The Use of Cerebral Oximetry in Cardiac Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Xin Hui Chiong, Zhen Zhe Wong¹, Siu Min Lim², Tyng Yan Ng², Ka Ting Ng²

School of Medicine, University of Aberdeen, United Kingdom, ¹School of Medicine, International Medical University, Kuala Lumpur, Malaysia, ²Department of Anesthesiology, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

ABSTRACT

High prevalence of cerebral desaturation is associated with postoperative neurological complications in cardiac surgery. However, the evidence use of cerebral oximetry by correcting cerebral desaturation in the reduction of postoperative complications remains uncertain in the literature. This systematic review and meta-analysis aimed to examine the effect of cerebral oximetry on the incidence of postoperative cognitive dysfunction in cardiac surgery. Databases of MEDLINE, EMBASE, and CENTRAL were searched from their inception until April 2021. All randomized controlled trials comparing cerebral oximetry and blinded/no cerebral oximetry in adult patients undergoing cardiac surgery were included. Observational studies, case series, and case reports were excluded. A total of 14 trials (n = 2,033) were included in this review. Our pooled data demonstrated that patients with cerebral oximetry were associated with a lower incidence of postoperative cognitive dysfunction than the control group (studies = 4, n = 609, odds ratio [OR]: 0.15, 95% confidence interval [CI]: 0.04 to 0.54, P = 0.003, I² = 88%; certainty of evidence = very low). In terms of postoperative delirium (OR: 0.75, 95%CI: 0.50–1.14, P = 0.18, I² = 0%; certainty of evidence = low) and postoperative stroke (OR: 0.81 95%CI: 0.37–1.80, P = 0.61, I² = 0%; certainty of evidence = high), no significant differences (P > 0.05) were reported between the cerebral oximetry and control groups. In this meta-analysis, the use of cerebral oximetry monitoring in cardiac surgery demonstrated a lower incidence of postoperative cognitive dysfunction. However, this finding must be interpreted with caution due to the low level of evidence, high degree of heterogeneity, lack of standardized cognitive assessments, and cerebral desaturation interventions.

Keywords: Cardiac surgery, cerebral oximetry, cognitive dysfunction, delirium, desaturation, meta-analysis

INTRODUCTION

Cardiac surgery is known as a high-risk operation, which is susceptible to causing an imbalance in oxygen demand and supply to other vital organs intraoperatively, particularly the brain.¹,² Some commonly performed cardiac surgeries include coronary artery bypass graft (CABG), valve repair or replacement, and aortic surgery,³ which are often conducted with the use of cardiopulmonary bypass (CPB).⁴-⁶ Several studies reported that the incidence of cerebral desaturation was highly prevalent, ranging from 26% to as high as 74% in cardiac patients undergoing CPB.⁷-¹⁰ However, the definition of cerebral desaturation varied across studies, depending on the decrement of cerebral oxygenation from baseline or an absolute value as predefined by each study.¹,⁷-¹⁰ Several mechanisms of cerebral desaturation include altered cerebral autoregulation...
from rapid changes in cerebral perfusion pressure, cerebral microemboli, and acute hemodilution during CPB, which could result in an imbalance of oxygen supply and demand in the brain tissues.\(^{[11-14]}\) In recent years, some studies demonstrated a significant correlation between cerebral desaturation and postoperative neurological complications, namely postoperative cognitive dysfunction (POCD)\(^{[7,15,16]}\) and postoperative delirium (POD).\(^{[17,18]}\)

The introduction of cerebral near-infrared spectroscopy (NIRS) can be used to determine perioperative cerebral oxygenation when cardiac surgical patients receive general anesthesia to minimize postoperative neurological complications.\(^{[15,16,19-21]}\) The principle of cerebral near-infrared spectroscopy involves the transmission and absorption of near-infrared light (700–900 nm) that passes through the skull and brain tissue.\(^{[22]}\) The change in light attenuation reflects the concentration of chromophores, which consists of hemoglobin and cytochrome c oxidase, thereby providing intraoperative insight into regional cerebral saturation.\(^{[22-24]}\) Detection of cerebral desaturation during surgery allows early correction of cerebral desaturation event by applying interventions, which consist of excluding mechanical obstruction, adjusting mean arterial pressure, increasing inspired oxygen fraction, normalizing arterial end-tidal carbon dioxide levels, and increasing cardiac output to return cerebral saturation to its baseline value.\(^{[25]}\) It is believed that the correction of cerebral desaturation with cerebral oximetry can reduce postoperative complications, particularly POCD,\(^{[15,16,19]}\) shortening the duration of intensive care unit stay\(^{[19]}\) and hospitalization.\(^{[26]}\) Two randomized controlled trials demonstrated that patients without cerebral oximetry monitoring had a higher risk of POCD than those with cerebral oximetry in cardiac surgery.\(^{[15,16]}\) In view of the higher risk of cerebral desaturation during CPB in cardiac surgery, the authors believed that a systematic review and meta-analysis are timely warranted to synthesize the evidence of cerebral oximetry monitoring, specifically in cardiac surgery before any recommendation is made.

We hypothesized that the use of cerebral oximetry monitoring reduced the incidence of POCD in adult patients undergoing cardiac surgery. The primary objective was to examine the clinical benefits of cerebral oximetry monitoring in the reduction of POCD in cardiac surgery. Secondary objectives were to investigate the implications of cerebral oximetry on postoperative complications, namely incidence of POD, postoperative stroke, postoperative kidney injury, postoperative myocardial infarction, mortality rate, number of patients having cerebral desaturation, duration of mechanical ventilation (hours), and length of hospital stay (days).

**MATERIALS AND METHODS**

This systematic review and meta-analysis was conducted and reported with the guideline of the Cochrane Handbook for Systematic Reviews and Interventions\(^{[27]}\) and the Quality of Reporting of Meta-Analyses (QUOROM) statement.\(^{[28]}\) This review protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020224496).

