EFFECTS OF NEURAXIAL BLOCKADE AND GENERAL ANESTHESIA ON THE RELEASE OF BRAIN NATRIURETIC PEPTIDE IN PATIENTS AT CARDIAC RISK UNDERGOING SURGICAL PROSTATECTOMY

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ABSTRACT

Background: Elevated brain natriuretic peptide (BNP) level can predict postoperative cardiac complications in patients at cardiac risk undergoing non cardiac surgery.

Aim: To compare the effect of general anesthesia versus neuraxial blockade on the release of brain natriuretic peptide intra- and postoperatively in patients at cardiac risk undergoing surgical prostatectomy.

Patients and Methods: 60 male patients at cardiac risk scheduled for surgical prostatectomy were divided into 3 equal groups: Group (G) received general anesthesia, Group (S) received spinal anesthesia and Group (E) received lumbar epidural anesthesia. Hemodynamics were recorded perioperatively. BNP, epinephrine and norepinephrine plasma concentrations were measured preoperatively, at the end of surgery and at 24 hours postoperatively. Also, postoperative cardiac complications were recorded in every group.

Results: At the end of surgery and at 24 hours postoperatively, the BNP plasma concentrations were significantly higher in group (G) than the other two groups (P<0.001) [80.2±12.2 and 60.4±11.2 pg/ml for group (G), 45.7±15.2 and 38.5±10.3 pg/ml for group (S), 40.4±17.4 and 37.1±9 pg/ml for group E]. The norepinephrine plasma concentrations were significantly increased intra and postoperatively in the three groups when compared with the baseline values (P<0.05). However, norepinephrine recorded significantly higher plasma concentration at the end of surgery in group (G) than the other tow groups (P<0.05) [in group (G): 354.2±26.4 versus group (S) 318.2±20.7 and group (E) 324±22.6 pg/ml]. Meanwhile, there were no significant differences between groups regarding hemodynamics and epinephrine plasma concentrations throughout measured time points (P>0.05). The recorded postoperative cardiac complications (ECG changes, hypotension or hypertension) were (35% in group (G), 20% in group (S) and 15% in group (E)).

Conclusion: The plasma BNP level was higher intra- and postoperatively in general anesthesia group of patients compared to spinal and lumbar epidural groups suggesting that neuraxial blockade may attenuate the release of BNP in patients at cardiac risk undergoing surgical prostatectomy.

Key words: BNP, Neuraxial, General anesthesia, Surgical prostatectomy

INTRODUCTION

The choice of anesthesia and surgical techniques for operations are playing an important role in improving outcomes and reducing postoperative complications [1]. Preoperative risk assessment provide guidance to anesthesiologists for the choice of anesthetic techniques and the need for postoperative care [2]. Natriuretic peptides are well known risk markers in various acute and chronic cardiac conditions [3,4].

Brain natriuretic peptide (BNP) is secreted by cardiac myocytes in response to elevation in ventricular wall stress or myocardial ischemia [5,6].

BNP regulate arterial blood pressure, electrolyte balance and fluid volume [7].

Increased plasma concentration of BNP is present with hypertension, hypervolemia, congestive heart failure, myocardial hypertrophy, coronary artery disease, arrhythmias and renal insufficiency [8].

Previous studies demonstrated the diagnostic and prognostic values of BNP in non surgical patients with or without symptomatic cardiac disease [9,10].

Neuraxial blockade have many benefits including : attenuation of stress response and reducing the incidence of venous thrombosis and pulmonary embolism which
results in reduction of intra-and postoperative ischemia [11].

There were few studies on the effect of neuraxial blockade on the release of BNP in patients undergoing major operation [12].

In this prospective study we hypothesized that neuraxial blockade would reduce BNP plasma concentration in patients at cardiac risk undergoing surgical prostatectomy more than general anesthesia.

The aim of this study was to compare the effect of neuraxial blockade versus general anesthesia on the release of BNP in patients at cardiac risk undergoing surgical prostatectomy.

PATIENTS AND METHODS

After obtaining the ethics committee approval and a written informed consent from each patient, 60 consecutive eligible male patients scheduled to undergo surgical prostatectomy were enrolled prospectively in this study.

