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REPORTS OF ORIGINAL INVESTIGATIONS

Intraoperative cerebral oximetry-based management for optimizing perioperative outcomes: a meta-analysis of randomized controlled trials

Gestion peropératoire basée sur l'oxymétrie cérébrale pour améliorer les résultats périopératoires : méta-analyse d'essais randomisés contrôlés

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Abstract

Purpose *Although evidence from observational studies in a variety of clinical settings supports the utility of cerebral oximetry as a predictor of outcomes, prospective clinical trials thus far have reported conflicting results. This systematic review and meta-analysis was designed to evaluate the influence of management associated with intraoperative cerebral oximetry on postoperative outcomes. The primary outcome was postoperative cognitive dysfunction (POCD), with secondary outcomes that included postoperative delirium, length of intensive care unit (ICU) stay, and hospital length of stay (LOS).*

Source *After searching the PubMed, EMBASE, Cochrane Library, Scopus, and Google Scholar databases, all randomized controlled trials (RCTs) assessing the impact of intraoperative cerebral oximetry-guided management on clinical outcomes following surgery were identified.*

Principal findings *Fifteen RCTs comprising 2,057 patients (1,018 in the intervention group and 1,039 in control group) were included. Intraoperative management guided by the use of cerebral oximetry was associated with a reduction in the incidence of POCD (risk ratio [RR] 0.54; 95% confidence interval [CI], 0.33 to 0.90; P = 0.02; I^2 = 85%) and a significantly shorter length of ICU stay (standardized mean difference [SMD], −0.21 hr; 95% CI, −0.37 to −0.05; P = 0.009; I^2 = 48%). In addition, overall hospital LOS (SMD, −0.06 days; 95% CI, −0.18 to 0.06; P = 0.29; I^2 = 0%) and incidence of postoperative delirium (RR, 0.69; 95% CI, 0.36 to 1.32; P = 0.27; I^2 = 0%) were not impacted by the use of intraoperative cerebral oximetry.*

Conclusions *Intraoperative cerebral oximetry appears to be associated with a reduction in POCD, although this result should be interpreted with caution given the significant heterogeneity in the studies examined. Further large (ideally multicentre) RCTs are needed to clarify whether POCD can be favourably impacted by the use of cerebral oximetry-guided management.*

Résumé

Objectif *Alors que les données probantes provenant d'études observationnelles réalisées dans différents cadres cliniques témoignent de l'intérêt de l'oxymétrie cérébrale comme élément prédictif des résultats, les essais*

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cliniques prospectifs ont — jusqu'à ce jour — fourni des résultats contradictoires. Cette étude et méta-analyse systématique a été conçue pour évaluer l'influence de la gestion associée à l'oxymétrie cérébrale peropératoire sur les résultats postopératoires. Le critère d'évaluation principal était la dysfonction cognitive postopératoire (POCD) et les critères d'évaluation secondaires étaient, notamment, le délirium postopératoire, la durée du séjour en unité de soins intensifs (USI) et la durée de séjour à l'hôpital (DSH).

Source *Après une recherche dans les bases de données PubMed, EMBASE, Cochrane Library, Scopus et Google Scholar, tous les essais contrôlés randomisés (ECR) évaluant l'impact de la gestion peropératoire guidée par l'oxymétrie cérébrale sur les résultats cliniques postopératoires ont été identifiés.*

Constatations principales *Quinze essais cliniques randomisés ayant inclus 2 057 patients (1 018 dans le groupe interventionnel et 1 039 dans le groupe témoin) ont été inclus. La gestion peropératoire guidée par l'utilisation de l'oxymétrie cérébrale a été associée à une réduction de l'incidence du POCD (rapport de risque [RR] 0,54; intervalle de confiance à 95 % [IC] : 0,33 à 0,90; P = 0,02; I^2 = 85 %) et à une plus brève durée de séjour en USI (différence moyenne standardisée [SMD] : −0,21 h; IC à 95 % : −0,37 à −0,05; P = 0,009; I^2 = 48 %). De plus, la durée de séjour globale à l'hôpital (SMD : −0,06 jour; IC à 95 % : −0,18 à 0,06; P = 0,29; I^2 = 0 %) et l'incidence du delirium postopératoire (RR : 0,69; IC à 95 % : 0,36 à 1,32; P = 0,27; I^2 = 0 %) n'ont pas été affectées par l'utilisation de l'oxymétrie cérébrale peropératoire.*

