Original Article

Impact of Ketamine versus Propofol for Anesthetic Induction on Cognitive Dysfunction, Delirium, and Acute Kidney Injury Following Cardiac Surgery in Elderly, High-Risk Patients

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ABSTRACT

Objective: Evaluate the effects of ketamine versus propofol when used for induction of anesthesia in elderly, high-risk cardiac surgical patients on postoperative complications including cognitive dysfunction, delirium, and acute kidney injury.

Methods: Prospective, randomized study performed at a tertiary medical center. A total of 52 patients aged 70 and older presenting for complex cardiac surgery were randomized to receive either ketamine or propofol for induction of anesthesia. Patients underwent a battery of cognitive testing preoperatively and postoperatively and the incidence of delirium and acute kidney injury were measured. Norepinephrine (NEE) equivalents following induction were assessed for each group.

Results: A total of 49 patients were included, 25 in the ketamine group and 24 in the propofol group with 3 patients excluded from the analysis. No difference was found between groups in either postoperative cognitive dysfunction or delirium incidence. Acute kidney injury occurred in 6 (24%) patients in the ketamine group in 12 (50%) patients in the propofol group, but the difference did not meet statistical significance ($P = 0.08$; Relative Risk = 2.1, 95% CI 0.9–4.7). NEE equivalents were lower in the ketamine group, 9.6 ± 22.2 versus 32.7 ± 46.0, $P < 0.03$.

Conclusions: The use of ketamine versus propofol for induction of anesthesia did not impact the incidence of postoperative cognitive dysfunction or delirium. Twice as many patients in the propofol group developed acute kidney injury, although not reaching statistical significance and warranting further investigation. In elderly, high-risk patients, ketamine was associated with a significantly reduced need for vasopressor support following induction.

Keywords: Acute kidney injury, cardiac surgery, delirium, ketamine, postoperative cognitive dysfunction

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INTRODUCTION

Ketamine is a Food and Drug Administration (FDA)-approved non-barbiturate anesthetic and acts as an N-methyl-D-aspartate receptor antagonist. This medication is commonly used in the induction of anesthesia as well as in the performance of sedation for procedures. While ketamine has been shown to have potentially beneficial properties as a postoperative sedative agent in the cardiac surgical population,[1] very little data

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exists comparing ketamine to propofol for induction of anesthesia in these patients. One study examined the use of ketamine versus propofol for anesthetic induction and demonstrated increased peri-induction hemodynamic stability in patients receiving ketamine compared to propofol, but postoperative outcomes were not assessed.[2] Additionally, ketamine has been demonstrated in several studies to have anti-inflammatory effects including in cardiac surgical patients.[3] Elevations in inflammatory mediators associated with cardiac surgery and cardiopulmonary bypass (CBP) have been implicated in ventricular wall motion abnormalities, delirium, postoperative hemodynamic instability, postoperative cognitive dysfunction (POCD), and renal dysfunction.[3-6] Aside from anti-inflammatory effects, ketamine has also been shown to have a positive impact on the reduction of neurologic injury after an ischemic or traumatic event.[7,8] This study was performed to test the hypothesis that the anti-inflammatory or neuroprotective effects of ketamine may result in a reduced incidence of cognitive dysfunction, delirium, and acute kidney injury after cardiac surgery in addition to increased hemodynamic stability following induction.

METHODS

Institutional review board (IRB) approval was obtained for the study design, July 2015, and written informed consent was obtained from each patient. This study was registered at ClinicalTrials.gov (NCT02554253). The primary outcomes of interest were the incidence of postoperative cognitive dysfunction, delirium, and acute kidney injury. Inclusion criteria were ≥70 years of age and older with the need for complex cardiac surgery at our tertiary care center. Complex cardiac surgery was defined as surgery involving more than one heart valve, redo sternotomy procedures, or combined valvular and Coronary artery bypass grafting (CABG) procedures. These criteria select patients at higher risk of developing the outcomes of interest. Exclusion criteria included left or right ventricular assist device implantation or explantation, procedures not requiring CBP, active infection or sepsis, severe hepatic disease or ascites, preoperative renal dysfunction including a baseline creatinine ≥1.5 mg/dL or requiring dialysis, immunosuppressive medication use (including steroid use), immunodeficiency syndrome, known neurologic or psychiatric disorder, or use of drugs for psychosis.

