Delirium associated with buprenorphine use in cardiac surgery: A retrospective cohort study

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ABSTRACT

Background and Aims: Delirium is defined as an acute disturbance in consciousness along with impaired thought processing and easy distraction. Buprenorphine is a mixed agonist–antagonist opioid analgesic. Few case reports have been published about the possible association between buprenorphine and delirium. The aim of this study was to look for an association between buprenorphine and postoperative delirium in patients undergoing off-pump coronary artery bypass grafting (CABG) surgery. Methods: Retrospective data from 100 cases of off-pump CABG were collected. The patients were divided into two groups (50 patients each). In group I, buprenorphine was used for postoperative analgesia. In group II, buprenorphine was not used for postoperative analgesia. Results: On post-operative day 0, there was no incidence of delirium in both groups. On post-operative days two and three, there was no incidence of delirium in group II, but a statistically significant incidence of delirium was seen in group I (P = 0.012, relative risk >1). The overall (all four days) incidence of delirium was higher in group I which was statistically significant (P = 0.006). The total number of delirium cases was seven (14%) in group I and out of the seven delirium cases, five patients (10%) had hyperactive delirium, and two patients (4%) had hypoactive delirium. Conclusion: Use of buprenorphine was associated with post-operative delirium, particularly of the hyperactive motoric subtype in off-pump CABG patients.

Key words: Aged, buprenorphine, coronary artery bypass off-pump, delirium, postoperative pain

INTRODUCTION

Delirium is defined as an acute disturbance in consciousness along with impaired thought processing and easy distraction.¹ There are three types of delirium: hyperactive, hypoactive and mixed.² Hyperactive delirium is the most easily recognised type. Hypoactive delirium is the most common type. Postoperative delirium is seen in 10% to 60% of patients, and the rate of occurrence is higher in elderly patients.³ The incidence of postoperative delirium is 50% to 67% in cardiac surgical patients.⁴ The cause of postoperative delirium in cardiac surgery patients is multifactorial. Delirium after cardiac surgery is associated with a prolonged hospital stay, increased morbidity and mortality. The pathophysiology of delirium is not entirely understood. Few studies have examined events in the perioperative period that may contribute to the occurrence of post-operative delirium.

Buprenorphine is a mixed agonist–antagonist opioid analgesic. It is more potent and longer-lasting than morphine. It is commonly used for the treatment of moderate to severe pain. Likewise, it is commonly used for post-operative analgesia in cardiac surgical patients in developing countries. Few case reports

How to cite this article: Selvaraj T, Thangavel P, Siddhaarth K. Delirium associated with buprenorphine use in cardiac surgery: A retrospective cohort study. Indian J Anaesth 2022;66:266-71.
are published about the possible association between buprenorphine and delirium.\textsuperscript{[5,6]}

This study aimed to look for an association between buprenorphine and postoperative delirium in cardiac surgical patients.

**METHODS**

The study was approved by the institutional human ethics committee. It was a retrospective study, conducted in a tertiary referral medical college hospital. Retrospective data from 100 off-pump CABG surgery cases, from May 2019 to April 2020, were collected. Data from four patients with psychiatric illnesses were excluded. Demographic variables such as age, gender, marital status and educational status were collected. Each group was further divided based on the level of education; above high school, high school or below high school. Other relevant pre-, intra- and post-operative data were also collected [Table 1]. The patients were divided into two groups (50 patients in each group). The preoperative interview typically occurred within less than 24 h before surgery in the preoperative clinic and included the assessment of depressive symptoms, medical history focusing on the central nervous system (CNS) status, assessment of cognitive status, pain and functional status. In all the patients, the routine hospital protocol of anaesthetic technique was followed. The anaesthetic technique used was general anaesthesia. The premedication was diazepam 10 mg, given orally on the night before surgery. Injection morphine 0.1 mg/kg intramuscularly was given one hour before the procedure. Anaesthesia was induced with injection thiopentone, and the trachea was intubated after achieving adequate muscle relaxation with the injection rocuronium.