Conclusions *L'oxymétrie cérébrale peropératoire semble associée à une réduction du POCD, mais ce résultat doit être interprété avec prudence compte tenu de l'importante hétérogénéité entre les études analysées. D'autres essais cliniques randomisés avec suffisamment de patients (idéalement multicentriques) sont nécessaires pour savoir si le POCD peut être favorablement influencé par l'utilisation de la gestion cérébrale guidée par oxymétrie.*

Cerebral oximetry uses near-infrared spectroscopy (NIRS) to provide real-time non-invasive interrogation of regional cerebral oxygen saturation (rSO_2) and has become an increasingly popular intraoperative monitoring technique.[1] Measuring rSO_2 in a representative volume of frontal cortex brain tissue (and assuming stable metabolic suppression of the brain under anesthetic conditions), it has been seen as a surrogate of cerebral blood flow and thus as a useful technology to detect cerebral hypoperfusion.[1,2] It is thought to be particularly beneficial in the perioperative setting when hemodynamic fluctuations often occur that can lead to postoperative complications such as cognitive impairment or delirium.[2-6] Anesthesiologists have utilized cerebral oximetry monitoring in an attempt to optimize both blood pressure and oxygen delivery to maintain adequate cerebral perfusion and decrease the incidence of these neurocognitive complications.[2,5]

Several observational studies have pointed to the predictive value of cerebral oxygenation monitoring for both short- and long-term functional outcomes.[7-9] It has been suggested that in cardiac surgery patients, in addition to those following cardiac arrest or with a diagnosis of sepsis, rSO_2 (< 60%) may be associated with an increased risk of adverse outcomes.[10-12] An additional study in aortic arch surgery patients concluded that reduced intraoperative cerebral oxygen saturation was not only associated with extended hospital stay, but also increased overall hospital costs.[13] Furthermore, given an inherent increase in the physical and financial burden of patient care associated with cognitive dysfunction following surgery,[14] additional efforts directed towards cerebral monitoring and postoperative cognitive dysfunction (POCD) prevention are warranted. Although cerebral oximetry monitoring has been available as a clinical tool for two decades, little consensus exists regarding the role of cerebral oximetry-based management in the perioperative period. Several prospective trials have attempted to assess the impact of cerebral oximetry on postoperative cognitive outcomes; however the results have remained conflicting.

The purpose of this systematic review and meta-analysis was to determine the overall beneficial effect of cerebral oximetry on select outcomes after surgery.

Methods

This meta-analysis followed the guidelines outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[15] It was also registered on the International Prospective Systematic Reviews Registry database (PROSPERO 2017: CRD42017057293) on 14 February 2017.

Search strategy

The MEDLINE/PubMed, EMBASE, Cochrane Library, Scopus, and Google Scholar databases were searched from inception to 2 December 2017 for randomized-controlled trials (RCTs) assessing the effects of intraoperative cerebral oximetry monitoring on postoperative outcomes following cardiac and non-cardiac surgery. There was no restriction on language. In addition, article citations were

reviewed to ensure inclusion of relevant studies not captured in our initial literature search. The clinicaltrials.gov registry was also searched to evaluate for any ongoing RCT where results might be expected to be published in the near future. Two authors (A.Z.V. and R.J.H.) reviewed the literature and screened the abstracts independently. Full-text articles that met the inclusion criteria were reviewed for detailed comprehension and further assessment of the quality and risk of bias. All disagreements between reviewers in the selection and evaluation processes were resolved by discussion with a third reviewer (M.C.G.). All demographic data, including year of publication, sample size, intervention algorithm, type of surgery, anesthetic management, and specified outcomes, were abstracted in a predefined manner.

Eligibility criteria

We limited our meta-analysis to RCTs of adult patients (age $>$ 18 yr) who underwent either cardiac or non-cardiac surgery. The intervention group was monitored with NIRS (interventions specified below) while the control group was not.