The inclusion criteria were: patients aged 60-75 years with ASA physical status II and those who had cardiovascular risk factors. A patient was considered at risk for coronary artery disease if he had at least two of the following cardiac risk factors: age ≥65 years, hypertension on B blocker therapy, current smoking, diabetes mellitus and a serum cholesterol >240 mg/dl [13].

The exclusion criteria were liver dysfunction, renal insufficiency requiring hemodialysis, known allergies to the drugs used in the present study and any contraindication to neuraxial blockade. A total of 60 male patients who met the inclusion criteria were randomly divided into three equal groups:

1- Group (G): (n=20) received general anesthesia.

2- Group (S): (n=20) received spinal anesthesia.

3- Group (E): (n=20) received lumbar epidural anesthesia.

Preoperatively, all patients had a routine clinical evaluation which included a detailed medical history, physical examination, chest radiography, laboratory tests and 12-lead electro-cardiogram. Antihypertensive drugs were continued until the day of operation. All patients were premedicated with intramuscular midazolam 3.5mg one hour before operation. An intravenous (IV) cannula was inserted into an antecubital vein in all patients. In the spinal and epidural groups patients were preloaded with I.V infusion of 10-12 ml/kg of ringer lactate solution.

Anesthetic techniques:

For group (G): induction of general anesthesia was done with sleep dose of thiopental (3-5mg/kg), fentanyl (1µg/kg) and rocuronium bromide (0.6 mg/kg). After endotracheal intubation, anesthesia was maintained with halothane (0.5-1.5 minimum alveolar concentration) and additional boluses of rocuronium bromide according to patient's need.

Patient were ventilated with oxygen and keep the patient ventilation in normocapnic range without PEEP. At the end of surgery, muscle relaxant was reversed with I.V neostigmine 0.05 mg/kg and I.V atropine 0.02 mg/kg guided by the use of peripheral nerve stimulator.

For group (S): spinal needle was inserted at L3-L4 intervertebral space. Spinal block was established with a bolus of 2.5-3 ml of hyperbaric bupivacaine. Sensory dermatome level of spinal anesthesia up to T6 was obtained by horizontal manipulation of the surgery table and the use of hyperbaric anesthesia solution. The anesthesia level was defined as the dermatome below which there was a lack of sensory response to pin prick.

For group (E): an epidural needle was inserted at L3-L4 intervertebral space through the median approach. Epidural blockade was done by a bolus of 12-16 ml of 0.5% isobaric bupivacaine.

All patients were continuously monitored with pulse
oximetry, 5 leads electrocardiograph, capnography and non-invasive blood pressure measurement.

Peripheral venous blood samples were obtained preoperatively, at the end of surgery and at 24 hours postoperatively.

These samples were used for measuring plasma concentrations of BNP and catecholamines (epinephrine and norepinephrine).

Heart rate and mean arterial blood pressure (MAP) were recorded preoperatively, immediately after anesthesia, 30 min after anesthesia, at the end of the surgery and at 24 hours postoperatively. All patients were transferred to ICU for 24 hours monitoring.

Postoperative analgesia was provided with petidine 1-1.5 mg/kg I.M as clinically indicated. Any ECG changes, hypertension or hypotension during this period were recorded.

Sample collection: blood was collected in tube for BNP assay and in EDTA tube for epinephrine and norepinephrine assay. Both serum and EDTA plasma were separated and stored at 70ºC until analysis. Serum BNP was assayed using BNP ELISA kit (Cat. No SE90541Hu) (use Life Science inc., USA). The kit is a sandwich enzyme immunoassay for vitro quantitative measurement of BNP.

The EDTA plasma was assayed for epinephrine and norepinephrine by competitive ELISA assay using epinephrine/norepinephrine ELISA kit (Cat. No KA1877) (Abnova). Assays were performed according to the manufactures recommendations.

As the BNP plasma concentration of one group was 162.4±29.4 pg/ml compared to 69.0±6.9 pg/ml of another group [1], the estimated sample will be 20 patients at 80% power and 95% confidence interval (Epi-Info version 6).

**Statistical analysis:**

Data were analysed by using SPSS version 20 software computer package. Data were expressed as mean ±SD for quantitative variables, number and percentage for categorical variable. ANOVA (F-test), paired t-test, Chi-squared, or Fisher exact were used when appropriate. P<0.05 was considered statistically significant.

