Original Article

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

Address for correspondence:
Dr. Thiruvenkadam Selvaraj, Department of Anaesthesiology, Karpagam Faculty of Medical Sciences and Research, Coimbatore - 641 032, Tamil Nadu, India.
E-mail: mail2drthiru@gmail.com

Submitted: 23-Aug-2021
Revised: 11-Mar-2022
Accepted: 28-Mar-2022
Published: 20-Apr-2022

Access this article online
Website: www.ijaweb.org
DOI: 10.4103/ija.ija_780_21
Quick response code

Thiruvenkadam Selvaraj, Periyasamy Thangavel[1], Siddhaarth K[2]
Department of Anaesthesiology, Karpagam Faculty of Medical Sciences and Research, Coimbatore, Tamil Nadu, [1]Department of Cardiovascular and Thoracic Surgery, Sri Ramachandra Medical Centre, Chennai, Tamil Nadu, [2]Department of General Medicine, Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Sciences, Wardha, Maharastra, India

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.[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	CAM-ICU
Ejection fraction		RASS scale
Cardiogenic shock		Type of delirium
Severity of PAH		Fluid balance
Atrial fibrillation		Lowest haematocrit
Premedication		Amount of fentanyl use
Dyspnoea on exertion		Use of buprenorphine
Emergency surgery		Dose of buprenorphine
Oral narcotics		ICU reintubation
Use of vasoconstrictors		
Serum bilirubin		
Serum sodium		
PaO_2 level		
ASA physical status		
Pain score (VAS scale)		
CAM-ICU		
RASS scale		
COPD		
Recent MI		

DM: Diabetes mellitus, CABG: Coronary artery bypass grafting, PAH: Pulmonary arterial hypertension, PaO_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].

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

Variables	Group I Number	Group II Number	*P*
Sex-Male	43	37	0.134
Age ≤50 years (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
Atrophine use	3	0	0.079
Sodium	47	49	0.307
PO_2 <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, PO_2: partial pressure of oxygen, Hypotension: systolic <90 mmHg or diastolic<60 mmHg, ASA: American Society of Anesthesiologists

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 3: Mean and standard deviation of surgery-related variables - groupwise

Variables	Group I		Group II		*P*
	Mean	SD	Mean	SD	
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 No.	Group II No.	*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 Number	Group II Number	*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	Mean	SD	Source	*P*
Postoperative day one	3.40	1.552	3.92	1.209	Between Subjects	0.001
Postoperative day two	1.66	0.717	2.16	0.548		
Postoperative day three	0.94	0.240	1.34	0.479		
					Within Subjects	0.000

SD: Standard deviation; ANOVA: Analysis of variance

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.[7]

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.[8] Delirium can be reliably diagnosed by non-psychiatrists, with the use of validated monitoring instruments like CAM-ICU.[9] 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.[10] Post-operative delirium is a frequent condition after cardiac surgery with a reported incidence between

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.[11] Rarely, delirium has been reported as a feature of opioid withdrawal.[12] Subsyndromal delirium typically describes patients in whom many signs are present, but not all diagnostic criteria are met.[13] 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.[14] 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.[15] 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.[11] 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.[4] 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.[16,17] A study found that meperidine was related to the development of postoperative delirium.[18] Several authors have reported that dexmedetomidine sedation reduces the incidence of postoperative delirium as compared with propofol.[19,20]

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.[21] 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.[22] Van Dellen *et al.*[22] 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.[23] 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.*[24] 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.