Interventions considered

Management guided by the use of intraoperative cerebral oximetry was considered the primary intervention and was triggered by evidence of cerebral oxygen desaturation. Specific interventions included the use of fluids and/or vasopressors for hypotension, an increase in pump flow to maintain the cardiac index above 2 $L{\cdot}m^{-2}{\cdot}min^{-1}$, changes in ventilatory parameters (i.e., optimizing the partial pressure arterial oxygen and carbon dioxide), and blood transfusion if anemic. Thresholds for intervention were generally an $rSO_2 < 55$-60% or $rSO_2 < 75\%$ of baseline. Prior experimental work has suggested that critical neurologic deficits are more likely to occur with more than a 30% reduction in rSO_2,[16] and to establish a rational approach, our search also involved the selection of studies wherein a more conservative intervention threshold was utilized.[17]

Outcomes

The primary outcome in this meta-analysis was the incidence of POCD as defined by the individual studies. Most articles used a combination of standardized assessments of cognitive functions such as the Mini-Mental Status Examination (MMSE), grooved pegboard, anti-saccadic eye movement, color trail, and Montreal Cognitive Assessment. Secondary outcomes included intensive care unit (ICU) length of stay (LOS), overall hospital LOS, as well as the incidence of total transfusion, delirium, surgical site infection, cardiac complications, and mortality. Individual study definitions were also used for secondary outcomes. The time interval to evaluate delirium and POCD outcomes was within one week after surgery.

Assessment of methodologic quality and quality of evidence

Methodologic quality assessment was performed using the Cochrane risk of bias tool for randomized studies.[18] Each study was assessed based upon seven domains of potential bias (random sequence generation, allocation concealment, blinding of intervention, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias). The overall risk of bias of individual studies was classified as high if at least one domain was determined at high risk or if there were more than two domains of unclear risk, moderate if at least two domains were determined at unclear risk, and low if all the domains were determined at low risk. The quality of the evidence provided in this meta-analysis was also assessed using five levels of evidence, ranging from level I to III with three subcategories in level II, as previously reported.[19]

Statistical analysis

Initially, an exploratory qualitative analysis was conducted to describe the characteristics of the studies included in this meta-analysis. The incidence of POCD was extracted as a dichotomous variable (present or absent) and compared using risk ratios (RR) with their respective 95% confidence intervals (CI). We used forest plots to illustrate the estimations and overall effect sizes with pooled RR represented as a solid diamond at the bottom of the forest plot. Outcomes presented as continuous variables were compared using the standardized mean difference (SMD). In cases of publication of median values with their ranges, we converted these measures into mean and standard deviations (SD) using the method of Wan *et al*.[20] In cases where 95% CI of mean values was included, the SD was calculated using a standard formula. Predetermined subgroup analyses were performed based upon type of surgery (cardiac versus non-cardiac surgery) and type of cerebral oximetry-based intervention. Sensitivity analysis was performed based upon overall study quality (high or moderate versus low) as determined by quality of evidence assessment.

Heterogeneity (I^2) was assessed using the correspondent Chi-squared test ($I^2 < 50\%$ and $I^2 > 50\%$ were considered insignificant and significant heterogeneity, respectively). Publication bias was calculated using the Begg's and Egger's tests[21] with funnel plots constructed to represent

any tendency for publishing in favour of positive effects. Significant publication bias was considered when there was asymmetry in the funnel plot and a statistically significant bias coefficient was noted on the Beggs's test.[21] $P < 0.05$ was considered statistically significant for all the statistical tests. All analyses were performed using a random-effect model (DerSimonian and Laird method).[22] All statistics were performed using Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) or Stata version 13.0 (Stata, College Station, TX, USA).

Results

Literature search and selection

Our initial search yielded 3,177 records. After excluding duplicate studies, we screened a total of 1,454 titles and abstracts. Of these, 26 full-text articles met the full inclusion criteria. Two RCTs were excluded because of a lack of demographic and/or outcomes data.[23,24] An additional nine RCTs were excluded as they did not involve the target intervention comparison.[25-34] Two additional RCTs were excluded because they were published as an abstract[35,36] and one RCT was excluded because although it correlated anesthetic depth with cerebral oximetry, it did not detail the associated intervention.[37] Finally, three additional trials were identified from reference lists of the articles included.[7,38,39] Figure 1 outlines the full results of article selection. In total, 15 RCTs were included in this meta-analysis.[7,17,38-50]