**Search strategy**

Three databases (Ovid MEDLINE, Ovid EMBASE, and the Cochrane Central Register of Controlled Trials [CENTRAL]) were systematically searched from their inception until April 2021. Trial registries (the Clinicaltrial.gov.my and the International Clinical Trials Registry Platform) were searched for any ongoing trials. ZW and XC conducted the search independently with the search terms and strategy listed in Supplementary Table S1 and Table S2. The inclusion criteria were randomized controlled trials (RCTs) comparing either cerebral oximetry or control (blinded/no cerebral oximetry) in adult patients undergoing cardiac surgery. All observational studies, case–control studies, cohort studies, case reports, and case series were excluded from this review. The references of all included studies were manually checked for any additional trials. Study authors were contacted at least twice if there were any incomplete or missing data.

**Study outcomes**

The primary outcomes of this review were the incidence of POCD (before discharge, at 1 week, and at 3 months). Secondary outcomes included the incidence of POD, postoperative stroke, postoperative myocardial infarction, renal failure, mortality, number of patients who had cerebral desaturation, the time on mechanical ventilation, and duration of stay in hospital.

**Study selection and data collection**

The inclusion and exclusion criteria were discussed among all authors (XC, ZW, and KN). Titles and abstracts were screened by two authors independently (XC and ZW). All articles were grouped into three folders: “yes” for included studies, “maybe” for uncertain studies, and “no” for excluded studies. Studies in the “maybe” folder were discussed with a senior author (KN) to achieve consensus. All studies in the “yes” folder were screened for full text by two authors (XC and ZW) independently. Any discrepancies between the two authors (XC and ZW)
during the screening were brought up for discussion with a third author (KN).

XC and ZW extracted the data from all finally included studies into an online datasheet independently. A third author (KN) cross-checked all the extracted data. Any conflicts during data extraction were resolved with a third author (KN). In addition to the measured outcomes, other relevant data, namely author, year of publication, country, sample size, types of surgeries, brands of the cerebral oximeter, and type of anesthesia were extracted. Data that were presented as median and interquartile range were converted into mean and standard deviation.\footnote{29}

Methodological quality and risk of bias assessment
Two authors (XC and ZW) independently assessed the risk of bias in all the included RCTs using the Cochrane Risk of Bias assessment tool. It consists of six domains, namely selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. The judgment from both authors (XC and ZW) was discussed with the third author (KN) to reach a general consensus on the risk of bias in the included studies. The certainty of the evidence was performed by two authors (XC and ZW) independently, based on the risk of bias, inconsistency, imprecision, indirectness, and publication bias. Any discrepancies were discussed with the third author (KN).

Statistical analysis
Review Manager (version 5.4) was used for statistical meta-analysis. All findings on primary and secondary outcomes are reported as odds ratio (OR) for binary outcomes and mean difference (MD) for continuous outcomes, respectively along with a 95% confidence interval (CI). Any results with \( P \)-value < 0.05 were denoted statistically significant. All included RCTs were assessed for heterogeneity using the \( I^2 \) statistic. The values of \( I^2 \) were interpreted as described: \( I^2 < 40\% \) was considered low, \( 40\% \) to \( 60\% \) as moderate, and \( > 60\% \) as substantial heterogeneity. A fixed-effect model was utilized to pool the estimate for the measured outcomes, and a random-effect model was used for data analysis if there was substantial heterogeneity (\( I^2 > 60\% \)).

RESULTS
The PRISMA flow chart is illustrated in Figure 1. Our search identified 2,721 articles for the title and abstract screening. Of all, 43 articles were retrieved for full-text screening. Fourteen RCTs (2,033 participants: 1,015 participants in the cerebral oximetry group and 1,018 participants in the control group) were included for qualitative analysis.\footnote{7,10,15,16,19‑21,30‑34} However, only 13 RCTs were included for meta-analysis because one RCT\footnote{30} did not report any of our measured outcomes. The details of excluded studies are reported in Supplementary Table S3. Searching trial registries identified three ongoing studies [Supplementary Table S4].

Study characteristics
The clinical characteristics of included RCTs are listed in Table 1. The sample size of each RCT ranged from 25 to 249. The mean age of patients in all included RCTs ranged from 34.6 to 74.2 years. Eleven RCTs\footnote{9,10,15,16,19‑21,31‑34} were conducted in a single-center, whereas two RCTs took place in multiple centers\footnote{8,30} and one RCT did not specify.\footnote{7} Five RCTs focused on patients undergoing CABG,\footnote{7,15,16,20,31} and nine RCTs\footnote{8,10,19,21,30,32‑34} involved various combinations of cardiac surgeries, including open valve surgery, valve replacement, and aortic arch surgery. All included RCTs used CPB in surgery except one RCT.\footnote{13} The definition of cerebral desaturation varied across all RCTs, which were 10%\footnote{8} or 20%\footnote{8,10,15,16,19,30} or any drop\footnote{21} of regional cerebral oxygen saturation from patients’ baseline value with a duration of \( \geq 15 \) s\footnote{10} or \( \geq 1 \) min.\footnote{13} Most RCTs used INVOS cerebral oximeters, except three RCTs that used different brands (Nonin\footnote{19} and Fore‑sight\footnote{8,38}). Nine RCTs\footnote{7,10,19,20,31,32,34} had blinded cerebral monitoring and...
Table 1: Clinical characteristics of included studies

| Study                  | Control Type of cerebral oximetry monitoring | Age (mean±SD) | Mean follow-up period after surgery (weeks) | Type of control | Type of cerebral oximetry monitoring | Sample size | Country                  | Design Surgery Anesthesia |
|------------------------|--------------------------------------------|---------------|--------------------------------------------|----------------|-------------------------------------|-------------|--------------------------|--------------------------|
| Colak et al.[10]       | No cerebral oximetry monitoring            | 65.4±8.8      | -                                          | RCT            | INVOS 5100                          | 48 (25/23)  | Turkey                   | RCT                      |
| Deschamps et al.[8]    | No cerebral oximetry monitoring            | 69.0±12.6     | -                                          | RCT            | INVOS 4000                          | 20 (10/10)  | Canada                   | RCT                      |
| Lau et al.[9]          | No cerebral oximetry monitoring            | 60.5±9.41     | -                                          | RCT            | Nonin Equinox 7600                   | 100 (50/50) | United States            | RCT                      |
| Kara et al.[16]        | No cerebral oximetry monitoring            | 62.8±10.3     | -                                          | RCT            | INVOS 5100C                         | 74 (36/38)  | United Kingdom           | RCT                      |
| Mohandas et al.[30]    | No cerebral oximetry monitoring            | 67.3±8.5      | -                                          | RCT            | INVOS 5100                          | 64.7±11.75 | Croatia                  | RCT                      |
| Malik et al.[33]       | No cerebral oximetry monitoring            | 60.5±9.41     | -                                          | RCT            | Equinox Classic                     | 40 (20/20)  | India                    | RCT                      |
| Bennett et al.[19]     | No cerebral oximetry monitoring            | 64.9±9.5      | -                                          | RCT            | INVOS 5100                          | 74 (36/38)  | United Kingdom           | RCT                      |

