

# Low baseline proBNP associated with increased risk of intraoperative hypotension during spinal anaesthesia for cesarean delivery

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**BACKGROUND AND OBJECTIVES:** Brain natriuretic peptide (BNP) has a role in the regulation of body fluid volume and blood pressure (BP). BNP remains within a normal range during spinal anaesthesia (SA) in patients undergoing cesarean delivery. However, the effect of BNP on changes in BP during the perioperative period has not been evaluated. We aimed to investigate the effect of preoperative serum BNP on the risk of hypotension during cesarean delivery with SA.

**DESIGN AND SETTING:** Patients were randomly selected among the patient group who were attending routine clinic visits for pregnancy monitoring. All had a healthy pregnancy and no other acute or chronic disease by their obstetrician. The study design was cross-sectional.

**PATIENTS AND METHODS:** Patients who had uncomplicated pregnancy process and no known medical disease were selected consecutively during their last outpatient clinical examination. Baseline BP was recorded before SA. Simultaneously, blood samples were drawn for routine biochemistry and BNP. BP, SaO<sub>2</sub>, and electrocardiography were monitored during surgery. Intraoperative hypotension (IOH) was defined as  $\geq 25\%$  decrease in mean arterial pressure (MAP) at the 5th minute of SA.

**RESULTS:** In 41 term pregnant women, 18 of the 41 patients (43.9%) fulfilled the criteria for IOH, while 23 (56.1%) showed a decrease 13.1 (11.3%) and were classified as normotensive. Baseline BNP was significantly lower in patients with IOH compared with normotensive patients 45.7 (26.9) vs.70.2 (40.5);  $P=.05$ . Baseline BNP had no significant correlation MAP at any time point. Age, body mass index, hemoglobin, baseline MAP and heart rate were not different between patients with and without IOH.

**CONCLUSION:** Those findings suggest that higher baseline BNP levels might have a protective role in development of hypotension in healthy term pregnant women during SA for cesarean delivery.

Pregnancy is a state of physiologic volume expansion as maternal blood volume increases 40%-45% above nonpregnancy volumes.<sup>1</sup> Dramatic changes occur to the cardiovascular system during pregnancy. Initially marked increases in circulating blood volume are met with an increase in stroke volume and a 15% to 20% increase in heart rate. The net effect is a 30% to 50% increase in cardiac output by the end of the first trimester. This effect peaks between the second and third trimesters.<sup>2,3</sup> Besides the finding of elevated renin levels in the setting of an expanded intravascular volume, the integration of the renal and

cardiovascular systems is also evident by the release of atrial natriuretic peptide and B-type natriuretic peptide (BNP) in response to atrial and ventricular distension, respectively.<sup>4</sup>

BNP is a neurohormone secreted by the cardiac ventricles in response to multiple physiological stimuli including ischemia, myocardial stretch, inflammation, and other neuroendocrine stimuli.<sup>5,6</sup> NT-proBNP (N-terminal pro-brain natriuretic peptide) is used as a quantitative marker of heart failure that may reflect systolic and diastolic left and/ or right-ventricular dysfunction.<sup>7</sup>

Several studies have demonstrated that elevated pre-operative proBNP concentrations are powerful independent predictors of perioperative cardiovascular complications (i.e. mortality, myocardial infarction [MI], and heart failure).<sup>8,9</sup> BNP induces diuresis and vasodilatation and inhibits renin and aldosterone production.<sup>10</sup> The BNP level is elevated in certain conditions and is routinely used today for the diagnosis and follow-up of patients with cardio-pulmonary disorders.<sup>11,12</sup> Despite the growing role of BNP in the regulation of volume homeostasis in the nonpregnant state, there is limited data available in normal pregnancies. Some studies have investigated normal range and serial changes in BNP levels in the first, second and third trimesters of pregnancy as well as in the postpartum period.<sup>1-3,8</sup> Hameed et al evaluated longitudinal changes in BNP levels in normal pregnancies and the postpartum period in comparison to healthy nonpregnant controls. Their study demonstrated that pregnant BNP levels are approximately 2-fold higher than in their nonpregnant counterparts and do not significantly fluctuate during pregnancy.<sup>13</sup>

Spinal anaesthesia is the most common process for cesarean delivery. Most common complication of spinal anaesthesia is maternal hypotension. The mechanisms of maternal hypotension after spinal anaesthesia are well described, but there is no predictive marker defined as yet. Therefore, we aimed to investigate a possible role of baseline proBNP concentrations on maternal hemodynamic changes during spinal anaesthesia for cesarean delivery.