Study characteristics

The Table summarizes the characteristics of the included studies. Ten RCTs included patients undergoing cardiac surgery (coronary artery bypass, valve replacement or

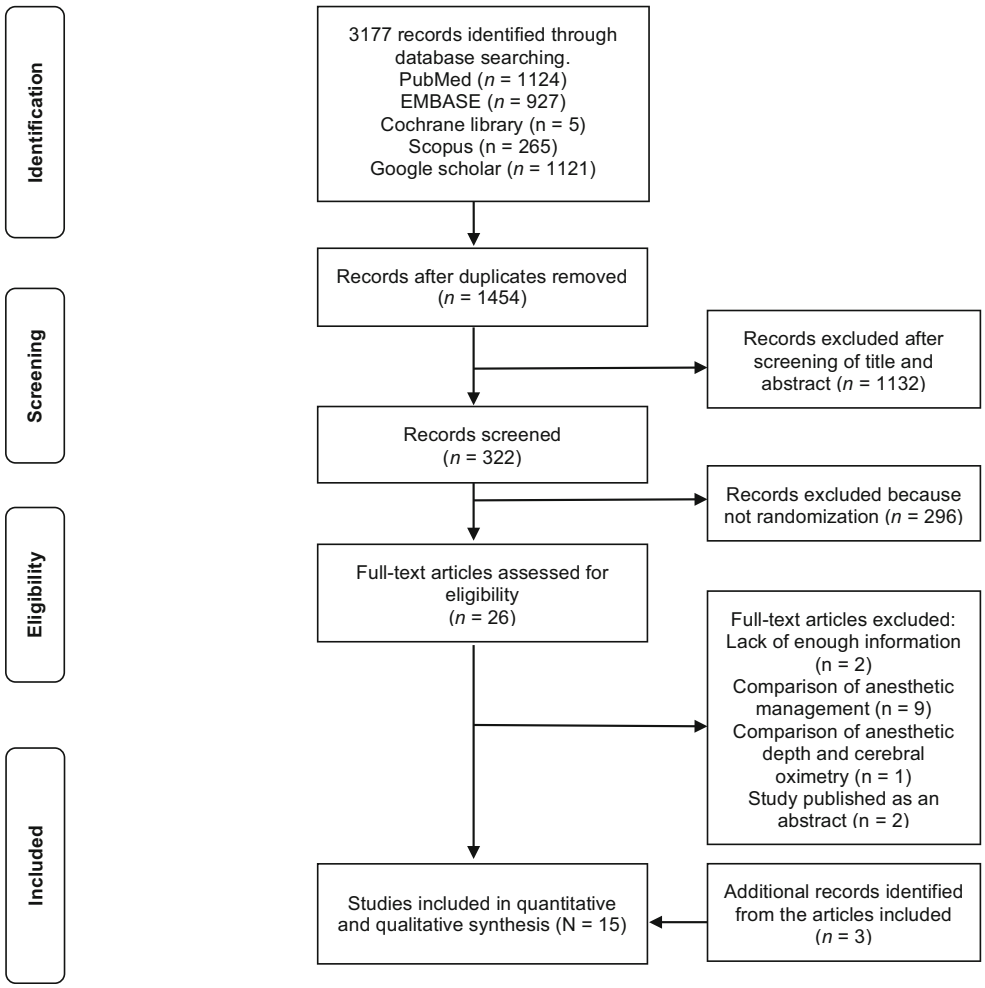

Fig. 1 PRISMA flow chart of the selection of studies

Table Characteristics of studies included in the analysis

Study, (reference)	Surgery/number of participants	Anesthetic management	NIRS device	Definition of desaturation	Intervention	Extracted outcomes
Casati *et al.* 2005[40]	Major abdominal surgery (laparoscopic gastric resection, colon resection, hepatic resection) Intervention: 56 Control: 66	General anesthesia (induction: 2 $\mu g \cdot kg^{-1}$ *iv* fentanyl + 5 $mg \cdot kg^{-1}$ sodium thiopental, maintenance: sevoflurane)	INVOS monitor	$rSO_2 < 75\%$ of baseline values	The first step included checking the ventilator, head position, and tubing system, increasing F_iO2, increasing end-tidal CO2 partial pressure if the etCO2 was > 35 mmHg, and increasing arterial blood pressure with intravascular fluid administration (250 mL hetastarch) and vasoconstrictors (ethylephrine 2–5 mg *iv*) if systolic arterial blood pressure was < 90 mmHg. If the first step did not restore acceptable rSO2 values within 60 sec, the second step included the reduction of brain oxygen consumption with an intravenous bolus of propofol (0.5 $mg \cdot kg^{-1}$)	POCD (at one week), MMSE (at one week), PACU discharge, length of hospital stay
Murkin *et al.* 2007[45]	Coronary artery bypass graft Intervention: 100 Control: 100	General anesthesia (induction: 10-30 $\mu g \cdot kg^{-1}$ *iv* fentanyl + 5 $mg \cdot kg^{-1}$ sodium thiopental, maintenance: isoflurane 0.5%)	INVOS-5100	rSO_2 values at or above 75% of the baseline	Head positioning, achieve $PaCO_2$ > 40 mmHg, achieve an MAP > 60 mmHg, jugular venous pressure < 10 mmHg, heart repositioning, achieve cardiac index > 2.0 $L \cdot m^{-2} \cdot min^{-1}$ (pump flow increased to 2.5 $L \cdot m^{-2} \cdot min^{-1}$), increase in F_iO_2, or propofol 50-100 mg bolus. If hematocrit was below 20% red blood cell transfusion was administered	ICU stay, length of hospital stay, patients transfused, wound infection, myocardial infarction
Slater *et al.* 2009[46]	Cardiac surgery (patent foramen ovale repair, mitral valve repair) Intervention: 125 Control: 115	NA	INVOS-5100BTM	rSO_2 drop more than 20% of the baseline value	Head repositioning, increasing $PaCO_2$, increasing MAP, adjusting pump flow rate or anesthetic depth; reduction of temperature; vasodilation; or blood transfusion	POCD (at hospital discharge), length of hospital stay
Cohn *et al.* 2010[47]	Elective open colorectal surgery Intervention: 18 Control: 9	NA	InSpectra-650 monitor	rSO_2 drop more than 20% of the baseline value	Additional fluids were only administered when the Restricted Hypovolemia Fluid Regimen was activated for: StO2 < 75%, or 20% below baseline, sustained for at least three minutes	LOS, infection rate

Table continued