**RESULTS**

A total of 60 male patients were scheduled for surgical prostatectomy. There were no significant differences between the three groups as regard age, weight, cardiac risk factors, duration of surgery and anesthesia (P>0.05) (Table 1).

Hemodynamic variables didn't significantly differ among the three groups throughout all measured time points (P>0.05) (Fig. 1).

Preoperatively, BNP values were similar in the three groups (P=0.31). It was 25.9±6.8 pg/ml for group (G), 27.8±5.7 pg/ml for group (S) and 28.9±6.0 pg/ml for group (E) (Table 2).

At the end of surgery and at 24 hours postoperatively, BNP values were significantly increased in each group when compared with the preoperative values (P<0.001) (Table 2).

When the three groups were compared together, there was significant increase in BNP values in group (G) at the end of surgery and at 24 hours postoperatively compared to the other two groups (P<0.001) (Table 2).

BNP values at the end of surgery were 80.2±12.2 pg/ml for group (G) versus 45.7±15.2 pg/ml for group (S) and 40.4±17.4 pg/ml for group (E) (Table 2).

At 24 hours postoperatively the BNP values were 60.4±11.2 pg/ml for group (G) versus 38.5±10.3 pg/ml for group (S) and 37.1±9.0 pg/ml for group (E) (Table 2).

There were no significant differences in BNP values between spinal group and epidural group at the end of surgery and at 24 hours postoperatively when compared
As regard the baseline values of epinephrine, there were no significant differences between the three groups. It was 79.25 + 14.2 pg/ml for group (G), 75.91 + 15.4 pg/ml for group (S) and 73.32 + 16.3 pg/ml for group (E) (P= 0.19) (Fig. 2).

At the end of surgery, the values of epinephrine showed slight increase in all groups without significant differences, it was 83.6 + 12.5 pg/ml for group (G), 86.21 + 12.8 pg/ml for group (S) and 82.45 + 13.2 pg/ml for group (E) (P= 0.64) (Fig. 2).

At 24 hours postoperatively epinephrine values began to decrease in all groups without significant differences, it was 77.3 + 16.4 pg/ml for group (G), 78.81+15.6 pg/ml for group (S) and 74.6+ 17.23 pg/ml for group (E) (P= 0.59) (Fig. 2). Also, there were no significant differences when comparing the baseline values of epinephrine with the values at the end of surgery and at 24 hours post-operatively in all groups (P>0.05) (Fig. 2).

The baseline values of norepinephrine concentration were similar among the three groups, it was 285+25.2 pg/ml for group (G), 269.5 + 24.6 pg/ml for group (S) and 278 + 27.5 pg/ml for group (E) (P= 0.17) (Fig. 3). At the end of surgery, there was a significant increase of norepinephrine concentration in group (G) when compared with other two groups (P<0.05) (Fig. 3). It was 354.2 + 26.4 pg/ml for group (G) versus 318.2 + 20.7 pg/ml for group (S) and 324 + 22.6 pg/ml for group (E) (Fig. 3).

At 24 hours postoperatively there were no significant differences in norepinephrine values among the groups, it was 305.6 + 24.6 pg/ml for group (G), 295.6 + 21.7 pg/ml for group (S) and 300 + 26.8 pg/ml for group (E) (P= 0.44) (Fig. 3).

At the end of surgery and at 24 hours postoperatively the norepinephrine values were significantly increased in each group when compared with the baseline values (P<0.001) (Fig. 3).

There were no significant differences in plasma epinephrine and norepinephrine values between spinal group and epidural group at the end of surgery and at 24 hours postoperatively when compared together (P>0.05) (Figs. 2,3).

As regard the postoperative cardiovascular complications, the highest percentage was observed in group G (35%) when compared to group S (20%) and group E (15%). However, the differences between three groups were not statistically significant (P>0.05) (Table 3).