## PATIENTS AND METHODS

Patients were randomly selected from among the patients attending routine clinic visits at our obstetrics and gynecology clinic for pregnancy monitoring. Baseline medical history, clinical and laboratory data were collected from patient data files and direct interviews with the patients. The anesthesiologist reported operative, intraoperative and postoperative patient monitoring for vital signs (blood pressure, pulse, oxygen saturation, electrocardiography, urine output), transfusions, medications, data collection and records, delivery and monitoring of laboratory tests. Selected patients were confirmed to have a healthy pregnancy and no other acute or chronic disease by their obstetrician. The study design was cross-sectional.

Oral and written informed consent was taken from all patients and the study was performed according to the principles of declaration of Helsinki.<sup>14</sup> The study was approved by the local ethics committee of Baskent University Faculty of Medicine.

After a quiet resting period of 5 min, a standard venous angiocatheter (16-gauge) was placed into the superficial vein of the forearm. A fast infusion of 10 mL/kg of saline solution was completed approximately 5 minutes before anaesthesia. Blood samples were drawn from the contralateral antecubital vein for routine laboratory analyses and determination of NT-proBNP after this infusion. Those data were recorded as baseline laboratory values. Spinal anaesthesia was induced with the patient in a sitting position. A midline approach at the L3-L4 interspace was used and 2.4 mL 0.5% hyperbaric bupivacaine was administered successfully via a 27-G Quincke needle on the first attempt. Parturient patients were placed in a supine position immediately after the injections were completed. A left lateral tilt was applied by default to all parturients and a sensory block was assessed according to loss of pinprick sensation every 5 minutes for 15 minutes, beyond which the parturient was excluded if the sensory level was below T6. Surgery started as soon as the T6 dermatome was anesthetized; patients who failed to reach at least this level were excluded from the study.

All patients were monitored for BP, SaO<sub>2</sub>, and electrocardiography before and during operation. BP and heart rate values were recorded at 0th, 3rd, 5th, 10th, 15th and 20th minutes after administration of spinal anaesthesia. Any event during operation (nausea, vomiting, and arrhythmia) and the amount of vasoconstrictive agent used to treat maternal hypotension was recorded.

Although there is no widely accepted definition of intraoperative hypotension (IOH), in the present study, we accepted a 25% or more decrease in mean arterial pressure (MAP) at the 5th minute after induction of spinal anaesthesia as a significant IOH, which is taken as a definition of IOH in 5 different articles cited in a meta-analysis.<sup>15</sup> The IOH was treated by the infusion of crystalloids (100 ml/hr) and bradycardia defined as a 30% drop in HR or  $\leq 45$ /bpm was treated by IV atropine.

### Exclusion criteria

Patients with a history of cardiovascular disorders, venous thromboembolism, preeclampsia, hypertension, heart murmurs were excluded. Patients with a body mass index (BMI)  $>40$  kg/m<sup>2</sup> were excluded. Patients with known renal disease, gestational diabetes and severe anemia (Hb  $<8.0$ gr/dL) were also excluded.