*SD, Standard deviation; †RCT, Randomized controlled trial

Risk of bias assessment

The risk of bias assessment for the included RCTs is shown in Figure 2 and Supplementary Table S5. The domains of random sequence generation and allocation concealment were well-described in nine RCTs[7,9,15,21,30,31,33,34] and seven RCTs[13,16,20,21,30,33] respectively. There were adequate evidence of blinding of personnel,[9,15,30–33] participants,[9,15,30–33] and assessors.[9,15,30–33] All RCTs were graded low risk for incomplete outcome data as their attrition rate was less than 50%.[7,10,15,19,21,30–34] However, three RCTs were graded high risk as these received either grant or sponsorship from the manufacturers of cerebral oximetry devices.[8,9,30] The PRISMA checklist is outlined in Supplementary Table S6.

Primary outcome

Incidence of postoperative cognitive decline

Four RCTs (n = 709) examined the incidence of POCD in patients undergoing cardiac surgery.[7,15,16,19] Our pooled meta-analysis demonstrated that cardiac patients with cerebral oximetry were associated with a lower incidence of POCD than the control group (OR: 0.15, 95%CI 0.04–0.54, P = 0.003) [Figure 3]. The incidence of POCD for cerebral oximetry and control groups were 29.8% and 56.2%, respectively. A substantial degree of heterogeneity (I² = 88%) was noted across all included RCTs. Different cognitive assessment tools were used across RCTs, including Mini‑Mental State Examination (MMSE),[7,15,19] Montreal Cognitive Assessment (MoCa),[16] and other neuropsychological assessments.[7,15,19] The level of evidence for POCD was rated as very low due to inconsistency, indirectness, and publication bias.

In the subgroup analysis based on the duration of POCD assessment, the magnitude and direction of effect became insignificant in those with POCD assessment before discharge (studies = 2, n = 319, OR: 0.42, 95%CI: 0.08–2.11, P = 0.29, F = 87%)[7,10] and postoperative 1 week (studies = 2, n = 290, OR: 0.09, 95%CI: 0.01–1.63, P = 0.10, F = 92%).[13,15] The effect of cerebral oximetry in the reduction of POCD remained significant in those with POCD assessment at 3 months postoperatively (study = 1, n = 100, OR: 0.01, 95%CI: 0.00–0.21, P = 0.003).[19]

Secondary outcomes

Postoperative delirium and postoperative stroke

Five RCTs[8,9,15,21,34] (n = 825) and seven RCTs[7,9,19,21,30,31] (n = 1,228) assessed the incidence of POD (OR: 0.75, 95%CI: 0.50–1.14, P = 0.18, F = 0%; certainty of evidence = low)

five RCTs[15,16,21,30,33] had no cerebral oximetry monitoring as their control group.
and postoperative stroke (OR: 0.81, 95%CI: 0.37–1.80, P = 0.61, I² = 0%; certainty of evidence = high) in cardiac surgery, respectively. No significant differences were observed between both the cerebral oximetry and control groups.

**Postoperative myocardial infarction and renal failure**

Our pooled data analysis demonstrated no significant differences in the incidence of postoperative myocardial infarction (studies = 7, n = 1,287, OR: 0.90, 95%CI: 0.46–1.76, P = 0.76, I² = 0%; certainty of evidence = high) and postoperative renal failure (studies = 6, n = 1,029, OR: 0.96, 95%CI: 0.59–1.56, P = 0.88, I² = 0%; certainty of evidence = moderate) in patients undergoing cardiac surgery.

**Intraoperative cerebral desaturation**

A combination of five RCTs (n = 938) showed no significant difference in the number of patients who had intraoperative cerebral desaturation (OR: 0.75, 95%CI: 0.55–1.01, P = 0.06, I² = 19%; certainty of evidence = moderate) between both cerebral oximetry and blinded cerebral oximetry groups.

**Mortality rate**

Eight RCTs (n = 1,189) assessed the mortality rate between the cerebral oximetry and control groups in cardiac surgery. No significant difference was observed (OR: 0.89, 95%CI: 0.47–1.69, P = 0.72, I² = 0%; certainty of evidence = high).

**Duration of mechanical ventilation (hours)/duration of hospital stay (days)**

In terms of the duration of mechanical ventilation (studies = 5, n = 592, MD: 0.74, 95%CI: −0.19–1.68, P = 0.12, I² = 0%) and duration of hospital stay (studies = 6, n = 728, MD: −0.05, 95%CI: −0.42–0.31, P = 0.77, I² = 3%), no significant
Table 2: Summary of findings for primary and secondary outcomes

| No. | Outcomes                                                                 | Trials | n   | I² (%) | Effect model | MD/OR (95%CI) | P    |
|-----|--------------------------------------------------------------------------|--------|-----|--------|--------------|---------------|------|
| 1   | Postoperative cognitive decline                                          | 4[7,15,16,19] | 709  | 88     | REM          | 0.15 (0.04,0.54) | 0.003|
|     | Postoperative cognitive decline prior to discharge                       | 2[7,16] | 319  | 87     | REM          | 0.42 (0.08,2.11) | 0.29 |
|     | Postoperative cognitive decline at 1 week postoperatively                | 2[7,19] | 290  | 92     | REM          | 0.09 (0.01,1.63) | 0.10 |
|     | Postoperative cognitive decline at 3 months postoperatively              | 1[18]  | 100  | -      | REM          | 0.01 (0.00,0.21) | 0.003|