Study, (reference)	Surgery/number of participants	Anesthetic management	NIRS device	Definition of desaturation	Intervention	Extracted outcomes
Zogogiannis *et al.* 2011[39]	Carotid endarterectomy Intervention: 83 Control: 86	General anesthesia (induction: fentanyl and propofol, maintenance: remifentanil infusion, sevoflurane in oxygen and nitrous oxide)	INVOS-4100	rSO_2 drop more than 20% of the baseline value	INVOS-4100 (Somanetics Inc., Troy MI) was visible and intervention was based on the methodology described by Denault *et al.*[51] (verify head position, administer vasopressors if hypotension, raise $etCO_2$, raise F_iO_2)	POCD (at one week)
Ballard *et al.* 2012[48]	Orthopedic and abdominal elective surgeries Intervention: 34 Control: 38	General anesthesia (induction: propofol; maintenance: isoflurane)	INVOS monitor	rSO_2 drop more than 15% of baseline value or absolute $rSO_2 < 50\%$	Bring blood pressure to within 10% of baseline using fluids or inotropes, increasing F_iO_2 to 50%, $etCO_2$ increased to above 5.5%, consider transfusion if hemoglobin < 9 g·dL^{-1}	POCD (one week), MMSE (at one week), postoperative delirium (at one week)
Mohandas *et al.* 2013[44]	Cardiac surgery (atrial septum defect, patent foramen ovale repair, mitral valve repair) Intervention: 50 Control: 50	General anesthesia (induction: midazolam [1-3 mg], propofol [0.5 mg·kg^{-1}] and fentanyl [5-10 μg·kg^{-1} *iv*]; maintenance: fentanyl boluses, and isoflurane in oxygen)	Equanox-7600	rSO_2 below 85% of the baseline or an absolute value below 50% for one minute or longer	Repositioning of the head, increasing $PaCO_2$; increasing MAP, adjusting the pump flow rate; adjusting the anesthetic depth; reduction of temperature; vasodilatation; increase in the hematocrit. Followed the algorithm proposed by Denault *et al.*[51]	Length of ICU stay, POCD (at one week), MMSE (at one week)
Deschamps *et al.* 2013[42]	High-risk cardiac surgery Intervention: 25 Control: 25	NA	INVOS-4000	20% decrease in rSO_2 value relative to baseline for a duration exceeding 15 sec	Interventions were based on the methodology described by Denault *et al.*[51] (verify head position, administer vasopressors if hypotension, raise $etCO_2$, raise F_iO_2)	Length of ICU stay, LOS
Vretzakis *et al.* 2013[38]	Coronary artery bypass graft and other cardiac surgeries (patent foramen ovale repair, mitral valve repair) Intervention: 75 Control: 75	Total intravenous anesthesia with propofol and remifentanil	INVOS-5100	rSO_2 less than 60 or decreased by 20% of baseline	Transfusion if rSO_2 was less than 60 or decreased by 20% or more compared with the mean value during pulmonary artery catheter insertion	Blood transfusion requirement, length of ICU stay, length of hospital stay
Cowie *et al.* 2014[7]	Total knee or hip arthroplasty or bowel resection surgery Intervention: 20 Control: 20	General anesthesia (not specified)	INVOS monitor	rSO_2 drop more than 25% of the baseline value	Avoid obstruction of neck veins and optimizing MAP, $etCO_2$, and hemoglobin concentration	Length of hospital stay, infection rate

