Spinal anesthesia reduces postoperative delirium in opium dependent patients undergoing coronary artery bypass grafting

O. TABATABAIE (*), N. MATIN (*), A. HEIDARI (**), A. TABATABAIE (***) and K. TABATABAIE (****)

Abstract : We investigated the effect of high spinal anesthesia on postoperative delirium in opium dependent patients undergoing coronary artery bypass grafting (CABG). The study was conducted in a tertiary referral university hospital on a population of 60 opium dependent patients undergoing CABG surgery. Patients were divided into two groups based on anesthesia protocol. One group were given general anesthesia (GA Group), the other group additionally received intrathecal morphine and bupivacaine (SGA Group). Postoperative delirium (POD) was defined as the main outcome of interest. Incidence of POD was significantly higher in patients of GA Group as compared with those in SGA Group (47% and 17% for GA and SGA respectively; P-value = 0.01). Time to extubation was on average 2.2 h shorter in SGA than in GA (7.1 h and 9.3 h respectively, P-value < 0.001). Intrathecal morphine and bupivacaine reduced the risk of POD after CABG in a population of opium dependent patients.

Key words : Coronary artery bypass grafting; opioid dependence; delirium; spinal anesthesia; intrathecal morphine; treatment outcome.

INTRODUCTION

Postoperative delirium (POD) is a dreaded complication of surgery especially coronary artery bypass grafting (CABG) (1-3) and is independently associated with increased mortality and morbidity in post cardiac surgery patients (4-6). Risk factors for POD include : advanced age, previous cerebrovascular accident (CVA), concomitant peripheral vascular disease, diabetes mellitus (DM), chronic renal failure, use of blood products after surgery, and extended length of intensive care unit stay (1, 6-10).

Postoperative pain is another important risk factor for POD (11, 12). Opioid drugs have traditionally been used for the control of pain in postoperative patients; however, opioids especially those given through an IV route, are associated with an increased risk of delirium, particularly when high doses are used, and in older patients (11, 13). This tradeoff often challenges the anesthesiologists in cardiac intensive care units (CICU), particularly if the patient is not opioid naïve (7, 14). Furthermore, opioid dependence itself is associated with an increased risk of POD in patient undergoing CABG (7, 15). Unfortunately, opioid dependence due to illicit drug abuse or chronic illnesses requiring long term opioid therapy has become a widespread problem. A recent study showed that UK, USA, Russia and Australia are especially suffering from illicit drug abuse (> 650 DALY per 100,000 of population) (16). In some parts of the world, a considerable proportion of patients undergoing CABG are opioid dependent (12-15%), with opium being the most frequently abused drug (17, 18).

Opioid sparing strategies such as concomitant use of regional anesthesia are well studied, but only in opioid naïve populations. Preoperative intrathecal morphine has been shown to reduce the amount of postoperative opioid consumption and enhance analgesia in patients undergoing CABG (19-22). Use of such measure to reduce the risk of postoperative delirium in the population of opioid tolerant

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patients is reasonable; however, to this date, no study has been done with this regard in cardiac surgery patients.

The aim of this study was to test the hypothesis that using a combination of spinal and general anesthesia, in opioid dependent patients undergoing CABG, would decrease their postoperative pain as well as opioid consumption, and thus reduce the incidence of postoperative delirium.

**Patients and methods**

This study was an observational retrospective study. The study setting was a tertiary referral University hospital. Two independent cardiac surgery teams operate at this center; however, the anesthesiologist is the same for both teams. Patients are referred to surgical teams by the hospital, so that equal number of patients is allocated to each team. One team implemented spinal anesthesia in addition to general anesthesia (SGA group), while the other team preferred general anesthesia only (GA group).

The study was approved by the Institutional Review Board (IRB). Study population consisted of patients who underwent cardiac surgery between August 2012 and January 2014. Inclusion criteria were opium dependence and elective first time CABG surgery. Opium dependence was defined as daily use of opium (via ingestion or inhalation) for the previous 12 months, tolerance to opium, and experiencing withdrawal symptoms with abstinence. Heroin abusers were not included in this study because of different and often more severe comorbidities caused by intravenous use of this drug. Since opium dependence was rare in our female patients, all participants were males.

Patients with CVA history, alcoholism, altered mental status before the surgery, any cardiac surgery other than CABG, as well as redo and off pump CABG surgeries were excluded (due to the small number of cases with those potentially confounding factors).

Sixty two patients met our inclusion criteria of whom two were excluded (one had a history of CVA and the other excluded patient had off pump CABG). Because patients were divided equally between the two surgical teams operating in the hospital, the resulting 60 patients had been serendipitously divided into two equal 30 patient groups, based on the implemented anesthesia protocol. Thirty patients were given spinal anesthesia in addition to general anesthesia (SGA Group), while the remaining 30 received only general anesthesia (GA Group).