Randomization to the study group (ketamine or propofol) occurred on the morning of surgery via delivery of a sealed envelope by a member of the study staff who was not directly involved with patient care. Patients randomized to the ketamine group received 1–2 mg/kg of intravenous ketamine for induction of anesthesia and patients randomized to the propofol group received 0.5–1 mg/kg of intravenous propofol for induction of anesthesia with additional medication administered as needed to achieve intubating conditions. The anesthesiologist was not blinded to the anesthetic agent. Inhalation anesthetic for induction in combination with either propofol or ketamine was permitted as well as the administration of opioid and muscle relaxants. The remainder of the anesthetic was as per institutional routine including a maximal fentanyl bolus dosing of 10 μg/kg and maintenance with isoflurane. Benzodiazepines were not administered. Dexmedetomidine was started as an infusion at sternal closure for patient transfer to the intensive care unit (ICU) and ICU sedation as per our standard practice, dose 0.5–1.5 mcg/kg/hr. On CPB flow was maintained to provide a cardiac index ≥2.4 L/min/m^2. Vasopressor support prebypass and on CPB was provided with boluses of phenylephrine, ephedrine, or vasopressin and norepinephrine as an infusion. Other aspects of patient care were as per routine.

Baseline cognitive assessment included evaluation of immediate and delayed verbal memory, cognitive speed and flexibility, verbal fluency, executive management of attention, and overall function. Tests were administered by a professional psychometrist before the day of surgery and included: Trail Making Test A and B, the Mini-Mental State Examination, Hopkins Verbal Learning Test-Revised (forms 1 and 2), Digit Span from the Wechsler Adult Intelligence Test-III, Controlled Oral Word Association, and the Stroop Color and Word Test.

The Confusion Assessment Method (CAM) score was recorded every 12 h postoperatively as per routine. Before hospital discharge, the patient underwent the second round of cognitive function studies. After inclusion in the study, demographic and medical data was recorded. The primary outcomes included incidence of delirium, POCD, and Acute kidney injury (AKI) as defined by Kidney Disease Improving Global Outcomes criteria. The secondary outcome included hemodynamic change from baseline as assessed by the total dose of vasopressor required in the first 10 min following induction and expressed in NEE equivalents.[9,10]

Statistical analysis

The incidence of delirium after cardiac surgery has been reported over a broad range of up to 52%.[5,11,12] Ketamine was previously shown to reduce the incidence of delirium in cardiac surgery patients from 31 to 3%.[11] The inclusion criteria are designed to include patients at the highest

incidence (50%) and assuming a more conservative reduction in the incidence of delirium to approximately 12%, a sample size of 44 patients would be required. Additionally, a study of POCD demonstrated a reduction from 81% in the placebo group to 27% in the ketamine group.[6] Again using a more conservative reduction from 70 to 30% would require 46 patients. Using these estimates, a study of 52 patients was planned, 26 in each group.

Data are summarized using mean ± standard deviation (SD) for continuous variables and frequency counts and percentages for categorical variables with comparisons between groups performed using the two-sample *t*-test and Chi-square test, respectively. The incidence of AKI was compared between groups using Fisher's exact test. For the neurocognitive tests, raw scores were converted to z-scores using published references.[13-18] For each neurocognitive test, the within-group change from baseline was compared to zero using the one-sample *t*-test, and the mean change from baseline was compared between groups using the two-sample *t*-test. The percentage of patients experiencing a decline of >1 SD was compared between groups using Fisher's exact test. The outcome of POCD was defined a-priori as a decline of >1 SD (i.e. z-score decline of >1) on at least 2 neurocognitive tests and was compared between groups using Fisher's exact test. In all cases, two-tailed *P* values are reported. For the comparison of AKI and total NEE equivalents, a *P* value <0.05 was considered statistically significant. Given the number of secondary outcomes, a *P* value of <0.01 was considered statistically significant for all other comparisons.