REFERENCES

1. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, *et al*. Delirium in mechanically ventilated patients: Validity and reliability of the confusion assessment method for the Intensive Care Unit (CAM-ICU). JAMA 2001;286:2703–10.
2. Albrecht JS, Marcantonio ER, Roffey DM, Orwig D, Magaziner J, Terrin M, *et al*. Stability of postoperative delirium psychomotor subtypes in individuals with hip fracture. J Am Geriatr Soc 2015;63:970-6.
3. Parikh SS, Chung F. Postoperative delirium in the elderly. Anesth Analg 1995;80:1223-32.
4. van der Mast RC, Roest FH. Delirium after cardiac surgery: A critical review. J Psychosom Res 1996;41:13–30.
5. Kaptsan A, Telias D. Delirium due to buprenorphine therapy. Am J Case Rep 2003;4:182-5.
5. Saddichha S, Subodh BN, Chand PK. Sublingual buprenorphine-induced psychomimetic effects. Am J Ther 2016;23:e242-3.
6. Slooter AJC. Delirium, what's in a name? Br J Anaesth 2017;119:283–5.
7. Ture P, Ramaswamy AH, Shaikh SI, Alur JB, Ture AV. Comparative evaluation of anaesthetic efficacy and haemodynamic effects of a combination of isobaric bupivacaine with buprenorphine vs. isobaric levobupivacaine with buprenorphine for spinal anaesthesia - A double blinded randomised clinical trial. Indian J Anaesth 2019;63:49-54.
8. Lawlor PG, Bush SH. Delirium diagnosis, screening and management. Curr Opin Support Palliat Care 2014;8:286-95.
9. Grover S, Kate N. Assessment scales for delirium: A review. World J Psychiatry 2012;2:58-70.
10. Oh ES, Fong TG, Hshieh TT, Inouye SK. Delirium in older persons: Advances in diagnosis and treatment. JAMA 2017;318:1161-74.
11. Brown CH 4th, Probert J, Healy R, Parish M, Nomura Y, Yamaguchi A, *et al*. Cognitive decline after delirium in patients undergoing cardiac surgery. Anesthesiology 2018;129:406–16.
12. Das S, Sah D, Nandi S, Das P. Opioid withdrawal presenting as delirium and role of buprenorphine: A case series. Indian J Psychol Med 2017;39:665-7.
13. Serafim RB, Soares M, Bozza FA, Lapa E Silva JR, Dal-Pazzol F, Paulino MC, *et al*. Outcomes of subsyndromal delirium in ICU: A systematic review and meta-analysis. Crit Care 2017;21:179.
14. Ali S, Patel M, Jabeen S, Bailey RK, Patel T, Shahid M, *et al*. Insight into delirium. Innov Clin Neurosci 2011;8:25-34.
15. Hudetz JA, Iqbal Z, Gandhi SD, Patterson KM, Byrne AJ, Pagel PS. Postoperative delirium and short-term cognitive dysfunction occur more frequently in patients undergoing valve surgery with or without coronary artery bypass graft surgery compared with coronary artery bypass graft surgery alone: Results of a pilot study. J Cardiothorac Vasc Anesth 2011;25:811-6.
16. MacEvilly M, O'Carroll C. Hallucinations after epidural buprenorphine. BMJ 1989;298:928-9.
17. Paraskevaides EC. Near fatal auditory hallucinations after buprenorphine. Br Med J (Clin Res Ed) 1988;296:214
18. Marcantonio ER, Juarez G, Goldman L, Mangione CM, Ludwig LE, Lind L, *et al*. The relationship of postoperative delirium with psychoactive medications. JAMA 1994;272:1518–22.
19. Djaiani G, Silverton N, Fedorko L, Carroll J, Styra R, Rao V, *et al*. Dexmedetomidine versus propofol sedation reduces delirium after cardiac surgery: A randomized controlled trial. Anesthesiology 2016;124:362-8.
20. Chawdhary AA, Kulkarni A, Nozari A. Substitution of propofol for dexmedetomidine in the anaesthetic regimen does not ameliorate the post-operative cognitive decline in elderly patients. Indian J Anaesth 2020;64:880-6.
21. Palanca BJA, Wildes TS, Ju YS, Ching S, Avidan MS. Electroencephalography and delirium in the postoperative period. Br J Anaesth 2017;119:294-307.
22. van Dellen E, van der Kooi AW, Numan T, Koek HL, Klijn FA, Buijsrogge MP, *et al*. Decreased functional connectivity and disturbed directionality of information flow in the electroencephalography of intensive care unit patients with delirium after cardiac surgery. Anesthesiology 2014;12:328-35.
23. Wyrobek J, LaFlam A, Max L, Tian J, Neufeld KJ, Kebaish KM, *et al*. Association of intraoperative changes in brain-derived neurotrophic factor and postoperative delirium in older adults. Br J Anaesth 2017;119:324-32.
24. Sprung J, Roberts RO, Weingarten TN, Nunes Cavalcante A, Knopman DS, Petersen RC, *et al*. Postoperative delirium in elderly patients is associated with subsequent cognitive impairment. Br J Anaesth 2017;119:316-23.