### Data collection

Gestational age, number of pregnancies, medical history for any disease and current medications were

**Table 1.** Baseline characteristics of the study group (n=41).

| Variable                                   | Mean (SD)   | Range       |
|--|-------------|-------------|
| Age (years)                                | 28.3 (4.8)  | 18.0-40.0   |
| pro-BNP                                    | 64.9 (42.2) | 18.0-199.0  |
| Body-mass index (kg/m <sup>2</sup> )       | 28.5 (4.3)  | 18.7-39.7   |
| Percent decrease in MAP at 5th minute (%)  | 23.7 (16.7) | -15-52.0    |
| Percent decrease in MAP at 10th minute (%) | 22.4 (19.4) | -11.3-85.0  |
| Percent decrease in MAP at 15th minute (%) | 20.5 (14.6) | -14.7-53.3  |
| Percent decrease in MAP at 20th minute (%) | 20.7 (16.0) | -4.30-58.60 |
| Dosage of ephedrine used (mg)              | 10.5 (12.4) | 0.0-60.0    |
| Saturation O <sub>2</sub> (%)              | 99.82 (0.5) | 98.0-100.0  |
| Hemoglobin (gr/dl)                         | 11.2 (1.8)  | 8.2-17.1    |
| Gestational age (days)                     | 270.9 (7.3) | 249.0-289.0 |
| No of pregnancies                          | 1.8 (1.1)   | 1.0-6.0     |

**Table 2.** Comparison of variables between patients with intraoperative hypotension and the normotensive group.

| Variables                            | Patients with IOH | Normotensive group |
|--------------------------------------|-------------------|--------------------|
| Number of patients                   | 18                | 23                 |
| Age                                  | 29.2 (4.0)        | 28.1 (4.7)         |
| Body-mass index (kg/m <sup>2</sup> ) | 28.6 (3.9)        | 28.5 (3.7)         |
| Decrease in BP (%) at 5th minute     | 29.2 (11.6)       | 13.1 (11.3)        |
| 0-minute MAP                         | 98.5 (9.3)        | 99.7 (16.2)        |
| 5th-minute MAP                       | 70.9 (20.5)       | 86.2 (15.3)        |
| Change in MAP from 0 to 5th minute   | 28.1 (16.2)       | 13.1 (13.9)        |
| Heart rate at 0 min.                 | 93.6 (18.5)       | 96.6 (10.5)        |
| Hemoglobin (g/dL)                    | 10.8 (0.9)        | 11.7 (2.1)         |
| Number of pregnancies                | 1.9 (1.1)         | 1.6 (0.7)          |
| Gestational age (days)               | 270.1(5.8)        | 271.9 (9)          |
| SaO <sub>2</sub> 0th minute          | 99.8 (0.5)        | 99.8 (0.5)         |

Data are mean (SD) unless otherwise indicated.

derived from hospital records and patient interviews. BMI was calculated with the formula current body weight (kg)/[height (m)]<sup>2</sup> after preoperative measurements for body weight and height in all of the patients. Before collection of blood samples, 10 mL/kg of isotonic (0.9 NaCl) saline solution was given intravenously all patients. BP, SaO<sub>2</sub>, and electrocardiography were monitored before and during operation. BP and heart rate were recorded at the 0 th minute and at

the 3 rd, 5th, 10th, 15th and 20th minute after administration of spinal anaesthesia.

#### Measurement of levels B- type natriuretic peptide

Blood samples were drawn from the antecubital vein by standard venipuncture before performing spinal anaesthesia. B-type natriuretic peptide levels were studied using a standard point-of-care assay. After centrifugation of the whole blood samples, plasma was isolated and frozen at -20°C until determination of BNP levels. Quantitative plasma BNP levels were determined with a fluorescence immunoassay kit (Triage Biosite Inc. San Diego, CA; USA). The precision of the analytic sensitivity and stability of this system has been determined.<sup>5,16</sup>

#### Statistical analyses

Statistical analyses were performed using software SPSS 11.0.1 (April 2002; IBM Corp.; NY;USA). Assumption of a normal (Gaussian) distribution was tested by the one sample Kolmogorov-Smirnov test. Simple correlations were performed Pearson or Spearman correlation analyses as appropriate. Comparisons of variables between groups with and without IOH were performed by the *t* test or Mann-Whitney U tests depending on the distribution of a variable. Multiple linear regression analyses (both step-wise and by entering all variables) were performed to search for independent predictors of baseline MAP and percent decrease of BP during spinal anaesthesia.