As a part of the standard protocol of the hospital, patients were allowed to use opium while preparing for surgery in hospital (via ingestion only), but were instructed to discontinue their use 12 h before the procedure. Since the anesthesiologist for both groups was the same, anesthesia procedures were similar in both SGA and GA groups except for the use of spinal anesthesia. Premedication with intramuscular midazolam (5 mg) was administered 30 min before induction of anesthesia. Normal saline (15 mg/Kg) was given preoperatively. Patients in GA Group were given intravenous midazolam (0.15 mg/Kg), fentanyl (3 µg/Kg), sodium thiopental (3 mg/Kg) and atracurium (0.5 mg/Kg), while those in SGA Group received intrathecal bupivacaine (20 mg; 4 ml of 0.5% solution) and morphine (0.4 mg) before induction of anesthesia, using a 25 gauge needle in the sitting position. The bevel of the needle had cephalic orientation and the patients were put back to supine position immediately after the injection. Induction of general anesthesia was performed immediately after the intrathecal injection. Next, the operating table was tilted 15 degrees head down for ten minutes before returning to operating position, in order to achieve high spinal block. Continuous infusion of atracurium (0.4 mg/Kg/h), midazolam (0.1 mg/Kg/h) and fentanyl (2-6 µg/Kg/h) were used for maintenance of anesthesia. Systolic blood pressure was maintained between 90-110 mmHg throughout the procedure. Hypotension was anticipated in SGA group due to the sympathetic block and resulting systemic vasodilation, and was managed with norepinephrine infusion immediately (1-3 µg/min). Hypertension episodes during surgery were managed by bolus infusions of fentanyl (400 µg).

Standard cardiac monitoring was implemented for all patients. A left radial artery catheter was placed preoperatively for continuous monitoring of systemic blood pressure throughout and after surgery. A right subclavian central venous access was placed for central venous pressure monitoring. Electrocardiography (EKG) monitoring was performed during and after surgery. All patients were admitted to CICU after surgery. Patient postoperative pain was managed using intravenous morphine (2-5 mg) as circumstance arose (PRN). All data were recorded during and after surgery by the respective service provider, and were retrieved retrospectively for this study from medical records.

POD on the first three days after the surgery was considered as the main outcome of the study. Measurements were performed by an anesthesiologist each evening. Confusion assessment method
for intensive care unit (CAM-ICU) was used for measurement of POD (23, 24). Other variables of interest were: time to tracheal extubation, postoperative CVA, survival to hospital discharge, and postoperative myocardial infarction (MI). Postoperative MI was defined as EKG changes (new pathological Q-waves and/or new left bundle branch block) in the presence of rise of plasma troponin I levels above five times the upper limit of reference range during the first 72 hours after the surgery (25). Postoperative opioid consumption could not be measured reliably due to continued unrecorded opium use by the patients and suboptimal documentation of per required need administered doses of opioids.

Continuous variables were reported using means and standard deviations (SD), while categorical variables were described using frequencies and percent. Chi-square ($\chi^2$) and t-test analyses were performed for comparison of categorical and continuous variables respectively. Statistical Package of Social Science software (SPSS version 16, IBM, USA) was used for statistical analyses.

**RESULTS**

Age and other baseline characteristics of the study population for each group are shown in Table 1. Mean age was 65.3. No significant difference was observed between patients in GA and SGA groups regarding preoperative ejection fraction (EF) and past medical history.

Procedure-related determinants of postoperative delirium are presented in Table 2. Time to extubation was on average 2.2 h shorter in SGA than in GA (7.1 h and 9.3 h respectively, P-value < 0.001). Total intraoperative fentanyl consumption was significantly lower in SGA group as compared to GA (8 µg/Kg vs. 29 µg/Kg respectively; P-value < 0.001). Transient episodes of hypotension were significantly higher in SGA group and were managed with norepinephrine (9 vs. 2, respectively). Conversely, hypertension episodes were significantly more common in GA group as compared to SGA (8 vs. 1 respectively). Two patients in each group were reintubated after initial extubation.

Outcome variables are given in Table 3. Overall, 32% of patients experienced POD by the third postoperative day. Eighty-four % of POD cases were diagnosed on the first postoperative day. Incidence of POD was significantly higher in patients of GA Group as compared with those in SGA Group on the first postoperative day (40% and 13% for GA and SGA respectively; P-value = 0.02). Three patients died after the surgery, two in SGA Group and one in GA Group (6% vs. 3%, P-value = 0.55). Postoperative MI and CVA were not significantly different between groups. There was no case of spinal epidural hematoma.

**DISCUSSION**

To our knowledge, this is the first study to evaluate SGA and GA regarding the risk of POD, in opium dependent patients undergoing CABG.