Table continued

Study, (reference)	Surgery/number of participants	Anesthetic management	NIRS device	Definition of desaturation	Intervention	Extracted outcomes
Colak *et al.* 2015[41]	Coronary artery bypass graft Intervention: 94 Control: 96	General anesthesia (induction: midazolam and sufentanyl; maintenance: continuous sufentanyl infusion, propofol and sevoflurane)	INVOS-5100C	rSO_2 below 80% of the baseline value or absolute $rSO_2 < 50\%$	Repositioning of the head, increase cerebral oxygen delivery (increasing F_iO_2, pCO_2, MAP, cardiac output or pump flow and hematocrit) or to reduce cerebral oxygen consumption (increasing of anesthetic depth and reduction of temperature)	Transfusions requirement, myocardial infarction, infection rate, length of ICU stay, postoperative delirium (at one week) and POCD (at one week)
Kara *et al.* 2015[43]	Coronary artery bypass graft Intervention: 43 Control: 36	NA	INVOS-5100C	rSO_2 fall from baseline of greater than 20%	Head positioning, MAP > 60 mmHg, FiO_2, $PaCO_2 > 40$ mmHg, transfusion if hematocrit < 20%, increase depth of anesthesia, and reducing temperature	Length of ICU stay, LOS, POCD (no time specified), MoCA (no time specified)
Deschamps *et al.* 2016[17]	High-risk cardiac surgery (coronary bypass plus valve replacement or repair) Intervention: 99 Control: 102	Accordance with Canadian guidelines	INVOS-5100PB (Covidien, USA), FORE-SIGHT (CAS Medical Systems Inc., USA), Equanox Classic 7600 (Nonin Medical Inc., USA)	10% decrease in rSO_2 value relative to baseline for a duration exceeding 15 sec	Followed the Denault *et al.*[51] algorithm (verify head position, administer vasopressors if hypotension, raise $etCO_2$, raise F_iO_2)	Length of ICU stay, LOS, MOMM, postoperative delirium (at discharge), myocardial infarction, transfusion requirement, infection rate
Rogers *et al.* 2017[50]	Cardiac surgery (coronary artery bypass, valve surgery) Intervention: 98 Control: 106	Not available	INVOS 5100 (Medtronic Inc., Minneapolis, MN, USA)	Absolute rSO_2 value < 50% or below 70% of baseline	Followed the Murkin *et al.* algorithm	Length of ICU stay, LOS, myocardial infarction, transfusion requirement, infection rate, mortality
Lei *et al.* 2017[49]	Cardiac surgery (coronary artery bypass, valve replacement) Intervention: 123 Control: 126	General anesthesia (induction: fentanyl, propofol, rocuronium; maintenance: isoflurane)	INVOS 5100C (Covidien, USA)	SO_2 below 75% of the baseline value for one minute or longer	Followed the Denault *et al.*[51] algorithm (verify head position, administer vasopressors if hypotension, raise $etCO_2$, raise F_iO_2)	Length of ICU stay, LOS, postoperative delirium (at discharge), myocardial infarction, transfusion requirement, mortality