## RESULTS

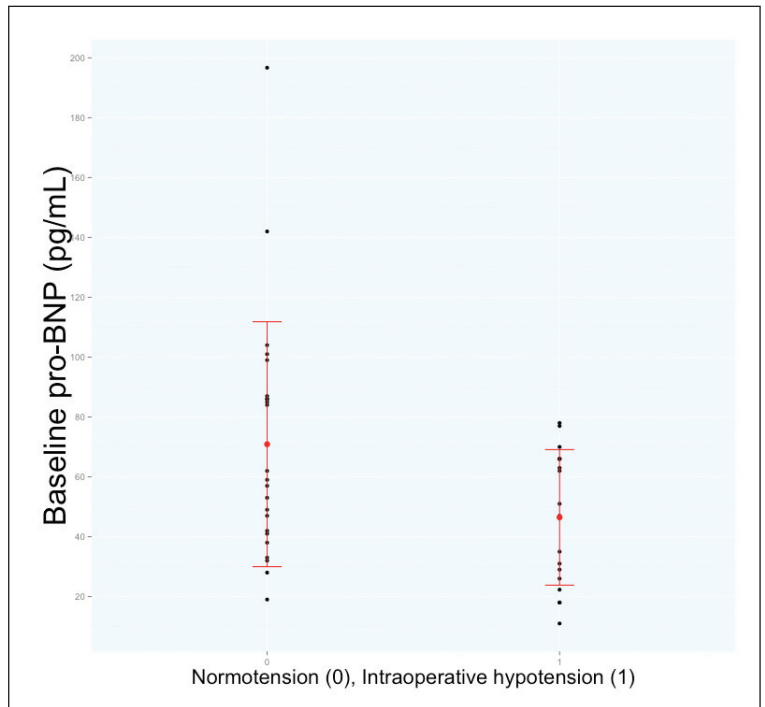
We studied 41 (mean age: 28.3±4.8) healthy pregnant woman. The baseline characteristics of the study group are shown in **Table 1**. At the 5th minute after induction of spinal anaesthesia, 18 of the 41 patients (43.9%) fulfilled the criteria for IOH (25% or more decrease in MAP at the 5th minute) with a substantial decrease in MAP 29.2 (11.6%). Twelve of those 18 patients described nausea concurrently with a hypotensive attack. The remaining 23 (23; 56.1%) did not experience IOH (decrease in MAP at the 5th minute <25%) a MAP decrease 13.1 (11.3) at the 5th minute and had no symptoms. The baseline proBNP level was significantly lower in patients with IOH compared with the normotensive group (mean [SD] 45.7 [26.9] vs. 70.2 [40.5]; *P*=.05), (**Figure 1**). Age, BMI (kg/m<sup>2</sup>), baseline hemoglobin, albumin, MAP and heart rate were similar between patients with and without IOH (**Table 2**). Comparison of MAP and heart rate between patients with IOH and the normotensive group are shown in **Table 3**.

Baseline proBNP levels had no correlation with baseline MAP, percent decrease in MAP at the 5th minute, patient's age, gestational age, number of pregnancies, BMI, hemoglobin and albumin levels ( $P > .05$ ). Stepwise linear regression analysis assessing baseline MAP as dependent variable, BMI, hemoglobin (g/dL), BNP (pg/mL), age, gestational age and number of pregnancies as independent variables revealed that BMI was the only significant predictor of baseline MAP (OR:2.3;  $P = .028$ ). Linear regression (enter method) analysis assessing decrease in BP at the 5th minute as dependent variable and age, gestational age, number of pregnancies, hemoglobin, BMI, BNP as independent variables revealed that none of mentioned parameters had a significant effect on decrease in BP at the 5th minute.