Intravenous fentanyl infusion was used for intraoperative analgesia. Intravenous midazolam and isoflurane were used for maintenance of anaesthesia. All the patients were electively ventilated in the post-operative period. The trachea was extubated with reversal of neuromuscular blockade, after regaining consciousness. In both groups, fentanyl infusion (0.5 µg/kg/h) was used for postoperative analgesia. In group I, buprenorphine (0.3 mg, intramuscular) was used as a rescue agent for post-operative analgesia, till the third postoperative day. Buprenorphine was repeated, whenever the patient complained of postoperative pain with a visual analogue scale (VAS) score >3. In group II, buprenorphine was not used for postoperative analgesia; instead, the fentanyl infusion was increased if the patient complained of post-operative pain with VAS >3. This regimen was followed till the third postoperative day. The primary outcome of the study was to find out any association between buprenorphine and the occurrence of delirium. The confusion assessment method for the intensive care unit (CAM-ICU) was the tool used to assess delirium in this study. It is an adaptation of the confusion assessment method (CAM) which was originally developed to allow non-psychiatrists to assess delirium at the bedside. The secondary outcome

| Table 1: Pre-, intra- and post-operative patient data |
|---------------------------------------------------|
| **Pre-operative data** | **Intra-operative data** | **Post-operative data** |
| **Diagnosis** | **Blood and blood product usage** | **Atrial fibrillation** |
| **Type II DM** | **IABP usage** | **Cardiogenic shock** |
| **Hypertension** | **Atropine usage** | **IABP use** |
| **Alcoholism** | **Hypotension** | **Infection** |
| **Smoking** | **Operating time** | **Hypotension** |
| **Drug abuse** | **Duration of anaesthesia** | **Sleep disturbance** |
| **Stroke** | **Number of proximal anastomosis** | **Blood loss** |
| **Carotid disease** | **Inotropes used** | **Mechanical ventilation time** |
| **Redo CABG** | **Fluid balance** | **Duration of ICU stay** |
| **Any psychiatric illness** | **Benzodiazepine usage** | **Pain score (VAS scale)** |
| **Renal dysfunction** | **Lowest haematocrit** | **Use of buprenorphine** |
| **Ejection fraction** | | **Dose of buprenorphine** |
| **Cardiogenic shock** | | **ICU reintubation** |
| **Severity of PAH** | | |
| **Atrial fibrillation** | | |
| **Premedication** | | |
| **Dyspnoea on exertion** | | |
| **Emergency surgery** | | |
| **Oral narcotics** | | |
| **Use of vasoconstrictors** | | |
| **Serum bilirubin** | | |
| **Serum sodium** | | |
| **PaO\textsubscript{2} level** | | |
| **ASA physical status** | | |
| **Pain score (VAS scale)** | | |
| **CAM-ICU** | | |
| **RASS scale** | | |
| **Type of delirium** | | |
| **Fluid balance** | | |
| **Lowest haematocrit** | | |
| **Amount of fentanyl use** | | |
| **Use of buprenorphine** | | |
| **Recent MI** | | |

DM: Diabetes mellitus, CABG: Coronary artery bypass grafting, PAH: Pulmonary arterial hypertension, PaO\textsubscript{2}: Partial pressure of oxygen in arterial blood, ASA: American Society of Anesthesiologists, VAS: Visual analogue scale, CAM-ICU: Confusion assessment method for intensive care unit, RASS: Richmond agitation and sedation scale, COPD: Chronic obstructive pulmonary disease, MI: Myocardial infarction, IABP: Intra-Aortic Balloon Pump, ICU: Intensive care unit.
of the study was to assess the amount of fentanyl needed post-operatively and to compare the visual analogue pain scales between the groups. Independent t-test was used to assess the primary outcome. For secondary outcome, two-way repeated-measures analysis of variance (ANOVA) was applied.

**RESULTS**

Demographic variables such as age, gender and marital status were comparable between the groups [Table 2]. There was no statistical difference in education status between the two groups (P = 0.300). It was observed that the two groups were statistically similar with respect to selected background variables except for the incidence of intraoperative hypotension which was more in group II, the difference being statistically significant (P = 0.043) [Table 2].

