while the secondary outcome was the cardiac outcome over 6 months postoperatively.
Results: CSE offers perioperative hemodynamic stability, and complication free early hospital stay, however it does not attenuate the rise of BNP. Mortality and morbidity rates were 8% and 41.6 % respectively over the next 6 months. Postoperative BNP ≥67.43pg/ml, provided the optimal BNP cutoff points for predicting major cardiac complications
Conclusion: CSE is a feasible technique of anesthesia in such patients with dilated cardiomyopathy undergoing vascular surgery in the lower half of the body. BNP study revealed that postoperative BNP levels are valuable bed side predictors of intermediate term post-operative cardiac death and major adverse cardiac events in cardiac patients undergoing peripheral vascular surgery.

Citation: Alaa M. Atia, Emad Z. Kamel, EmanMosad, Mahmoud A. M. Ashri, Nawal A. Gad Al Rab and Hassan I. M. Kotb, 2016. "Effect of spinal-epidural anesthesia on brain natriuretic peptide (bnp) in patients with ischemic dilated cardiomyopathy undergoing peripheral vascular surgery", *International Journal of Current Research*, 8, (09), 39399-39402.

INTRODUCTION

Neuroaxial anesthesia for patients with cardiac disease still a matter of debate, either for cardiac or non-cardiac surgery. some studies have suggested that epidural anesthesia may blunt the surgical stress response after major surgery (Ezhevskaya *et al*., 2013). Stress response measured by endocrine and inflammatory interleukins, has been attenuated by epidural anesthesia (Hadimioglu *et al*., 2012; Chloropoulou *et al*., 2013), and this has been reflected in less myocardial ischemic incidence in cardiac patients (Stenger *et al*., 2013). BNP has been added as a cardiac biomarker in response to stress, its increase reflects myocardial dysfunction, and ischemic changes. Effects of Neuroaxial anesthesia on the perioperative changes in BNP has been shown in few studies utilizing thoracic epidural block in cardiac and non-cardiac surgery to be attenuated with improved short term outcome, especially in elderly patients (Crescenzi *et al*., 2009). Lumbar epidural anesthesia has been shown in other studies to have no effect on perioperative rise of BNP levels and is comparable to general anesthesia (Canan ATALAY *et al*., 2010). Spinal-

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epidural anesthesia seems to full fill some criteria of therapeutic intervention in cardiac patients , i.e. avoidance of drug induced myocardial depression, avoidance of sudden increase of the afterload through the efficient sensory block and analgesia, and avoidance of sudden decrease of the blood pressure. For this, in a group of patients with impaired left ventricular function, we studied whether epidural–spinal anesthesia has an effect on BNP as well as testing the predictability of postoperative BNP for outcome.

MATERIALS AND METHODS

This study protocol was approved by the local research ethics committee of Assiut university medical school. A written informed consent was obtained from all patients. This prospective trial was a single-center observational study of 24 consecutive patients with ischemic dilated cardiomyopathy, with their EF < 40%, undergoing peripheral vascular surgery in the lower half of the body under combined spinal epidural anesthesia (CSE). The diagnosis of DCM was based upon M-mode and two dimensional echocardiographic evidence of dilated cardiomyopathy with global hypokinesia and EF< 40%. Patients with significant fluid and electrolyte imbalance, major arrhythmias, heart failure, unstable angina, systolic blood pressure at rest < 100 mmHg, heart rate < 50, serum Creatinine >2.0 mg /dl, and patients who required emergency surgery were excluded from the study.