## DISCUSSION

Our study demonstrated that subjects with IOH had lower baseline BNP levels compared with normotensive patients during spinal anaesthesia for cesarean delivery. Several mechanisms have been suggested to explain the high incidence and severity of hypotension during cesarean delivery performed under spinal anaesthesia.<sup>16,17</sup> They include the height (T5-T4) and density of the sensory block required for a comfortable procedure,<sup>18,19</sup> the increased sensitivity to local anaesthetics together with the effects of the sympathetic block during pregnancy; and the aggravating role of aortocaval compression by the gravid uterus.<sup>16,17,20</sup> Except for increased sensitivity to local anaesthetics, which can not be anticipated, all mentioned variables were standardized in our present study.

Another suggested mechanism is the accompanying decrease in arteriolar tone that is mostly due to hormonal changes during pregnancy.<sup>21</sup> In our study all participants were nearly term healthy pregnant women, so a significant variation in their hormonal status could not be expected. Previous studies have attempted to answer the question "What could be a predictor of IOH during spinal anaesthesia for cesarean delivery?" A recent study evaluated the effects of preoperative pulse oximetry parameters on IOH during spinal anaesthesia for cesarean delivery. They detected a significant correlation only between preoperative HR and IOH (OR: 1.06). They suggested that pre-anaesthetic heart rate, but not other parameters derived from pulse oximetry or heart rate variability, may be a prognostic factor for hypotension associated with spinal anaesthesia.<sup>22</sup> However, we could not detect a significant association between pre-anaesthetic HR and degree of IOH. Recently, the  $\beta_2$ -adrenoceptor (ADRB2 gene) and NO synthase gene polymorphisms



**Figure 1.** Baseline proBNP in normotensive (n=23) and intraoperative hypotensive (n=18) subjects ( $P = .05$ ) showing mean and standard deviation.

**Table 3.** Comparison of mean arterial pressure and pulse at 0 to 20 minutes between the intraoperative hypotension (IOH) and normotensive group.

|             | Patients with IOH |                   | Normotensive group |                   |
|-------------|-------------------|-------------------|--------------------|-------------------|
|             | MAP (mm Hg)       | Pulse (beats/min) | MAP (mm Hg)        | Pulse (beats/min) |
| 0th minute  | 98.9 (9.0)        | 97.8 (18.4)       | 99.7 (16.7)        | 95.8 (16)         |
| 3rd minute  | 78.3(16.7)        | 101.6(22.1)       | 87.5(18.5)         | 98.8(21.6)        |
| 5th minute  | 59.6(8.9)         | 96.9(24.0)        | 87.3(14.9)         | 98.1(24)          |
| 10th minute | 74.1(16.5)        | 89.7(15.1)        | 78.8(16.9)         | 95.4(15.2)        |
| 15th minute | 78.5(12.3)        | 95.7(14.2)        | 78.8(11.7)         | 97.8(16.4)        |
| 20th minute | 78.9(12.8)        | 101.2(14.5)       | 78.2(10.6)         | 100.1(15.2)       |

were reported to be responsible for maternal IOH after spinal anaesthesia in some studies.<sup>23</sup> To our knowledge there is no study that evaluated preoperative proBNP concentration as a potential predictive marker for IOH during spinal anaesthesia for cesarean delivery.

Pro BNP is a quantitative marker of heart failure.<sup>7</sup> The relationship between BNP and systemic hemodynamic parameters, its prognostic value in cardiac pathologies, preoperative and post operative cardiac status was reported previously in cardiac and non cardiac surgery.<sup>24-29</sup> A few studies reported a role of proBNP on