Table (1) : Patient characteristics, cardiac risk factors, duration of surgery and anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Group G (n=20)</th>
<th>Group S (n=20)</th>
<th>Group E (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>69 + 6.2</td>
<td>70.8 + 5</td>
<td>66.2 + 5.9</td>
<td>0.19</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>72.2 + 11.5</td>
<td>75.4 + 9.1</td>
<td>73.8 + 12.5</td>
<td>0.66</td>
</tr>
<tr>
<td>Cardiac risk factors (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>13</td>
<td>15</td>
<td>12</td>
<td>0.59</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4</td>
<td>3</td>
<td>6</td>
<td>0.39</td>
</tr>
<tr>
<td>Smoking</td>
<td>9</td>
<td>8</td>
<td>5</td>
<td>0.59</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>8</td>
<td>5</td>
<td>7</td>
<td>0.59</td>
</tr>
<tr>
<td>Duration of anesthesia (min)</td>
<td>107 + 10.8</td>
<td>106 + 12</td>
<td>110.2 + 13.3</td>
<td>0.52</td>
</tr>
<tr>
<td>Duration of surgery (min)</td>
<td>98 + 12</td>
<td>95.5 + 10.7</td>
<td>100 + 13</td>
<td>0.53</td>
</tr>
</tbody>
</table>

Values are expressed as means + SD or number of patients (n). There were no intergroup differences (P>0.05).
Group G : General anesthesia
Group S : Spinal anesthesia
Group E : Lumbar epidural anesthesia

Table (2) : Perioperative changes in BNP (pg/ml).

<table>
<thead>
<tr>
<th></th>
<th>Group G (n=20)</th>
<th>Group S (n=20)</th>
<th>Group E (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>25.9 + 6.8</td>
<td>27.8 + 5.7</td>
<td>28.9 + 6.0</td>
<td>0.31</td>
</tr>
<tr>
<td>At the end of surgery</td>
<td>80.2 + 12.2 S*</td>
<td>45.7 + 15.2 S</td>
<td>40.4 + 17.4 S</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24 hours postoperatively</td>
<td>60.4 + 11.2 S*</td>
<td>38.5 + 10.3 S</td>
<td>37.1 + 9.0 S</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Perioperative changes in brain natriuretic peptide (BNP), values are expressed as mean ± SD. They are reported at baseline (pre-anesthesia), at the end of surgery and at 24 hours postoperatively.

* P<0.001 compared to other groups.

S P<0.001 significantly different from baseline

Table (3) : Postoperative cardiovascular complications.

<table>
<thead>
<tr>
<th></th>
<th>Group G (n=20)</th>
<th>Group S (n=20)</th>
<th>Group E (n=20)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECG changes [n (%)]</td>
<td>4 (20%)</td>
<td>2 (10%)</td>
<td>1 (5%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Hypotension [n (%)]</td>
<td>0 (0%)</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Hypertension [n (%)]</td>
<td>3 (15%)</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
<td>0.41</td>
</tr>
<tr>
<td>Total [n (%)]</td>
<td>7 (35%)</td>
<td>4 (20%)</td>
<td>3 (15%)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Values are expressed as number (percentage) of patients. There were no intergroup differences (P>0.05).

Fig (1) Hemodynamic variables.

Values are expressed means ± SD. They are reported at baseline (pre-anesthesia), immediately after anesthesia, after 30 min of anesthesia, at the end of surgery and at 24 hours postoperatively

HR : Heart rate  MAP : Mean arterial blood pressure Non significant P>0.05

Fig (2)

Perioperative changes in epinephrine (pg/ml)
Values are expressed as mean ± SD. They are reported at baseline (pre-anesthesia), at the end of surgery and at 24 hours postoperatively. There were no intergroup differences (P>0.05)

DISCUSSION

Appropriate choice of anesthetic techniques can offer stability to the patients [14]. The preoperative detection of the patients at risk for adverse events after surgery can help the anesthesiologist for choosing the best anesthetic management to improve the outcome [2].

BNP is considered a risk marker in patients at risk for cardiac complications [15]. This study was designed to compare the effect of neuraxial blockade and general anesthesia on the release of BNP in patients at cardiac risk undergoing prostatectomy surgery.

The hypothesis of this study was based on that blocking nociceptive inputs by neuraxial anesthesia would decrease the release of BNP than general anesthesia in patients at cardiac risk undergoing prostatectomy surgery. It has been reported that the increased plasma level of BNP reflects the extent and severity of an ischemic insult and the degree of the left ventricular dysfunction even in the absence of myocyte necrosis [16].

In this study intra- and post-operative BNP levels in general anesthesia group of patients were significantly high when compared to the other two groups.