RESULTS

Fifty-two subjects were enrolled in the study between August 2015 and October 2019 and randomized to either the ketamine or propofol groups. Three were excluded from the analysis; one due to receipt of both ketamine and propofol intraoperatively, one found to be ineligible after enrollment, and one was converted to a transcatheter valve procedure after enrollment [Figure 1]. The patient and procedural characteristics can be found in Table 1 and were similar between the study groups. Neurocognitive testing results are summarized in Table 2. Success in neurocognitive testing was defined as completing postoperative testing without missing more than one test and 88% of patients met this benchmark. For both treatment groups, a significant decline from preoperative to postoperative testing was observed for many of the cognitive tests. However, the difference between groups, in either mean change from baseline, or in the percentage of patients experiencing a decline of >1 SD, did not meet the criteria for statistical significance for any test. From an analysis that was restricted to subjects who were missing no more than one neurocognitive test (N = 22 ketamine, N = 21 Propofol), the percentage of subjects who met the criteria for POCD (i.e. decline >1 SD on 2 or more tests) was not found to differ significantly between groups (64 vs. 43% for ketamine vs. propofol, Fisher's exact test P = 0.23). Only 1 patient (in the propofol group) had a positive postoperative CAM score indicating delirium. More subjects in the propofol group (12 out of 24; 50%) developed AKI compared with the ketamine group (6 out of 25; 24%), but this difference failed to meet statistical significance (Fisher's exact test P = 0.08; Relative Risk = 2.1, 95% CI 0.9–4.7).

Table 1: Patient and procedural characteristics*

	Ketamine (n=25)	Propofol (n=24)	*P*
Age, years	76.4±3.5	76.1±5.3	0.81
Sex			0.68
Male	16 (64)	14 (58)	
Female	9 (36)	10 (42)	
Body Mass Index, kg/m^2	28.3±4.7	30.7±7.1	0.18
ASA status			0.19
III	13 (52)	8 (33)	
IV	12 (48)	16 (67)	
Anesthesia duration, min	396±102	426±90	0.28
CBP duration, min	111±39	117±48	0.59
Aortic cross-clamp duration†, min	85±34	87±36	0.84

ASA=American Society of Anesthesiologists; CPB=Cardiopulmonary bypass; Min=minute; N=number.*Continuous variables are summarized using mean±SD and compared between groups using the two-sample *t*-test. Categorical variables are summarized using *n* (%) and compared between groups using the Chi-square test. †There were two patients (both in the ketamine group) who did not have aortic cross-clamp

In the ketamine group, seven patients (28%) required vasopressor support versus 14 in the propofol group (58%), P = 0.03. NEE equivalents were calculated for all patients, and the ketamine group required significantly less total vasopressor dose postinduction, 9.6 mcg ± 22.2 compared to 32.7 mcg ± 46.0, P < 0.03 [Table 3].

DISCUSSION

POCD is common following cardiac surgery with causes that are likely multifactorial. Inflammation, cerebral ischemia (whether micro-embolic or flow related), and hypoxemia have all been postulated to contribute to the development of POCD.[19] Pre- and postoperative cognitive testing in this high-risk population was successful with postoperative testing completed in 88% of patients. Many interventions have been attempted to improve POCD including pharmacologic agents (lidocaine, steroids), maintaining high mean arterial pressure, and optimizing cerebral oxygen delivery with the use of cerebral oximetry,