Characteristics of the patients is shown in table (1). preoperative optimization including fluids, electrolytes, as well as cardiac stability was done. Anesthesia technique : was done under standard anesthetic monitoring, in addition to invasive central venous and arterial blood pressure mnitoring for better handling of fluids and ephedrine usage to keep CVP around 10 : 12 cm.H_2O and the arterial blood pressure not to decrease beyond 15% of the patients' base line. CSE was established using needle through needle technique, initial injection of 5mg heavy bupivacaine 0.2 mg morphine sulphate in the subarachnoid space, followed by 3:5 ml of 0.5 % bupivacaine and 2% lidocaine through the epidural catheter every 10 minutes intervals to attain sensory level at T10. BNP level was assayed with EVOLIS BIORAD system based on RAYBio BNP. Enzyme immunoassay (EIA) kit is a (BIO RAD LABORATORIES –USA) ® in vitro quantitative assay for detecting BNP peptide based on the principle of competitive Enzyme Immunoassay. The minimum detectable concentration of BNP is 1.45 pg/ml, Concentration range: 0.1 – 1000 pg/ml.

Study end points: firstly, the clinical outcome of patients which was evaluated in the hospital stay period and followed up to the period of 6 months. the second aim was the value of postoperative BNP as a predictor for major cardiac complications, including myocardial infarction, heart failure and heart block in the period of follow up.

Statistical analysis

Results for normally distributed continuous variables are expressed as mean value and standard deviation. Categorical data and dichotomous variables are shown as number and percentage. Comparison of continuous variables were performed using independent t-test. proportions were compared with chi square test. Differences were considered to be statistically significant if the null hypothesis could be rejected with 95% confidence ($p< 0.05$).

Receiver operator characteristic (ROC) curve is used to decide the optimum cutoff point of BNP level which predicts the major cardiac complications and mortality. The SPSS ver.17 statistical software package (SPSS, Chicago, USA) ® was used for all calculations, except ROC curve analysis which was done using " medcalc 7" statistical software package available at http://www.medcalc.org.

RESULTS

Table 1 shows: demographic data, coexisting diseases, operations done, cardiac findings, in addition to the preoperative cardiac state of the patients. Medications, and fluids given are listed in table (2). It is noticed that the percentage of hemodynamic changes was around the acceptable range throughout the surgery in the majority of patients, and postoperatively it showed gradual return toward the baseline.

Table 1. Patients characteristics, cardiac findings, comorbidities VPCS ventricular premature contractions. APCS atrial premature contractions

Patients characteristics	
Age (year)	64.55 ± 9.53
Gender	
Male	22 (91.6%)
Female	2 (8.4%)
Weight (KG)	69 ±13.072
Comorbidities	
Hypertension	33%
Dyspnea grade 1 : 2	24%
Coronary stent	4%
Diabetic	38%
Mild Renal impairment	12%
Serum Creatinine	0.8 -1.7 mg/dl
Surgery	
Femoro-popliteal bypass grafting	25%
Trans-metatarsal amputation	25%
Below knee amputation	50%
Electrocardiography	
Normal findings	15 %
Atrial fibrillation	15%
Ischemic changes	55%
VPCS	25%
APCS	4%
Old myocardial infarction	15%
Conduction abnormalities	30%
Echocardiographic	
Moderated to severe mitral regurge	(95.0%)
Moderate pulmonary hypertension	9 (45.0%)
Diastolic dysfunction grade 1 : grade 2	18 (75.0%)
Intraventricular thrombus.	2 (10.0%)
Systolic dysfunction	24 (100.0%)

Table 2. Given medications and fluids

	Medication	Mean ± SD
BUPIVACAINE 0.5%	mg	80.20± 25.35
LIDOCIANE 2%	mg	200.52±80.20
MORPHINE	mg	0.2±0.12
EPHEDRINE	mg	16.08±5.35
CRYSTALLOIDS	ml	575 ±197.123
COLLOIDS	ml	496.43± 203.25
Whole blood	ml	641.66±300.56

Brain natriuretic peptide level showed a highly significant increase in the post-operative day in comparison to the preoperative values, Table (3).