Previous studies found that the significantly higher plasma BNP concentration in general anesthesia group may be due to episodes of myocardial dysfunction and increased left ventricular wall stress as a result of transient myocardial ischemia [10].

The results of this study were similar to that obtained by Atalay et al. [1] who demonstrated that intra- and post-operative plasma concentrations of BNP were significantly lower in lumbar epidural group of patients when compared to the general anesthesia group.

Rodseth et al. [12] confirmed that the increased value of BNP in non surgical patient was considered a diagnostic and prognostic marker to detect asymptomatic myocardial ischemia without St segment elevation.

Mahla et al. [17] reported that the postoperative BNP values can provide additional prognostic information to the preoperative level.

Also, another study concluded that the change in BNP values pre- and postoperatively is considered the best detector of cardiac outcome [18].

The prognostic value of BNP in the acute coronary syndrome was determined by Delemos et al. [9] who concluded that a BNP level above 80 pg/ml indicate
high mortality or recurrent myocardial infarction than those with a level of \( \leq 80 \) pg/ml.

In the present study, there were no reported cases of death or patients having major cardiac events.

This result was in agreement with Maisel et al. [10] who reported that the accepted normal values for BNP was less than 100 pg/ml.

When there were no cardiac complications and death at pre-, intra- and postoperative periods, some investigators suggested that the cut-off point was neurohumoral [19]. Meanwhile, other studies demonstrated that the increased value of BNP may be a sign of reduced cardiac performance rather than structural myocardial damage [9, 20].

In the present study, there were no significant differences in the hemodynamic variables between the three groups. This may be due to incomplete sympathetic block as the level of the block was below T6. This is in agreement with Atalay et al. [1].

In this study, there were no significant changes in plasma concentration of epinephrine values in the three groups at the end of surgery and at 24 hours postoperatively when compared with baseline values. This result was supported by Pflug and Halter [21] who confirmed that the patient with low block had little or no change of catecholamine level compared with baseline values.

The lack of operative increase of the plasma concentration of epinephrine values in the general anesthesia group may be due to the inhibitory effect of halothane on the plasma level of epinephrine [21,22].

In this study, there was a significant increase of plasma concentration of norepinephrine in general anesthesia group of patients at the end of surgery when compared with the other two groups. These results were in accordance with Hak and Jae Kyu [23] who confirmed that the plasma norepinephrine value was increased during surgery in inhalation anesthesia group of patients but no changes of norepinephrine or epinephrine values, or mean arterial pressure in the patients receiving low spinal anesthesia.

The results of this study support the incompleteness of sympathetic blockade by spinal and epidural anesthesia as the level of anesthesia in our patients didn't reach above T6.

It had been reported that it is difficult to make a complete sympathetic block during epidural or spinal anesthesia when using the clinical doses of local anesthesia [24].

With respect to plasma concentrations of BNP, epinephrine and norepinephrine values at the end of surgery and at 24 hours postoperatively in this study, there were no significant differences between the spinal and epidural groups of patients when compared together. Similar results were obtained by Stevens et al. [25].

The postoperative cardiac complications in this study were minor and limited to a small number of patients among the three groups. This may be due to the stable cardiac conditions of patients and the short duration of the surgery.

In the present study, the general anesthesia group of patients had significantly higher BNP values which may explain the associated higher percentage of postoperative cardiac complications in this group of patients than the other two groups. Previous studies concluded that there was a significant relation between the elevated BNP level and the postoperative cardiac outcomes [26, 27,28]. Also, a meta-analysis by Karthikeyan et al. [2] demonstrated that the increased value of BNP was an indicator of adverse cardiac events within 30 days after non cardiac surgery.

This study had some limitations: the stable cardiac
condition of the patients and the small patient sample size were associated with a low number of adverse events and consequently low power of the statistical models.

In conclusion, the plasma BNP release was higher at the end of surgery and at 24 hours postoperatively in the general anesthesia group compared to spinal and epidural groups of patients at cardiac risk undergoing surgical prostatectomy. As neuraxial blockade may attenuate the release of BNP, it can be used safely in patients at cardiac risk undergoing non cardiac surgery. But, further studies with large surgical patients population at risk or had coronary artery diseases are required.

REFERENCES