On analysing surgery-related variables [Table 3], the duration of anaesthesia was higher in in group II than in group I (the mean difference was 21 minutes); the difference was statistically significant (P = 0.003). The duration of surgery was higher in group II than in group I; the difference was statistically significant (P = 0.001). The mean lowest haematocrit was higher in group I than in group II; the difference was statistically significant (P = 0.011). All other surgery-related variables were statistically similar in the two groups [Table 3]. On postoperative day 0, there was no incidence of delirium in both groups [Table 4]. On postoperative days two and three, there was no incidence of delirium in group II, but a statistically significant incidence of delirium was seen in group 1 (P = 0.012). The overall (all 4 days) incidence of delirium was higher in group I, which was statistically significant (P = 0.006) [Table 4]. The total number of delirium cases was 7 (14%) in group I. Out of seven delirium cases, five patients (10%) had hyperactive delirium, and two patients (4%) had hypoactive delirium.

There was a statistically significant difference in the Richmond Agitation and Sedation Scale scoring between the two groups on postoperative days one and two (P = 0.00) [Table 5].

During the intraoperative period, the mean dose of fentanyl used in group I was 988 µg and in group II it was 1013 µg. The difference was not significant statistically (P = 0.531). In the postoperative period (first 96), the mean difference between the two groups in terms of fentanyl use was 251 µg (group I-1150 µg, group II-1401 µg). The average amount of buprenorphine used in group I was 1.152 mg.

The pain level on postoperative days one, two and three were analysed between the groups [Table 6]. The mean difference in pain score was 0.52 for the first postoperative day, 0.50 for the second postoperative day and 0.40 for the third postoperative day. The pain level was significantly different for the two groups (P - 0.001). Those who did not receive buprenorphine, suffered more pain compared to those who received buprenorphine. In both groups, the pain level was significantly reduced from day one to day

**Table 2: Distribution of respondents by group and selected background variables**

| Variables | Group I | Group II | P |
|-----------|---------|----------|---|
| Sex-Male | Number | Number | 0.134 |
| Age ≤50 years | 43 | 37 |
| (Range - 33-77 years) | 16 | 13 | 0.509 |
| Diagnosis | SVD | 2 | 1 | 0.841 |
| | DVD | 11 | 11 |
| | TVD | 37 | 38 |
| | Diabetics | 31 | 28 | 0.542 |
| | Hypertension | 23 | 28 | 0.317 |
| | Stroke | 2 | 5 | 0.240 |
| | Carotid disease | 6 | 8 | 0.564 |
| | History of cardiac surgery | 1 | 2 | 0.558 |
| | Renal dysfunction | 6 | 3 | 0.295 |
| | EF <30% | 3 | 5 | 0.461 |
| | Cardiogenic shock | 2 | 2 | - |
| | Severe PAH | 4 | 4 | - |
| | Preoperative AF | 2 | 3 | 0.646 |
| | Pre medication | 46 | 48 | 0.400 |
| | NYHA >3 | 9 | 7 | 0.585 |
| | Emergency surgery | 2 | 1 | 0.558 |
| | Narcotic oral | 1 | 1 | - |
| | Vasopressors | 12 | 6 | 0.118 |
| | Blood transfusion | 7 | 4 | 0.338 |
| | Post-operative AF | 11 | 13 | 0.640 |
| | Post-operative cardiogenic shock | 1 | 0 | 0.315 |
| | IABP | 1 | 0 | 0.315 |
| | Post-operative infection | 3 | 2 | 0.646 |
| | High serum bilirubin | 2 | 0 | 0.153 |
| | Atropine use | 3 | 0 | 0.079 |
| | Sodium | 47 | 49 | 0.307 |
| | PO2 <80 mmHg | 7 | 5 | 0.538 |
| | Post-operative Hypotension | 10 | 12 | 0.629 |
| | Intra-operative Hypotension | 16 | 26 | 0.043 |
| | Sleep disturbance | 7 | 10 | 0.424 |
| | ASA physical status | 44 | 45 | 0.749 |

SVD: Single Vessel Disease, DVD: Double Vessel Disease, TVD: Triple Vessel Disease, EF: Ejection Fraction, PAH: Pulmonary arterial hypertension, AF: Atrial fibrillation, NYHA: New York Heart Association, IABP: Intra-aortic balloon pump, PO2: partial pressure of oxygen, Hypotension: systolic <90 mmHg or diastolic<60 mmHg, ASA: American Society of Anesthesiologists
three [Table 6]. The results clearly indicate that the pain levels were influenced by the drug alone, namely buprenorphine and not by other significant variables in the study.