$etCO_2$ = end-tidal carbon dioxide; F_iO_2 = fraction of inspired oxygen; INVOS = IN-Vivo Optimal Spectroscopy, ICU = intensive care unit, LOS = length of hospital stay, MAP = mean arterial pressure; MoCA = Montreal Cognitive Assessment; MSSE = Mini-Mental State Examination; MOMM = major organ morbidity and mortality; NA = not available, PACU = postanesthesia care unit; POCD = postoperative cognitive dysfunction; rSO_2 = regional cerebral oxygen saturation

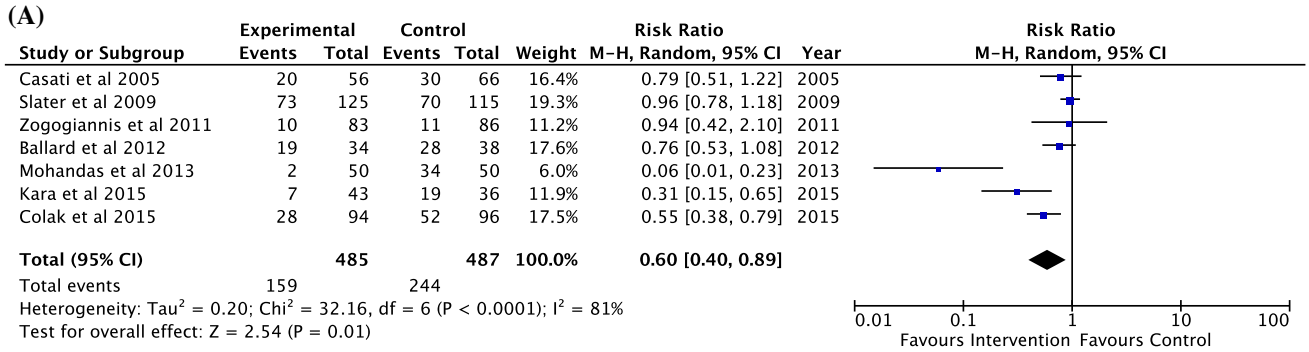

Fig. 2 Forest plots illustrating A) the incidence of postoperative cognitive dysfunction and B) Mini-Mental State Examination score between intervention and control groups

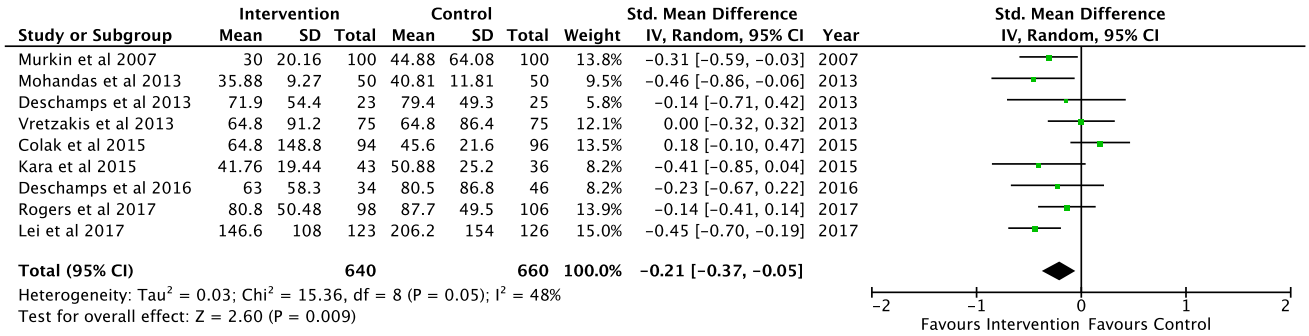

Fig. 3 Pooled effect of cerebral oximetry-guided management on the length of stay in the intensive care

repair),[17,38,39,41-46,50] one RCT was in carotid endarterectomy surgery,[39] two RCTs included only major abdominal surgery,[40,47] and two RCTs included both arthroplasty and abdominal surgeries.[7,48] A total of 2,057 patients (1,018 in the intervention group and 1,039 in control group) were included in the overall analysis. The intervention in 13 RCTs was the correction of cerebral oxygen desaturation (i.e., via modifying mechanical ventilation or administering vasopressors), of which seven RCTs followed an algorithm as outlined by Denault *et al.*[17,39,42,44,49-51] while the remainder applied other individualized algorithms. The intervention in two RCTs was a combination of fluid administration and/or transfusion if rSO_2 decreased by more than 20-25% below baseline.[47] The Table also shows the definitions of cerebral desaturation of each study.