Table 3. Shows the BNP values

Preoperative BNP Mean±SD pg/ml	Postoperative BNP Mean±SD pg/ml	P -value
44.76± 13.75	141.00±30.74	P< .000***

Table 4. Correlation between BNP values and the outcome

	No-complication "n=12"	Complication "n=12"	p-value	95% CI
Preoperative BNP	36.51 ± 12.86	58.15 ± 18.36	P < 0.03*	-32.8:102.85
Postoperative BNP	34.75 ± 10.08	223.08±105.36	P< 0.000***	-93:290.118

Outcome: This study showed mortality and morbidity rate of 8% and, 41.6 % respectively over intermediate postoperative follow up period of 6 months. 2 patients died at home after about 3 months, 4 patients developed heart failure (one case within the next 3 weeks and 3 cases after one month), 4 patients developed acute myocardial infarction (1 patient after 1st month, 2 patients in the 2nd month, 1 patient in the 4th month),one patient developed unstable angina after the 2nd month, and finally one patient underwent re-stenting in the 2nd month, as shown in Fig (1).

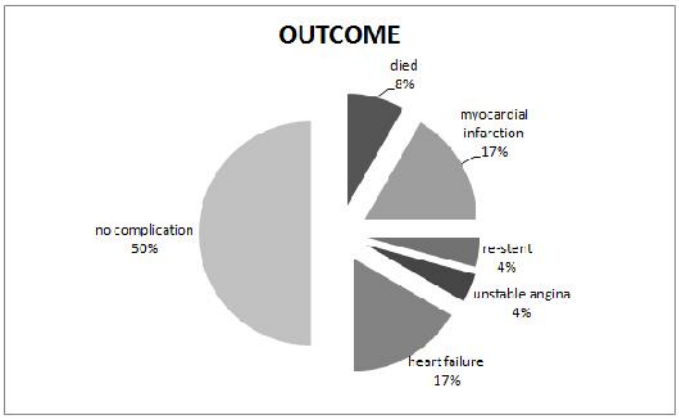

Fig. 1. Outcome

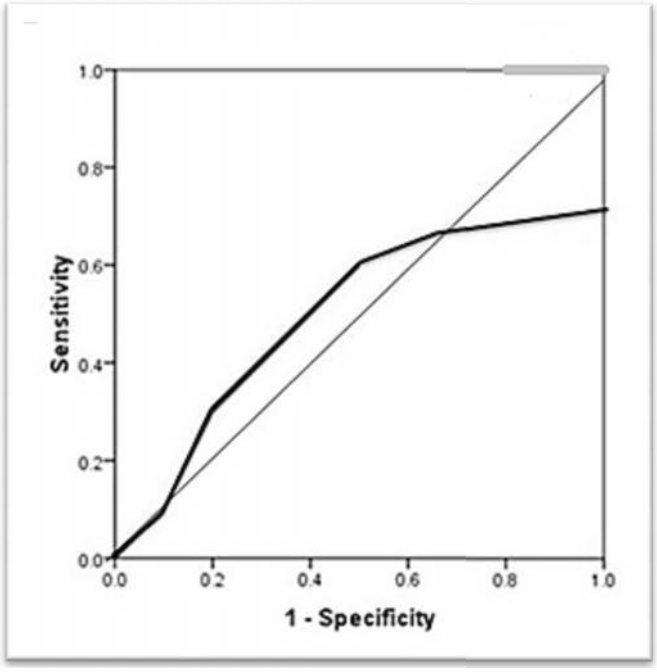

Fig. 2. Postoperative BNP ROC curve

BNP and the outcome

There were significant differences between the values of preoperative and postoperative BNP among the complicated versus uncomplicated outcome patients. It has been also found that there is significant correlation between the preoperative BNP level and the morbidity and mortality with p –value <0.03.However the correlation was getting stronger and highly significant when the postoperative BNP value was correlated with the complicated outcome. p-value < 0.000. as shown in Table (4). A (ROC) curve analysis demonstrated postoperative BNP ≥67.43pg/ml, provided the optimal BNP cutoff points for predicting major cardiac complications and death, with areas under ROC curve was 0.655 as demonstrated in Fig. (2) Patients with postoperative BNP above the cutoff point were fifteen cases, fourteen cases of them have more co morbidities.