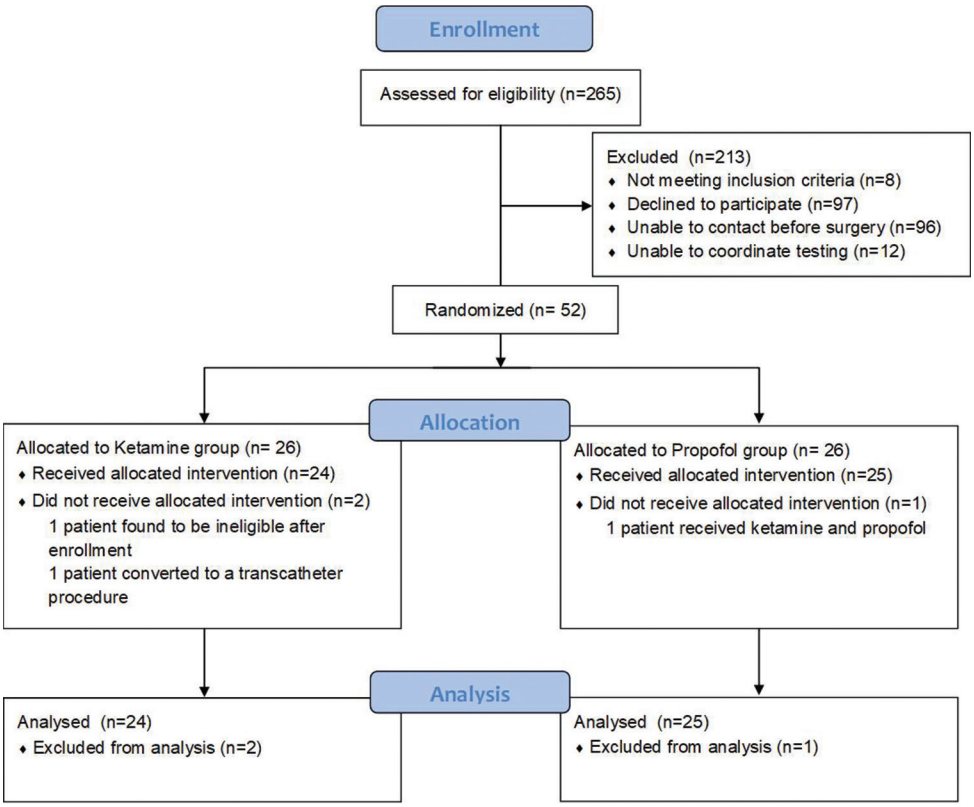


Figure 1: CONSORT flow diagram demonstrating the course of patient enrollment and progression through the study

transfusion of red blood cells, and adjustment of CBP flows. These interventions have demonstrated mixed results with pharmacologic interventions being largely ineffective.[19,20] Ketamine has shown promise in acute neurologic injury; however, there is limited data on POCD. In this study, patients at very high risk of postoperative complications were included, specifically those undergoing multi-valvular and complex cardiac procedures with advanced-stage disease. The current study did not find a difference in POCD as defined by the decline of >1 SD on at least 2 neurocognitive tests in the ketamine versus propofol groups. This differs from the study by Hudetz *et al*.[6] which demonstrated a significant reduction in POCD in cardiac surgical patients after receiving 0.5 mg/kg of intravenous ketamine on induction of anesthesia. Despite similar sized intervention groups and similar ketamine dose, the present study differed from the Hudetz study in the battery of cognitive testing performed. Our choice of testing was based on the recommendations taken from the Statement on Consensus on Assessment of Neurobehavioral Outcomes After Cardiac Surgery.[21] A systematic review by Rudolph *et al*.[22] looked at testing for POCD after cardiac surgery and the adherence with the 1995 Consensus Statement, finding that studies differed widely on not only testing used but the interpretation of test results making comparisons across studies and larger inferences difficult.

The incidence of delirium after cardiac surgery has been reported to range from 18 to 52%.[5,11,12] Pharmacologic treatments for postoperative delirium have been disappointing and the current clinical focus is on prevention. Concerns for worsening delirium with ketamine have been refuted with some studies suggesting ketamine may actually reduce delirium after cardiac surgery.[11] However, a large randomized study that included both cardiac and other major surgical procedures did not find a reduction in delirium associated with a single postinduction dose of ketamine.[23] Our study also did not find a difference in the incidence of delirium between the two groups; however, the overall incidence of delirium was quite low with only one patient reported in the propofol group. It appears that ketamine at anesthetic induction does not pose an advantage or disadvantage when compared with propofol in the development of delirium or POCD.

AKI remains a significant issue following cardiac surgery and is associated with both increased morbidity and mortality.[24] Although the incidence of AKI varies depending on the type of surgery and definition of AKI used, it has been reported to occur in 20–38% of cases.[24,25] Patients developing AKI are at increased risk for chronic kidney disease as well as end-stage renal disease (ESRD) with those who require renal replacement therapy being more than three times as likely to progress