Heterogeneity: Tau² = 1.56; Chi² = 34.75, df=4 (P<0.00001); I² = 88%  
Test for overall effect: Z=2.94 (P=0.0003)  
Test for subgroup differences: Chi² = 4.64, df=2 (P=0.10), I² = 56.9%

2 Postoperative delirium  
3 Postoperative stroke  
4 Mortality  
5 Postoperative myocardial infarction  
6 Postoperative renal failure  
7 Duration of stay in hospital (days)  
8 Time on mechanical ventilation (hours)  
9 Number of patients who had intraoperative cerebral desaturation

I²: Heterogeneity; MD: Mean difference; OR: Odds ratio; REM: Random effect model; FEM: Fixed effect model

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis examining the use of cerebral oximetry in the reduction of POCD in patients undergoing cardiac surgery. Cognitive dysfunction is characterized by a deficit in any cognitive domains, namely attention, language comprehension, memory, motor speed, and executive functions. Our meta-analysis demonstrated that patients who received cerebral oximetry monitoring with the correction of cerebral desaturation intraoperatively were associated with a lower incidence of POCD in cardiac surgery. The finding was consistent with two previous meta-analyses examining the use of cerebral oximetry in both cardiac and non-cardiac surgeries. The cognitive assessment tools and threshold values for the diagnosis of POCD varied across all included studies, which can introduce significant bias to our findings. 

The authors admitted that poor adherence to the interventions of cerebral desaturation in the cerebral oximetry group may introduce type II error to the finding. The duration of CPB and aortic cross clamp (AOX) time were 65 min and 39 min, respectively, which was shorter than the rest of the included RCTs (CPB time 77.7 to 91.18 min, AOX time 48.8 to 65 min). Prolonged CPB and AOX time are risk factors for a higher incidence of POCD in cardiac surgery. In an observational study, Ziyaeifard et al. showed that cardiac surgical patients diagnosed with moderate POCD had longer CPB and AOX time as compared to those with mild or without POCD groups. This may be due to the formation of microemboli during CPB and AOX reducing perfusion of brain tissues.

All our included RCTs for the outcome of POCD were cardiac surgery with CPB. A meta-analysis demonstrated that cardiac surgical patients requiring CPB were associated with two-folds higher risk of developing POCD than those without CPB. Thus, our findings may not be generalized to patients undergoing cardiac surgery without CPB. Slater et al. reported an insignificant difference in the incidence of POCD between the cerebral oximetry and control groups. The authors admitted that poor adherence to the interventions of cerebral desaturation in the cerebral oximetry group may introduce type II error to the finding. The duration of CPB and aortic cross clamp (AOX) time were 65 min and 39 min, respectively, which was shorter than the rest of the included RCTs (CPB time 77.7 to 91.18 min, AOX time 48.8 to 65 min). Prolonged CPB and AOX time are risk factors for a higher incidence of POCD in cardiac surgery. In an observational study, Ziyaeifard et al. showed that cardiac surgical patients diagnosed with moderate POCD had longer CPB and AOX time as compared to those with mild or without POCD groups. This may be due to the formation of microemboli during CPB and AOX reducing perfusion of brain tissues.

In this review, no significant differences were observed in the incidence of POD, mortality rate, intraoperative cerebral desaturation, postoperative stroke, myocardial infarction, and renal failure. These negative findings were in agreement with three previous systematic reviews and meta-analyses of non-cardiac and cardiac surgeries. In contrast, Ortega-Loubon et al. reported that the cerebral oximetry group had a lower incidence of POD in cardiac surgical
Table 3: GRADE assessment of primary and secondary outcomes

| Hazard of outcomes                             | Certainty assessment                                                                 | No. of patients | Effect Relative (95%CI) | Effect Absolute (95%CI) | Certainty | Importance |
|------------------------------------------------|---------------------------------------------------------------------------------------|-----------------|-------------------------|-------------------------|-----------|------------|
| Cognitive decline (ALL)                        |                                                                                      |                 |                         |                         |           |            |
| 4[16,17,18] Randomized trials                  | Not serious                                                                          | 108/362 (29.8%) | OR 0.15 (0.04 to 0.54)  | 401 fewer per 1,000 (from 513 fewer to 153 fewer) | □□□□□     | VERY LOW   |
| Incidence of postoperative delirium            |                                                                                      |                 |                         |                         |           |            |
| 5[9,15,21,35] Randomized trials                | Serious^a Not serious                                                                 | 48/400 (12.0%)  | OR 0.75 (0.50 to 1.14)  | 33 fewer per 1,000 (from 69 fewer to 18 more)  | □□□□□     | LOW        |
| Number of patients had cerebral desaturation   |                                                                                      |                 |                         |                         |           |            |
| 8[9,21,22,23] Randomized trials                | Not serious                                                                          | 127/473 (26.8%) | OR 0.75 (0.55 to 1.01)  | 59 fewer per 1,000 (from 115 fewer to 2 more)   | □□□□□     | MODERATE   |
| Mortality rate                                 |                                                                                      |                 |                         |                         |           |            |
| 7[9,15,16,21,30,31] Randomized trials          | Not serious                                                                          | 17/583 (2.9%)   | OR 0.89 (0.47 to 1.69)  | 4 fewer per 1,000 (from 18 fewer to 23 more)    | □□□□□     | HIGH       |
| Incidence of postoperative stroke              |                                                                                      |                 |                         |                         |           |            |
| 7[9,15,16,21,30,31] Randomized trials          | Not serious                                                                          | 10/611 (1.6%)   | OR 0.81 (0.37 to 1.80)  | 4 fewer per 1,000 (from 13 fewer to 16 more)     | □□□□□     | HIGH       |
| Incidence of postoperative myocardial infarction|                                                                                      |                 |                         |                         |           |            |
| 7[9,15,16,21,30,31] Randomized trials          | Not serious                                                                          | 17/640 (2.7%)   | OR 0.90 (0.46 to 1.76)  | 3 fewer per 1,000 (from 16 fewer to 21 more)     | □□□□□     | HIGH       |
| Incidence of postoperative renal failure        |                                                                                      |                 |                         |                         |           |            |
| 6[9,15,16,21,30,31] Randomized trials          | Not serious                                                                          | 38/505 (7.5%)   | OR 0.96 (0.59 to 1.56)  | 3 fewer per 1,000 (from 33 fewer to 42 more)     | □□□□□     | MODERATE   |