**DISCUSSION**

Our study demonstrated that the incidence of delirium, particularly, of the hyperactive motoric subtype was higher in the group that received buprenorphine. The postoperative pain level was less in the buprenorphine group as compared with the group that did not receive buprenorphine.

Buprenorphine, a semisynthetic derivative of thebaine, is a partial agonist at μ-receptor and a potent κ-receptor antagonist. The safety and side effects of buprenorphine are well studied. The most frequently reported side effect is sedation. Less than 1% patients had CNS side effects. The slower rate of dissociation of buprenorphine from the receptors may account for its prolonged duration of action.  

In delirium, the patient’s ability to receive information, store, recall and judge are disturbed. Inattention is a characteristic finding in delirium. The gold standard method for diagnosing delirium is psychiatric evaluation using diagnostic and statistical manual of mental disorders-V (DSM-V) criteria. Delirium can be reliably diagnosed by non-psychiatrists, with the use of validated monitoring instruments like CAM-ICU. There is also a huge divergence in risk factors for delirium and the actual incidence across the populations. Post-operative delirium is common in geriatric patients. The use of chemical restraints like benzodiazepines or physical restraints would lead to an increased incidence of delirium. Early recognition of delirium and its prevention is important as delirium correlates with increased length of hospital stay, increased morbidity and mortality, and impaired cognitive and functional recovery. Post-operative delirium is a frequent condition after cardiac surgery with a reported incidence between

| Table 3: Mean and standard deviation of surgery-related variables - groupwise |
|-------------------------------------------------|-----|-----|-----|-----|
| Variables                                      | Group I | Group II | P   |
| Duration of anaesthesia (minutes)              | 188.32 ± 31.419 | 209.30 ± 37.176 | 0.003 |
| Duration of Surgery (minutes)                  | 162.78 ± 29.884 | 185.94 ± 35.993 | 0.001 |
| Midazolam use in milligrams                    | 5.02 ± 0.979  | 5.12 ± 1.256   | 0.658 |
| Low HCT in %                                   | 33.08 ± 4.309 | 31.10 ± 3.209  | 0.011 |
| ICU stay in days                               | 3.26 ± 0.600  | 3.42 ± 0.673   | 0.212 |
| Blood loss in mL                               | 294.80 ± 150.662 | 274.00 ± 119.966 | 0.790 |
| Postoperative ventilation time (minutes)       | 203.44 ± 51.285 | 246.62 ± 213.689 | 0.127 |

SD: Standard deviation; HCT: Haematocrit, ICU: Intensive care unit

| Table 4: CAM-ICU status on postoperative days one, two and three |
|---------------------------------------------------------------|-----|-----|-----|
| Variables                                                    | Group I | Group II | P   |
| Postoperative day one                                        | 6    | 0    | 0.012 |
| Postoperative day two                                        | 6    | 0    | 0.012 |
| Postoperative day three                                      | 1    | 0    | 0.315 |
| overall                                                      | 7    | 0    | 0.006 |

CAM-ICU: Confusion assessment method for intensive care unit

| Table 5: RASS status on postoperative days one, two and three - group wise |
|-------------------------------|-----|-----|-----|
| Variables                      | Group I | Group II | P   |
| Postoperative day one          | 4+   | 1    | 0    | 0.000 |
|                               | 3+   | 4    | 0    |
|                               | 1+   | 1    | 0    |
|                               | 0    | 0    | 2    |
|                               | -1   | 11   | 34   |
|                               | -2   | 20   | 14   |
|                               | -3   | 13   | 0    |
| Postoperative day two          | 2+   | 4    | 0    | 0.000 |
|                               | 0    | 15   | 42   |
|                               | -1   | 20   | 8    |
|                               | -2   | 11   | 0    |
| Postoperative day three        | 1+   | 2    | 0    | 0.153 |
|                               | 0    | 48   | 50   |