Table 2: Neurocognitive testing results†

	Ketamine (*n*=25)		Propofol (*n*=24)		*P*‡
	n	Mean±SD	*n*	Mean±SD	
Trail making test					
Test A total time					
Baseline	25	−0.1±0.8	24	0.0±1.1	
Follow-up	20	−0.5±1.3	22	−0.8±1.1	
Delta	20	−0.5±1.4	22	−0.8±1.4*	0.60
Decline of >1 SD	20	5 (25)	22	7 (32)	0.74
Test B total time					
Baseline	25	0.2±1.0	24	−0.1±1.1	
Follow-up	22	−0.8±1.2	21	−0.9±1.0	
Delta	22	−1.0±1.0***	21	−0.7±0.8***	0.25
Decline of >1 SD	22	7 (32)	21	5 (24)	0.74
HVLT-R					
Learning trials total					
Baseline	25	−0.7±0.9	24	−0.5±0.8	
Follow-up	23	−1.6±1.0	22	−1.5±1.0	
Delta	23	−1.0±0.9***	22	−0.9±0.8***	0.83
Decline of >1 SD	23	11 (48)	22	10 (45)	1.00
Delayed Recall					
Baseline	25	−0.9±1.3	24	−0.8±1.2	
Follow-up	23	−1.7±1.0	22	−1.6±1.3	
Delta	23	−0.9±1.1***	22	−0.8±1.3*	0.71
Decline of >1 SD	23	13 (57)	22	10 (45)	0.56
Digit Span total					
Baseline	25	0.2±0.8	24	0.1±1.0	
Follow-up	23	−0.3±0.9	21	−0.3±1.1	
Delta	23	−0.5±0.8*	21	−0.4±0.7*	0.79
Decline of >1 SD	23	4 (17)	21	3 (14)	1.00
COWAT total					
Baseline	25	0.1±0.8	24	0.1±0.8	
Follow-up	23	−0.5±1.1	21	−0.6±0.9	
Delta	23	−0.6±0.7***	21	−0.7±0.5***	0.53
Decline of >1 SD	23	5 (22)	21	3 (14)	0.70
Stroop color/word					
Baseline	24	−0.3±1.0	24	−0.6±1.3	
Follow-up	21	−1.0±1.3	21	−1.0±1.1	
Delta	21	−0.7±1.0**	21	−0.3±0.6	0.10
Decline of >1 SD	21	7 (33)	21	1 (5)	0.04
MMSE					
Baseline	25	0.7±0.9	24	0.4±1.1	
Follow-up	23	−0.5±1.8	22	−0.2±1.3	
Delta	23	−1.1±1.5**	22	−0.6±1.1*	0.20
Decline of >1 SD	23	11 (48)	22	7 (32)	0.37

COWAT=Controlled oral word association test; HVLT-R=Hopkins verbal learning test—revised; MMSE=Mini-mental status examination; SD=Standard deviation. †For all neurocognitive tests the raw scores were converted to z-scores using published references.[13-18]. ‡The mean change from baseline (delta) was compared between groups using the two-sample *t*-test and the percentage of subjects who experience a decline from baseline of >1 SD was compared between groups using Fisher's exact test.. *$P<0.05$ one-sample *t*-test comparing the within-group change from baseline (delta) to zero. **$P<0.01$ one-sample *t*-test comparing the within-group change from baseline (delta) to zero. ***$P<0.001$ one-sample *t*-test comparing the within-group change from baseline (delta) to zero.

Table 3: Postinduction hemodynamics

	Ketamine (*n*=25) Mean±SD		Propofol (*n*=24)		*P*
	n	%	*n*	%	
Any vasopressor use					
10 min postinduction	7	28%	14	58%	*P*=0.03*
NEE equivalents					
10 min postinduction	9.6±22.2	32.7±46.0			*P*<0.03**

Min=minutes; *N*=number of subjects. NEE equivalents: (phenylephrine/10)+(ephedrine*8)+(vasopressin*2.5)+epinephrine. *Chi-squared test. **two-sample *t*-test

to ESRD.[26] Postoperative AKI is likely to be multifactorial with ischemia, reperfusion, and inflammation all playing a role.[24] The overall incidence of AKI in our study population was 37% suggesting that we were able to capture patients at the highest risk of AKI. In the ketamine group, 6 of the 25 patients developed AKI (24%) compared with 12 of 24 patients (50%) in the propofol group. This difference did not reach statistical significance, however, suggests an intriguing trend that may indicate a protective effect of ketamine induction against AKI compared with propofol.

If true, this protective effect may be secondary to anti-inflammatory effects from ketamine or potentially due to improved hemodynamics following induction. In this study, only 28% of patients in the ketamine group required vasopressor support of any kind in the first 10 min following induction while 58% of patients in the propofol group required vasopressor support. Additionally, three times more total vasopressor was required by the propofol group during the peri-induction period. In non-cardiac surgery patients, a significant amount of intraoperative hypotension is in the peri-induction period before skin incision and this may be associated with kidney injury.[27] An abstract presented at the 2021 IARS meeting discussed a propensity-matched cohort study that demonstrated an association between the use of intraoperative phenylephrine and increased risk of acute kidney injury.[28] The increased risk was seen with three or more phenylephrine boluses or infusions of higher dose or duration. This data suggests that anesthetic-related hypotension corrected by vasopressor administration may not be as benign as might be assumed. Selection of an induction agent associated with increased hemodynamic stability and reduction of vasopressor requirement may result in a decreased risk for acute kidney injury. A larger study is required to confirm these results.