CI: Confidence interval; OR: Odds ratio
Explanations: a. Substantial heterogeneity (I² > 60%) b. Different cognitive assessment tools and duration of follow-up after surgery were used across all included studies c. Funnel plot suggested of potential publication bias d. Majority of included studies were high risk of bias e. Different delirium assessment tool and duration of delirium assessment were used across all included studies
patients. However, this finding needs to be interpreted with a caveat as it pooled the data of two outcomes (POCD and POD). Hypoactive delirium accounts for the majority subtype of delirium in the postoperative period, which is often under-recognized in the wards. Of the included RCTs, only one RCT utilized the Confusion Assessment Method (CAM) to assess POD, whereas no specific delirium assessment tool was described in the rest of the RCTs. Thus, this can introduce measurement bias to our findings. Two studies showed promising results regarding the sensitivity and specificity of CAM in the detection of POD, ranging from 88% to 100% and 90% to 100%, respectively [Tables 2 and 3].

Postoperative stroke, renal failure, and death are known complications of cardiac surgery. Earlier studies demonstrated that the duration of CPB greater than 120 and 140 min increased the risk of postoperative stroke, renal failure, and cardiac surgery. It was also established that prolonged CPB time was associated with higher postoperative mortality. However, most of our included RCTs had short duration (<120 min) of CPB time, which may act as a protective factor against postoperative stroke, renal failure, and death. In addition, the definitions of myocardial infarction were inconsistent across the included RCTs. Five RCTs diagnosed myocardial infarction based on electrocardiogram changes (ST-elevation myocardial infarction, new pathological Q waves, or new left bundle bunch block) and/or elevated troponin assays whereas two RCTs did not specify any method of diagnosis for myocardial infarction. The use of either troponin assays or electrocardiogram alone for the diagnosis of myocardial infarction may be questionable after cardiac surgery. The AOX and CPB during cardiac surgery could cause tissue injury to the myocardium as a nature of cardiac surgery. Thus, it is likely that the measured incidence of myocardial infarction in our review did not accurately reflect the true occurrence rate of myocardial infarction. Crescenzi et al. showed that cardiac surgical patients with both the elevation of troponin and new Q waves had higher risk of developing cardiac adverse events, as compared to those with only electrocardiogram change. Therefore, the use of both electrocardiogram changes and troponin assay may improve the diagnostic accuracy for postoperative cardiac events. Future studies are recommended to follow the criteria listed in “The Fourth Universal Definition of Myocardial Infarction (2018)” for the diagnosis of myocardial infarction after cardiac surgery to minimize heterogeneity.

Several limitations were present in this review. Different definitions of POCD and assessment tools across the included studies may introduce variances to our findings. Most of the included RCTs did not extend the use of cerebral oximetry monitoring in the postoperative period, except three RCTs which reported a high incidence of cerebral desaturation in the intensive care unit (ICU), ranging from 17% to 75%. Future adequately powered studies are warranted to examine the extended use of cerebral oximetry in the postoperative period of cardiac ICU to minimize any postoperative complications. Cerebral oximetry is an important monitoring tool for early detection of cerebral desaturation with strict adherence to clinical intervention regimes to correct cerebral desaturation, leading to an improved outcome. However, the adherence rate to the intervention regime for cerebral desaturation was not assessed and reported, which could introduce bias to the result. We were also unable to perform a subgroup analysis on the use of cerebral oximetry based on the ages of cardiac surgical patients (adult vs. elderly) due to the limited number of studies and inadequate data for pooling.

CONCLUSION

In this meta-analysis, the use of cerebral oximetry monitoring in cardiac surgery demonstrated a lower incidence of postoperative cognitive dysfunction. However, the findings must be interpreted with caution due to a low level of evidence, high degree of heterogeneity, and lack of standardized cognitive assessments, and cerebral desaturation interventions.

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Conflicts of interest
There are no conflicts of interest.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this review article can be found online.

Table S1: PICO table

| Population | Intervention | Control | Outcome |
|------------|--------------|---------|---------|
| Adult patients (ages 18 and above) undergoing cardiac surgery | Cerebral oximetry monitoring | Blinded or no cerebral oximetry monitoring | Postoperative cognitive decline (prior to discharge, at 1 week postoperatively, at 3 months postoperatively) |
| | | | Postoperative delirium |
| | | | Postoperative stroke |
| | | | Mortality |
| | | | Postoperative myocardial infarction |
| | | | Postoperative renal failure |
| | | | Duration of stay in hospital (days) |
| | | | Time on mechanical ventilation (hours) |
| | | | Number of patients who had intraoperative cerebral desaturation |

APPENDIX A. SUPPLEMENTARY DATA

Table S2: Search strategy MEDLINE and EMBASE (from its inception until October 2020)

| Step | Search String |
|------|---------------|
| 1    | exp Monitoring, Intraoperative/or exp Spectroscopy, Near-Infrared/or cerebral oximetry.mp or exp Cerebrovascular Circulation/ |
| 2    | exp Randomized Controlled Trials as Topic/or randomized trial.mp. |
| 3    | Exp Clinical Trials as Topic/or randomised controlled trial.mp. |
| 4    | 2 or 3 |
| 5    | 1 and 4 |

Table S2: Search strategy MEDLINE and EMBASE (from its inception until October 2020)

| Step | Search String |
|------|---------------|
| 1    | MeSH descriptor: [Spectroscopy, Near-Infrared] explode all trees |
| 2    | cerebral oximetry |
| 3    | MeSH descriptor: [Monitoring, Intraoperative] explode all trees |
| 4    | MeSH descriptor: [Cerebrovascular Circulation] explode all trees |
| 5    | cerebral oxygen saturation |
| 6    | 1 or 2 or 3 or 4 or 5 |
| 7    | randomized trial |
| 8    | MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees |
| 9    | 7 or 8 |
| 10   | randomised controlled trial |
| 11   | MeSH descriptor: [Clinical Trials as topic] explode all trees |
| 12   | 10 or 11 |
| 13   | 9 or 12 |
| 14   | surgery |
| 15   | 6 and 13 and 14 |