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**Table 1**

Demographic characteristics and baseline risk factors of postoperative delirium

<table>
<thead>
<tr>
<th></th>
<th>SGA (n = 30)</th>
<th>GA (n = 30)</th>
<th>Total (n = 60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years*</td>
<td>65 (5.1)</td>
<td>65 (5.6)</td>
<td>65 (5.3)</td>
</tr>
<tr>
<td>Preoperative EF</td>
<td>42 (10.6)</td>
<td>40 (9.6)</td>
<td>41 (10.1)</td>
</tr>
<tr>
<td>DM*</td>
<td>10 (33%)</td>
<td>8 (26%)</td>
<td>18 (30%)</td>
</tr>
<tr>
<td>HTN*</td>
<td>7 (23%)</td>
<td>9 (30%)</td>
<td>16 (26%)</td>
</tr>
<tr>
<td>Smoking history*</td>
<td>20 (66%)</td>
<td>22 (73%)</td>
<td>42 (70%)</td>
</tr>
<tr>
<td>Male*</td>
<td>30 (100%)</td>
<td>30 (100%)</td>
<td>60 (100%)</td>
</tr>
<tr>
<td>Opium abuse</td>
<td>30 (100%)</td>
<td>30 (100%)</td>
<td>60 (100%)</td>
</tr>
<tr>
<td>Alcohol use</td>
<td>0</td>
<td>0</td>
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<td>CVA</td>
<td>0</td>
<td>0</td>
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<td>IDU</td>
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<td>0</td>
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<td>Off-pump surgery</td>
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* Categorical variables are presented by absolute number of patients and percentages in the parentheses. Continuous variables are given as means and standard deviations in the parentheses.

1 None of the variables approached statistical significance (p-value < 0.05).
POD incidence was high (40%) in patients who received GA. This is higher than results of most other studies. However, one study put that figure on 80% in opium dependent patients undergoing CABG, far above our outcome. Unlike the present study, Intensive Care Delirium Screening Checklist was used in that study for detection of delirium, which could explain the difference to some extent (15). Interestingly, the incidence rate was 13% for patients receiving SGA, which is comparable to rates of opioid naive patients undergoing CABG (2, 7, 26, 27).

This study shows that SGA reduces the incidence of POD in opium dependent patients undergoing CABG. Although the exact mechanism for POD itself is not yet fully understood, our findings are in line with the current understanding of the condition. Since poorly controlled pain as well as excessive opioid use to treat that pain are two well established precipitating factors for POD (9, 12, 13), it is possible, as suggested by the results of the present paper (Table 2), that patients in SGA group experience less pain and require lower doses of analgesics, intra- and postoperatively, which make them less likely to experience POD. This hypothesis is supported by other studies that state that intrathecal morphine leads to better pain management and less opioid use during and after CABG (19-21, 28).

The patients with known preoperative confounders of POD (such as CVA and alcoholism) were not included in the study to improve baseline comparability between groups (Table 1). Patient allocation by the hospital management could have improved baseline comparability as well. However, some of the surgical outcomes such as hypotension and hypertension episodes were different between the two groups. Nonetheless, cardio-pulmonary bypass time and operation time were similar (Table 2).

Our small sample size of 60 patients excluded the possibility of a multivariate analysis to adjust the effects of the intermediary factors of POD such as blood pressure and ET differences. Nevertheless, POD incidence was high (40%) in patients who received GA. This is higher than results of most other studies. However, one study put that figure on 80% in opium dependent patients undergoing CABG, far above our outcome. Unlike the present study, Intensive Care Delirium Screening Checklist was used in that study for detection of delirium, which could explain the difference to some extent (15). Interestingly, the incidence rate was 13% for patients receiving SGA, which is comparable to rates of opioid naive patients undergoing CABG (2, 7, 26, 27).

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This study has several limitations. The study population was comprised of only males. This was because of rarity of female opium dependent patients in our study population. This study does not take into consideration the amount of opium used by each patient. This was mainly due to unreliability of patients estimates regarding their opium consumption as well as the fact that opium is not a standard drug and its content cannot be assumed to be identical in different samples. A sample size of 60 patients may not be able to detect smaller effects especially uncommon outcomes such as mortality or CVA. Our small sample size also made confounder adjustment by multivariate analyses unfeasible. However, the most important known founders were excluded and the two groups were comparable in that regard. Nonetheless, like any other non-randomized study, we could not adjust for unknown confounders. That could only be done by proper randomization. Importantly, retrospective studies such as this one are inherently vulnerable to bias, especially treatment and selection biases. However, treatments in this study were based on surgical team (surgeon preference) and not the patients. Future prospective randomized clinical trials are highly recommended.

CONCLUSION

Incidence of POD is high in opium dependent patients after CABG. Intrathecal administration of bupivacaine and low dose morphine in opioid dependent patients undergoing CABG decreases the risk of POD and shortens time to extubation. Further randomized clinical trials are recommended to elucidate long term benefits and adverse effects of SGA in CABG, especially in opioid dependent patients.

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