This study has important strengths and limitations. It is a prospective, randomized trial with blinding of the neurocognitive test administrator. Limitations include study size for detecting the difference in AKI which may result in the group differences being a Type II error. Another limitation is the lack of long-term follow-up for cognitive outcomes. However, with the lack of signal for any short-term cognitive difference between groups, it is less likely long-term differences would be found. The overall low incidence of delirium was a surprising finding and may reflect unrecognized influences, such as nonpharmacologic prevention interventions, as well as the high variability in the incidence of delirium. The use of

dexmedetomidine following surgery as a sedation agent for transport and while intubated in the ICU is a confounder secondary to the proposed benefits on delirium and acute kidney injury. injury. However, a recent study revealed no reduction in delirium with intra and postoperative use of dexmedetomidine.[29] The effect of dexmedetomidine for reducing acute kidney injury appears to be most effective when started before or during surgery, rather than after the insult has occurred.[30] Future studies should evaluate the impact of ketamine on acute kidney injury as well as delineate the potential mechanism.

CONCLUSION

Consistent with other recent literature, this study did not detect a difference in POCD or delirium in elderly patients undergoing complex cardiac surgical procedures requiring CBP who received ketamine for anesthetic induction. A decrease in cognitive function was seen in the postoperative period, but this was not different between the two groups. However, twice as many patients in the propofol group developed AKI, although not reaching statistical significance. This interesting trend deserves further examination in a larger, adequately powered study. Ketamine was associated with an increase in hemodynamic stability and significantly reduced vasopressor requirement postinduction compared to propofol. Ketamine appears to be non-inferior to propofol for induction of anesthesia in elderly, high-risk cardiac surgical patients and demonstrates improved postinduction hemodynamic stability.

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.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Mazzeffi M, Johnson K, Paciullo C. Ketamine in adult cardiac surgery and the cardiac surgery Intensive Care Unit: An evidence-based clinical review. Ann Card Anaesth 2015;18:202-9.
2. Basagan-Mogol E, Goren S, Korfali G, Turker G, Kaya FN. Induction of anesthesia in coronary artery bypass graft surgery: The hemodynamic and analgesic effects of ketamine. Clinics (Sao Paulo) 2010;65:133-8.
3. Dale O, Somogyi AA, Li Y, Sullivan T, Shavit Y. Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. Anesth Analg 2012;115:934-43.
4. Musleh GS, Datta SS, Yonan NN, Grotte GJ, Prendergast BA, Hasan RI, *et al*. Association of IL6 and IL10 with renal dysfunction and the use of haemofiltration during cardiopulmonary bypass. Eur J Cardiothorac Surg 2009;35:511-4.
5. Li HC, Chen YS, Chiu MJ, Fu MC, Huang GH, Chen CC. Delirium, subsyndromal delirium, and cognitive changes in individuals undergoing elective coronary artery bypass graft surgery. J Cardiovasc Nurs 2015;30:340-5.
6. Hudetz JA, Gandhi SD, Iqbal Z, Patterson KM, Pagel PS. Elevated postoperative inflammatory biomarkers are associated with short- and medium-term cognitive dysfunction after coronary artery surgery. J Anesth 2011;25:1-9.
7. Carlson AP, Abbas M, Alunday RL, Qeadan F, William Shuttleworth C. Spreading depolarization in acute brain injury inhibited by ketamine: A prospective, randomized, multiple crossover trial. J Neurosurg 2018;130:1513-9.
8. Von der brelie C, Seifert M, Rot S, Tittel A, Sanft C, Meier U, *et al*. Sedation of patients with acute aneurysmal subarachnoid hemorrhage with ketamine is safe and might influence the occurrence of cerebral infarctions associated with delayed cerebral ischemia. World Neurosurg 2017;97:374-82.
9. Saravanan S, Kocarev M, Wilson RC, Watkins E, Columb MO, Lyons G. Equivalent dose of ephedrine and phenylephrine in the prevention of post-spinal hypotension in Caesarean section. Br J Anaesth 2006;96:95-9.
10. Goradia S, Sardaneh AA, Narayan SW, Penm J, Patanwala AE. Vasopressor dose equivalence: A scoping review and suggested formula. J Crit Care 2021;61:233-40.
11. Hudetz JA, Patterson KM, Iqbal Z, Gandhi SD, Byrne AJ, Hudetz AG, *et al*. Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2009;23:651-7.
12. Brown CH. Delirium in the cardiac surgical ICU. Curr Opin Anaesthesiol 2014;27:117-22.
13. Reitan RM. Trail Making Test: Manual for Administration and Scoring. Reitan Neuropsychological Laboratory; 1992.
14. Folstein MF, Folstein SE, McHugh PR. "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189-98.
15. Benedict RHB, Schretlen D, Groninger L, Brandt J. Hopkins verbal learning test-Revised: Normative data and analysis of inter-form and test-retest reliability. Clin Neuropsychol 1998:43-55. doi: 10.1076/clin.12.1.43.1726.
16. Benton A, Hamsher K. Multilingual Aphasia Examination. Manual of Instructions. 2nd ed. AJA Associates; 1989.
17. Wechsler D. WAIS-III: Administration and Scoring Manual. The Psychological Coorporation; 1997.
18. Golden C. The STROOP Color and Word Test (Manual). Stoelting; 1978.
19. Cropsey C, Kennedy J, Han J, Pandharipande P. Cognitive dysfunction, delirium, and stroke in cardiac surgery patients. Semin Cardiothorac Vasc Anesth 2015;19:309-17.
20. Klinger RY, Cooter M, Bisanar T, Terrando N, Berger M, Podgoreanu MV, *et al*. Intravenous lidocaine does not improve