CENTRAL (from its inception until April 2021)

| Step | Search String |
|------|---------------|
| 1    | MeSH descriptor: [Spectroscopy, Near-Infrared] explode all trees |
| 2    | cerebral oximetry |
| 3    | MeSH descriptor: [Monitoring, Intraoperative] explode all trees |
| 4    | MeSH descriptor: [Cerebrovascular Circulation] explode all trees |
| 5    | cerebral oxygen saturation |
| 6    | 1 or 2 or 3 or 4 or 5 |
| 7    | randomized trial |
| 8    | MeSH descriptor: [Randomized Controlled Trials as Topic] explode all trees |
| 9    | 7 or 8 |
| 10   | randomised controlled trial |
| 11   | MeSH descriptor: [Clinical Trials as topic] explode all trees |
| 12   | 10 or 11 |
| 13   | 9 or 12 |
| 14   | surgery |
| 15   | 6 and 13 and 14 |
Table S3: List of excluded studies

| No | Author       | Year | Design                                      | n  | Country                                             | Reasons for exclusion     |
|----|--------------|------|---------------------------------------------|----|----------------------------------------------------|---------------------------|
| 1  | Slater       | 2009 | Prospective, randomised                     | 250| United States                                      | Wrong study design        |
| 2  | Dullenkopf   | 2007 | Prospective, randomised                     | 35 | Switzerland                                        | Wrong study design        |
| 3  | Lomivorotov  | 2017 | Prospective, randomised                     | 120| Russia                                             | Wrong study design        |
| 4  | Pichler      | 2019 | Prospective, randomised                     | 726| Austria, Canada                                    | Wrong population          |
| 5  | Hansen       | 2019 | Prospective, randomised                     | 1600| Denmark                                            | Wrong population          |
| 6  | Mencin       | 2018 | Prospective, randomised                     | 75 | Slovenia                                            | Wrong intervention        |
| 7  | Murkin       | 2011 | Prospective, randomised                     | 200| Canada                                              | Wrong study design        |
| 8  | Plomgaard    | 2019 | Prospective, randomised                     | 115| Austria, Denmark, France, Ireland, Italy, Spain, Netherlands and United Kingdom | Wrong population |
| 9  | Claudia      | 2017 | Prospective, cohort                         | 150| Germany                                            | Wrong study design        |
| 10 | Trinh        | 2016 | Prospective, randomised                     | 125| United States                                      | Wrong study design        |
| 11 | Aukorsnchat  | 2018 | Prospective, randomised                     | 37 | Thailand                                            | Wrong study design        |
| 12 | Holmgaard    | 2019 | Prospective, randomised                     | 197| Denmark                                            | Wrong study design        |
| 13 | Baker        | 2006 | Prospective, randomised                     | 300| Australia                                          | Wrong study design        |
| 14 | Plomgaard    | 2016 | Prospective, randomised                     | 166| Austria, Denmark, France, Ireland, Italy, Spain, Netherlands and United Kingdom | Wrong population |
| 15 | Peličer      | 2013 | Literature review                            | -  | Spain                                              | Wrong study design        |
| 16 | Chok         | 2018 | Prospective randomised                      | 158| Hong Kong                                          | Wrong population          |
| 17 | Cecconi      | 2020 | Prospective, randomised                     | 200| Italy                                              | Wrong population          |
| 18 | Ballard      | 2012 | Prospective, randomised                     | 72 | United Kingdom                                     | Wrong study design        |
| 19 | Casati       | 2005 | Prospective, randomised                     | 122| Italy                                              | Wrong population          |
| 20 | Cowie        | 2014 | Prospective, randomised                     | 40 | Australia                                          | Wrong population          |
| 21 | Cox          | 2018 | Prospective, randomised                     | 41 | United States                                      | Wrong population          |
| 22 | Murniece     | 2019 | Prospective, randomised                     | 34 | Latvia                                             | Wrong population          |
| 23 | Trafído      | 2015 | Prospective, randomised                     | 43 | Poland                                             | Wrong population          |
| 24 | Zogogiannis  | 2011 | Prospective, randomised                     | 169| Greece                                             | Wrong population          |
| 25 | Cheng        | 2020 | Prospective, randomised                     | 146| China                                              | Wrong intervention        |
| 26 | Lian         | 2021 | Prospective, randomised                     | 100| Singapore                                          | Wrong population          |

Table S4: Clinical characteristics of ongoing studies

| Author       | Location | Status                        | Recruitment start date | Estimated completion date | Title                                                                 | Comparator                                                                 | n  | Clinical Trial Number          |
|--------------|----------|-------------------------------|------------------------|---------------------------|----------------------------------------------------------------------|----------------------------------------------------------------------------|----|-----------------------------|
| Sean R Bennett | United Kingdom | Completed                   | 1/2/2011               | 1/9/2014                  | Cerebral Oximetry in Cardiac Surgery to Reduce Neurological Impairment and Hospital Length-of-stay | Cerebral oximetry monitoring vs standard patient monitoring | 182| NCT04463563                  |
| Cathy Spence  | United Kingdom | No longer recruiting          | 01/03/2018             | 30/06/2020                | RECOGNISE: Using a Cerebral Oximeter monitoring device to identify and reduce postoperative complications in cardiac surgery | Cerebral oximetry monitoring vs blinded cerebral oximetry monitoring | 440| ISRCTN12937489               |
| Carlos Galhardo | Brazil     | Not yet recruiting            | -                      | -                         | Cerebral Oxygen Saturation Monitoring In Cardiac Surgery (COSMICS)    | Cerebral oximetry monitoring vs no cerebral oximetry monitoring          | 452| NCT04766554                  |