RASS: Richmond agitation and sedation scale

| Table 6: Mean and standard deviation of pain level on postoperative days one, two and three-groupwise |
|-------------------------------------------------|-----|-----|-----|
| Variables                                      | Group I | Group II | ANOVA repeated measures test result |
| Mean SD                                       | Group I | Group II | Source | P   |
| Postoperative day one                         | 3.40 ± 1.552 | 3.92 ± 1.209 | Between 0.001 Subjects |
| Postoperative day two                         | 1.66 ± 0.717 | 2.16 ± 0.548 | Subjects |
| Postoperative day three                       | 0.94 ± 0.240 | 1.34 ± 0.479 | Within 0.000 Subjects |
3% and 31%. Postoperative delirium is more frequent in patients with more complicated operative and post-operative courses. Cardiac patients developing post-operative delirium may have post-operative respiratory insufficiency and high prevalence of sternal instability and a need for revision surgery. The development of post-operative delirium is associated with a greater degree of cognitive decline 1 month after cardiac surgery. 

Rarely, delirium has been reported as a feature of opioid withdrawal. Subsyndromal delirium typically describes patients in whom many signs are present, but not all diagnostic criteria are met. Pain and pain management strategies are important factors related to the development of delirium in elderly patients. 

Hypoactive motoric subtype is the more common type, is often underdiagnosed, and has been associated with worse outcomes. Hypoactive delirium is unrecognised in 75% of patients in the absence of standardised assessment. Withdrawal, flat affect, apathy, lethargy and decreased responsiveness are the features of hypoactive delirium. Hyperactive motoric subtype is easily diagnosable. In the current study, the patients who developed hyperactive delirium were tachycardic, tachypnoeic, hypertensive, fearful, agitated, restless and confused. The patients had irrelevant, pressured speech, were disoriented to time, place and person and were extremely combative. The hyperactive delirium may be explained by the possible excitatory or disinhibitory effect of buprenorphine on extrapyramidal and limbic systems. The possible mechanisms need to be further studied.

The patients undergoing valve surgery with or without CABG surgery have a higher incidence of post-operative delirium and cognitive dysfunction, one week after surgery compared with those undergoing CABG alone. The reason for this observation may be related to air embolism during the valve procedure. Aortic atherosclerosis increases the risk of cerebral embolisation, particularly during intraoperative ascending aortic manipulation, which is common during valve or on-pump CABG. Avoidance of cardiopulmonary bypass might be the reason behind the low incidence of post-operative delirium in our study as compared with on-pump CABG cases. The current study examined the presence of delirium in the early post-operative period, whereas others have examined the occurrence of delirium in the later period. The timing of the assessment of delirium may also have accounted for the lower incidence in our study. Nevertheless, in the current study, a specific medication (buprenorphine) was found related to the development of hyperactive post-operative delirium in the study participants. Hallucinations have also been reported with epidural and sublingual administration of buprenorphine. 

Several authors have reported that dexmedetomidine sedation reduces the incidence of postoperative delirium as compared with propofol. There are no validated confirmatory electro physiological, laboratory or imaging tests for delirium. A study identified similarities in the electroencephalography (EEG) pattern associated with various encephalopathies and postoperative delirium. EEG is a potential tool for the diagnosis and monitoring of postoperative delirium. Postoperative delirium is associated with abnormal patterns of functional and directional connectivity in EEG. Van Dellen et al. concluded that postoperative delirium may be classified as a disconnection syndrome. A study found that patients developing postoperative delirium had a greater decline in intraoperative serum brain-derived neurotropic factor (BDNF) concentrations from the baseline value. The extent of the decline in BDNF correlated with the severity of postoperative delirium. Several studies suggested that postoperative delirium may be a risk factor for non-resolving minor and even major neuro-cognitive dysfunction. Sprung et al. found a significant association between postoperative delirium and persistent neurocognitive disorders at a median follow-up of 9 months.

The limitations of the current study were the retrospective design, lack of randomisation, selection bias, small sample size and the fact that the study was conducted in a single hospital setting. Additionally, postoperative nausea and vomiting were not evaluated, delirium assessment was done only once per day and because of the fluctuating nature of delirium, the prevalence of delirium might have been underestimated.

CONCLUSION

The use of buprenorphine in off-pump CABG patients is associated with postoperative delirium, particularly of the hyperactive motoric subtype. Routine utilisation of delirium rating scales and checklists can increase the percentage of recognition and ensure a better initiation of early treatment.
Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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