neurologic outcomes after cardiac surgery: A randomized controlled trial. Anesthesiology 2019;130:958-70
21. Murkin JM, Newman SP, Stump DA, Blumenthal JA. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. Ann Thorac Surg 1995;59:1289-95.
22. Rudolph JL, Schreiber KA, Culley DJ, McGlinchey RE, Crosby G, Levitsky S, *et al*. Measurement of post-operative cognitive dysfunction after cardiac surgery: A systematic review. Acta Anaesthesiol Scand 2010;54:663-77.
23. Avidan MS, Maybrier HR, Abdallah AB, Jacobsohn E, Vlisides PE, Pryor KO, *et al*. Intraoperative ketamine for prevention of postoperative delirium or pain after major surgery in older adults: An international, multicentre, double-blind, randomised clinical trial. Lancet 2017;390:267-75.
24. Fuhrman DY, Kellum JA. Epidemiology and pathophysiology of cardiac surgery-associated acute kidney injury. Curr Opin Anaesthesiol 2017;30:60-5.
25. Schopka S, Diez C, Camboni D, Floerchinger B, Schmid C, Hilker M. Impact of cardiopulmonary bypass on acute kidney injury following coronary artery bypass grafting: A matched pair analysis. J Cardiothorac Surg 2014;9:20.
26. Nadim MK, Forni LG, Bihorac A, Hobson H, Koyner JL, Shaw A, *et al*. Cardiac and vascular surgery-associated acute kidney injury: The 20th international consensus conference of the ADQI (Acute Disease Quality Initiative) group. J Am Hear Assoc 2018;7:e008834.
27. Maheshwari K, Turan A, Mao G, Yang D, Niazi AK, Agarwal D, *et al*. The association of hypotension during non-cardiac surgery, before and after skin incision, with postoperative acute kidney injury: A retrospective cohort analysis. Anaesthesia 2018;73:1223-8.
28. Khanna A, Saha A, Segal S. intraoperative phenylephrine use is associated with an increased risk of acute kidney injury after non-cardiac surgery: A propensity matched cohort analysis. Anesth Analg 2021;132:372.
29. Turan A, Duncan A, Leung S, Karimi N, Fang J, Mao G, *et al*. Dexmedetomidine for reduction of atrial fibrillation and delirium after cardiac surgery (DECADE): A randomised placebo-controlled trial. Lancet 2020;396:177-85.
30. Peng K, Li D, Applegate RL, Lubarsky DA, Ji F-H, Liu H. Effect of dexmedetomidine on cardiac surgery-associated acute kidney injury: A meta-analysis with trial sequential analysis of randomized controlled trials address reprint requests to. J Cardiothorac Vasc Anesth 2020;34:603-13.