Table S5: Risk of bias assessment

| Author       | Year | Overall | Random sequence generation (selection bias) | Allocation concealment (selection bias) | Blinding of participants and personnel (performance bias) | Blinding of outcome assessment (detection bias) | Incomplete outcome data (attrition bias) | Selective reporting (reporting bias) | Other bias |
|--------------|------|---------|--------------------------------------------|----------------------------------------|--------------------------------------------------------|---------------------------------------------|----------------------------------------|-----------------------------------|-----------|
| Bennett      | 2020 | Low     | Low                                        | Low                                    | Unclear                                                | Low                                         | Low                                    | Low                               | Low       |
| Colak        | 2014 | Low     | Low                                        | Low                                    | Unclear                                                | Low                                         | Low                                    | Low                               | Unclear   |
| Deschamps    | 2013 | Unclear | Unclear                                   | Unclear                                | Unclear                                                | Low                                         | Unclear                                | Low                               | Unclear   |
| Deschamps    | 2016 | High    | Low                                        | Unclear                                | Unclear                                                | Low                                         | Unclear                                | Low                               | High      |
| Hariall      | 2014 | Unclear | Unclear                                   | Unclear                                | Unclear                                                | Low                                         | Unclear                                | Unclear                           | Unclear   |
| Kara         | 2015 | Unclear | Unclear                                   | Unclear                                | Unclear                                                | Low                                         | Unclear                                | Low                               | Low       |
| Lau          | 2012 | Low     | Unclear                                   | Unclear                                | Unclear                                                | Low                                         | Low                                    | Low                               | Low       |
| Lei          | 2017 | High    | Low                                        | Unclear                                | Unclear                                                | Low                                         | Low                                    | High                              | Low       |
| Mohandas     | 2013 | Unclear | Unclear                                   | Unclear                                | Unclear                                                | Low                                         | Unclear                                | Unclear                           | Unclear   |
| Murkin       | 2007 | High    | Low                                        | Low                                    | Low                                                    | Low                                         | Low                                    | Low                               | Low       |
| Rogers       | 2017 | Unclear | Low                                        | Low                                    | Unclear                                                | Low                                         | Low                                    | Unclear                           | Unclear   |
| Slater       | 2009 | Unclear | Low                                        | Unclear                                | Unclear                                                | Low                                         | Unclear                                | Unclear                           | Unclear   |
| Uysal        | 2019 | Unclear | Low                                        | Unclear                                | Unclear                                                | Low                                         | Low                                    | Low                               | Low       |
| Vrettakis    | 2013 | Unclear | Low                                        | Low                                    | Unclear                                                | Low                                         | Low                                    | Low                               | Low       |
Table S6: QUOROM Statement checklist

| Heading     | Subheading                                                                 | Descriptor                                                                 | Reported? (Y/N) | Page Number |
|-------------|-----------------------------------------------------------------------------|-----------------------------------------------------------------------------|-----------------|-------------|
| Title       |                                                                             | Identify the report as a systematic review                                   | Y               | 1           |
| Abstract    |                                                                             | Use a structured format                                                      | Y               | 2           |
| Objectives  |                                                                             | The clinical question explicitly                                             | Y               | 2           |
| Data sources|                                                                             | The databases (ie, list) and other information sources                       | Y               | 2           |
| Review      |                                                                             | The selection criteria (ie, population, intervention, outcome, and study design); methods for validity assessment, data abstraction, and study characteristics, and quantitative data synthesis in sufficient detail to permit replication | Y               | 2           |
| Results     |                                                                             | Characteristics of the RCTs included and excluded; qualitative and quantitative findings (ie, point estimates and confidence intervals); and subgroup analyses | Y               | 2           |
| Conclusion  |                                                                             | The main results                                                            | Y               | 2           |
| Describe    | Introduction                                                                | The explicit clinical problem, biological rationale for the intervention, and rationale for review | Y               | 3, 4        |
| Methods     | Searching                                                                   | The information sources, in detail (eg, databases, registers, personal files, expert informants, agencies, hand-searching), and any restrictions (years considered, publication status, language of publication) | Y               | 5           |
| Selection   |                                                                             | The inclusion and exclusion criteria (defining population, intervention, principal outcomes, and study design) | Y               | 5, 6        |
| Validity    | assessment                                                                 | The criteria and process used (eg, masked conditions, quality assessment, and their findings) | Y               | 6           |
| Data        | abstraction                                                                | The process or processes used (eg, completed independently, in duplicate)   | Y               | 5, 6        |
| Study       | characteristics                                                             | The type of study design, participants’ characteristics, details of intervention, outcome definitions, and how clinical heterogeneity was assessed | Y               | 5, 6        |
| Quantitative data synthesis |                                                                           | The principal measures of effect (eg, relative risk), method of combining results (statistical testing and confidence intervals), handling of missing data; how statistical heterogeneity was assessed; a rationale for any a-priori sensitivity and subgroup analyses; and any assessment of publication bias | Y               | 7           |
| Results     | Trial flow                                                                  | Provide a meta-analysis profile summarising trial flow (see figure)          | Y               | 8           |
| Study       | characteristics                                                             | Present descriptive data for each trial (eg, age, sample size, intervention, dose, duration, follow-up period) | Y               | 8-11        |
| Quantitative data synthesis |                                                                           | Report agreement on the selection and validity assessment; present simple summary results (for each treatment group in each trial, for each primary outcome); present data needed to calculate effect sizes and confidence intervals in intention-to-treat analyses (eg 2X2 tables of counts, means and SDs, proportions) | Y               | 8-11        |
| Discussion  |                                                                             | Summarise key findings; discuss clinical inferences based on internal and external validity; interpret the results in light of the totality of available evidence; describe potential biases in the review process (eg, publication bias); and suggest a future research agenda | Y               | 12-15       |
Figure S1: Forest plots of all measured outcomes.
### Postoperative cognitive decline

| Study or Subgroup | NIRS monitoring Events | Control Events Total | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|------------------------|----------------------|-----------------------------|-------------------------------|
|                   | Total                  |                      |                             |                               |
| Kellra 2015       | 7                      | 43                   | 19 28 21%                   | 0.17 [0.06, 0.49]             |
| Slater 2009       | 73                     | 125                  | 70 115 24%                 | 0.90 [0.54, 1.51]             |
| Subtotal (95% CI) | 168                    | 151                  | 146.4%                      | 0.42 [0.08, 2.11]             |
| Total events      | 80                     | 69                   |                              |                               |
|                   |                        |                      |                             |                               |
|                   |                        |                      | Heterogeneity: Tau^2 = 1.18; Chi^2 = 7.72, df = 1 (P = 0.006); P = 87% |
|                   |                        |                      | Test for overall effect: Z = 1.95 (P = 0.29) |