hemodynamic changes in healthy pregnancies. The study of Maximillian et al demonstrated that proBNP values were higher during pregnancy than in non-pregnant controls.<sup>29</sup> There is only one study which evaluated the serial changes of natriuretic peptides (atrial and brain natriuretic peptide) after spinal anaesthesia for cesarean delivery in the literature.<sup>30</sup> Ohara et al demonstrated that BNP levels were not changed after spinal anaesthesia but increased 24 hours after surgery. However that study did not reported a relationship between BNP levels and blood pressure or an intraoperative decrease in BP. To our knowledge our study is first to show a significant association between low preoperative BNP levels and IOH during spinal anaesthesia for cesarean delivery. Although blood samples were drawn after loading of 1000 mL isotonic saline (0.9 NaCl) solution, we speculate that low baseline proBNP levels in the IOH group might be a predictor of inadequate extracellular volume in the preoperative period. Therefore, a superimposed vasodilator effect of spinal anaesthesia may aggravate the development of hypotension in this group. It was revealed that distension of the jugular vein (JV) at rest relative to the maximum diameter during a Valsalva maneuver (JVD ratio) identifies patients with heart failure who have higher plasma NT-proBNP levels, right ventricular dysfunction and raised pulmonary artery pressure compared to healthy controls.<sup>31</sup> That means that an increased BNP level was at least a marker of increased right ventricular filling pressure and hypovolemic status in patients with heart failure. So in our patients, low BNP levels may represent low right ventricular filling or intravascular volume.

In our study there was no correlation between the preoperative BNP levels and blood pressure. However, these results reflect a snapshot of data, cannot be generalized for the whole pregnancy process. On the other hand, BP, as a product of systemic vascular resistance (SVR) times the cardiac index (CI), may stay stable in case of opposite isolated changes in SVR and CI. In addition, changes in the intravascular volume may not be reflected in BP due to simultaneous changes in SVR. Previously a slight but significant correlation was found between BNP concentrations and BP in the overall pregnancy. Basically an increase in left ventricular size associated with an expansion in circulating volume and a decrease in systemic vascular resistance have been described during normal pregnancy.<sup>24</sup> The BNP levels have shown to be significantly elevated in patients with preeclampsia.<sup>32</sup> BNP levels had been shown to be 8 times higher in the preeclampsia group compared with normotensive counterparts.<sup>33</sup> We suggest that serial measurements of BP and BNP levels during the preoperative period or during

pregnancy may give us more accurate results about any relationship between BNP and BP.

Our study did not show any correlation between body mass index and blood pressure in term pregnant women. It is well known that increased body mass index is a component of the metabolic syndrome that is accompanied by hypertension. This finding also applies to patients in the pregnancy process. A novel Brazilian cohort study revealed that women with excessive early pregnancy BMI had higher SBP and DBP than their normal-weight counterparts throughout pregnancy.<sup>34</sup> In our study population, BNP levels before delivery were not influenced by parity or gestational age, which is consistent with a previous result.<sup>35</sup>

In the present study, mean serum concentration of BNP was 64.9 (42.3) pg/mL in term uncomplicated pregnant women. Previously Yoshimura et al detected a BNP level of 49 (9) pg/mL in term pregnant women. They concluded that BNP may play a role in controlling blood volume during normal human pregnancy at term and during transition to the postpartum period.<sup>4</sup> On the other hand, Resnik et al reported the median BNP levels in normal patients as 17.8 pg/mL, 21.1 pg/mL in mild preeclampsics and 101 pg/mL in severe preeclampsics.<sup>36</sup> Our results were close to the those of Yoshimura et al. However, our results were close to the values in preeclamptic women when compared with those of Resnik et al. We suggest that discrepancies in BNP levels may be due to study method and differences in the volume status of the patients.

## LIMITATIONS

First, our study group was too small to derive further conclusions. Second, we could have used more sophisticated methods, such as bioelectrical impedance analysis, measurement of jugular vein distension ratio or measurement of central venous pressure, to detect preoperative, intraoperative and postoperative volume status more accurately. Third, an echocardiographic evaluation to detect vena cava diameter of all patients before and after surgery could have been added to the study protocol to detect a more objective correlation between BNP and IV volume.

In conclusion, our study findings demonstrated that low proBNP levels in term pregnant women who are candidates for cesarean delivery with spinal anesthesia may be a marker for IOH. We speculate that low proBNP levels in the preoperative period may reflect inadequate intravascular or extracellular fluid volume and those patients should be more aggressively hydrated in the preoperative and intraoperative period to avoid intraoperative hypotension after spinal anesthesia.

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