DISCUSSION

This study was to evaluate the effects of spinal –epidural anesthesia on postoperative BNP release in vascular patients with ischemic dilated cardiomyopathy. None of the previous researches studied the impact of vascular surgery on the outcome in patients having ischemic dilated cardiomyopathy, with global left ventricular hypokinesia like this study. The working hypothesis of this trial was that spinal – epidural anesthesia would modulate the release of BNP after surgery, assuming the ability of this technique to modify the neurohormonal stress response to surgery, and to correlate the postoperative changes in BNP level to the outcome. BNP is increased in the 1st postoperative day up to 3 folds of the preoperative value, and this rise points to the loading changes and left ventricular response. Postoperative BNP reflects the immediate risk and predicts the outcome as well. The main finding was that postoperative BNP (141.00±30.74 75 pg/ml) was significantly raised in comparison to preoperative value (44.76± 13.75 pg/ml). Utility of BNP in dilated cardiomyopathy has been examined early in medical practice as early as 1998 (McDonagh *et al*., 1998), when they analyzed ECG and echocardiography in 1252 participants. Median concentrations of BNP were significantly higher in patients with left systolic dysfunction (24 pg/ ml) versus (7.7 pg/ml) without. Miller *et al.* (2007) also compared the levels of BNP between patients with ischemic dilated cardiomyopathy and those patients with non-ischemic cardiomyopathy. Concentrations of BNP were statistically significantly higher in patients with ischemic dilated cardiomyopathy and amounted to 779 ± 91 pg/ ml, compared to 532 ± 85 pg/ml in non-ischemic cardiomyopathy. The death rate of cardiovascular causes in 10 ± 1 months of observation amounted to 48 % in patients with heart failure of ischemic origin and 23 % with primary cardiomyopathy (p < 0.05). This could be due to the more marked degree of myocardial damage

that occurs in patients with ischemic cardiomyopathy. It may be of value to speculate that increased injury reflects the conjoint effects of increased wall stress and pericardial coronary artery disease. In a previous study by Miller *et al.* (2005) They mentioned that in the end stage heart failure, the heart may lose the ability to increase BNP and that may be considered as an adverse effect. Myocyte stretching and neurohormaonal activation both contribute to increased BNP expression in the failing heart. In addition, clinical studies have shown that plasma BNP and Pro BNP concentration are also elevated in patients presenting with acute myocardial infarction or acute coronary syndrome. Myocardial ischemia with normal left ventricular function has shown to augment cardiac BNP gene expression and increase plasma BNP and Pro BNP concentration (Goetze *et al*., 2003). Regarding the postoperative BNP, this study found that (62.5 %) of the patients showed increase of their postoperative BNP above the cutoff point which predicts the problematic outcome. It is noticed that this group of patients have more preoperative medical problems and their morbidity rate was 60% versus 11% in those with postoperative BNP < cutoff. The two recorded cases who died within the period of follow up was within this group.

Elevation of plasma BNP concentrations after surgery suggesting an increased ventricular production related to hemodynamic conditions. Myocardial ischemia can compromise left ventricular function and decrease contractile function of ventricle i.e. hibernating myocardium. Moreover, stunned myocardium is probably of importance in the first few hours after surgery, in reducing myocardial contraction, increased ventricular pressure, and secretion of BNP (Clerico *et al*., 2006). We cannot exclude the possibility that these results reflect small number of patients studied, however these findings may reflect the state of major adverse cardiac effect among such critical group of cardiac patients undergoing peripheral vascular surgery, suggesting that patient at risk had a higher biomarker level. There are marked differences in the sensitivity and cutoff values of different BNP assays so, our results cannot be extrapolated to other assays. In conclusion, CSEA is a feasible technique of anesthesia in such patients with IDC undergoing non cardiac surgery in the lower half of the body. BNP study revealed that perioperative BNP levels are valuable bed side predictors of short and long term perioperative cardiac death and major adverse cardiac events in cardiac patients undergoing peripheral vascular surgery.

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