| Study or Subgroup | NIRS monitoring Events | Control Events Total | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|------------------------|----------------------|-----------------------------|-------------------------------|
|                   | Total                  |                      |                             |                               |
| Colak 2014        | 26                     | 94                   | 50 96 24%                   | 0.35 [0.19, 0.64]             |
| Mohandas 2013      | 2                      | 50                   | 34 50 18.5%                | 0.02 [0.00, 0.09]             |
| Subtotal (95% CI) | 144                    | 146                  | 42.7%                      | 0.09 [0.01, 1.63]             |
| Total events      | 28                     | 84                   |                              |                               |
|                   |                        |                      | Heterogeneity: Tau^2 = 4.01; Chi^2 = 12.32, df = 1 (P = 0.0004); P = 92% |
|                   |                        |                      | Test for overall effect: Z = 1.63 (P = 0.10) |

| Study or Subgroup | NIRS monitoring Events | Control Events Total | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|------------------------|----------------------|-----------------------------|-------------------------------|
|                   | Total                  |                      |                             |                               |
| Mohandas 2013      | 0                      | 50                   | 22 50 11.0%                 | 0.01 [0.00, 0.21]             |
| Subtotal (95% CI) | 50                     | 50                   | 11.0%                       | 0.01 [0.00, 0.21]             |
| Total events      | 100                    | 195                  |                              |                               |
|                   |                        |                      | Heterogeneity: Chi^2 = 4.64, df = 2 (P = 0.10), P = 66.9% |
|                   |                        |                      | Test for overall effect: Z = 3.02 (P = 0.003) |

### Postoperative delirium

| Study or Subgroup | NIRS monitoring Events | Control Events Total | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|------------------------|----------------------|-----------------------------|-------------------------------|
|                   | Total                  |                      |                             |                               |
| Bennett 2020      | 4                      | 90                   | 6 91 10.9%                  | 0.66 [0.18, 2.42]             |
| Colak 2014        | 8                      | 94                   | 13 96 22.5%                 | 0.59 [0.23, 1.51]             |
| Deschamps 2016    | 4                      | 34                   | 7 46 10.0%                  | 0.74 [0.20, 2.77]             |
| Lei 2017          | 30                     | 123                  | 31 126 44.3%                | 0.99 [0.55, 1.76]             |
| Uysal 2019        | 2                      | 59                   | 7 66 12.2%                  | 0.30 [0.06, 1.48]             |
| Total (95% CI)    | 400                    | 425                  | 100.0%                      | 0.75 [0.50, 1.14]             |
| Total events      | 48                     | 64                   |                              |                               |
|                   |                        |                      | Heterogeneity: Tau^2 = 2.43, df = 4 (P = 0.66); I^2 = 0% |
|                   |                        |                      | Test for overall effect: Z = 1.34 (P = 0.18) |

### Number of patients who had intraoperative cerebral desaturation

| Study or Subgroup | NIRS monitoring Events | Control Events Total | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|------------------------|----------------------|-----------------------------|-------------------------------|
|                   | Total                  |                      |                             |                               |
| Mrukkin 2007      | 0                      | 100                  | 6 100 6.5%                  | 0.07 [0.00, 1.30]             |
| Slater 2009       | 33                     | 125                  | 35 115 27.4%                | 0.02 [0.01, 1.47]             |
| Deschamps 2013    | 16                     | 21                   | 10 26 8.7%                  | 0.72 [0.20, 2.69]             |
| Deschamps 2016    | 34                     | 102                  | 46 99 31.8%                 | 0.50 [0.33, 0.96]             |
| Lei 2017          | 44                     | 123                  | 44 126 28.5%                | 1.04 [0.52, 2.17]             |
| Total (95% CI)    | 473                    | 465                  | 100.0%                      | 0.75 [0.55, 1.01]             |
| Total events      | 127                    | 150                  |                              |                               |
|                   |                        |                      | Heterogeneity: Chi^2 = 4.94, df = 4 (P = 0.29); P = 19% |
|                   |                        |                      | Test for overall effect: Z = 1.87 (P = 0.06) |

### Mortality

| Study or Subgroup | NIRS monitoring Events | Control Events Total | Odds Ratio M-H, Fixed, 95% CI | Odds Ratio M-H, Random, 95% CI |
|-------------------|------------------------|----------------------|-----------------------------|-------------------------------|
|                   | Total                  |                      |                             |                               |
| Murkin 2007       | 0                      | 100                  | 1 100 7.5%                  | 0.33 [0.01, 8.20]             |
| Lau 2012          | 1                      | 12                   | 0 13 2.1%                   | 3.52 [0.13, 95.09]            |
| Vretzakis 2013    | 1                      | 75                   | 1 75 5.0%                   | 1.00 [0.06, 16.29]            |
| Deschamps 2016    | 4                      | 34                   | 6 46 22.7%                  | 0.89 [0.23, 3.43]             |
| Rogers 2017       | 1                      | 89                   | 2 89 10.0%                  | 0.49 [0.04, 5.53]             |
| Lei 2017          | 3                      | 123                  | 4 126 19.5%                 | 0.76 [0.17, 3.48]             |
| Uysal 2019        | 2                      | 59                   | 1 66 4.6%                   | 2.28 [0.20, 25.82]            |
| Bennett 2020      | 5                      | 91                   | 6 91 28.6%                  | 0.82 [0.24, 2.80]             |
| Total (95% CI)    | 583                    | 606                  | 100.0%                      | 0.89 [0.47, 1.69]             |
| Total events      | 17                     | 21                   |                              |                               |
|                   |                        |                      | Heterogeneity: Chi^2 = 1.90, df = 7 (P = 0.97); I^2 = 0% |
|                   |                        |                      | Test for overall effect: Z = 0.35 (P = 0.72) |

Figure S1: Contd...