Primary outcome

Among the seven trials examining the primary outcome, management associated with the use of intraoperative cerebral oximetry was associated with a significant reduction in POCD at one week (Fig. 2A; RR, 0.60; 95% CI, 0.40 to 0.89; $P < 0.001$, $I^2 = 81\%$) compared with patients who did not receive therapy guided by cerebral oximetry. Subgroup analysis that included only trials involving cardiac surgery resulted in a similar association (RR, 0.55; 95% CI, 0.36 to 0.86; $P = 0.009$; $I^2 = 85\%$), but we found no significant association in non-cardiac surgery (RR, 0.79; 95% CI, 0.61 to 1.02; $P = 0.07$; $I^2 = 0\%$). Among the studies that did not follow the Denault *et al.* algorithm, the results again show a significant association between the use of cerebral oximetry to guide intervention

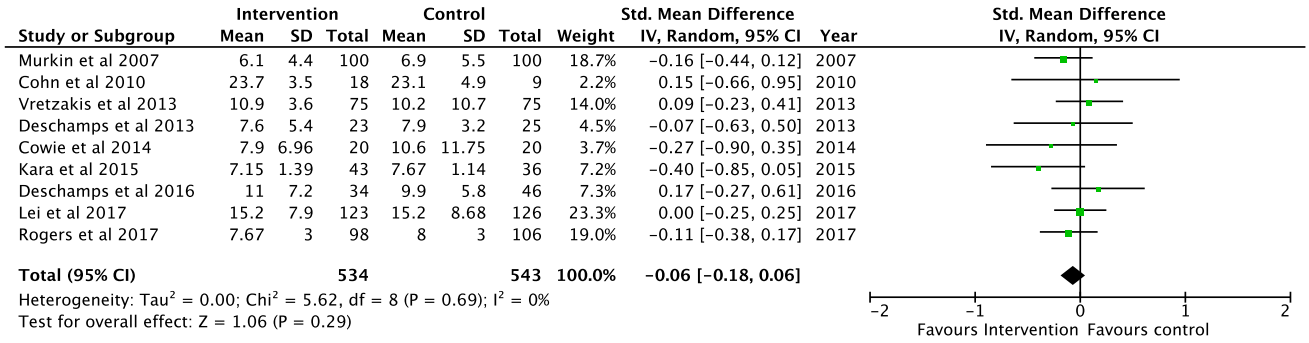

Fig. 4 Pooled effect of cerebral oximetry-guided management on length of hospital stay

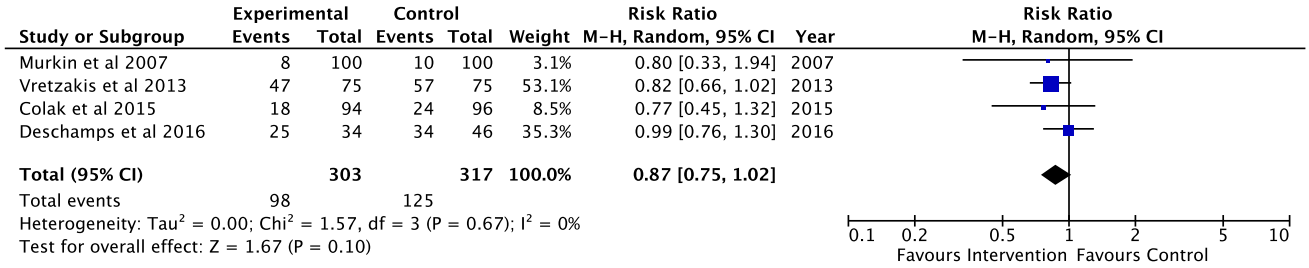

Fig. 5 Pooled effect of cerebral oximetry-guided management on incidence of total red blood cell transfusion

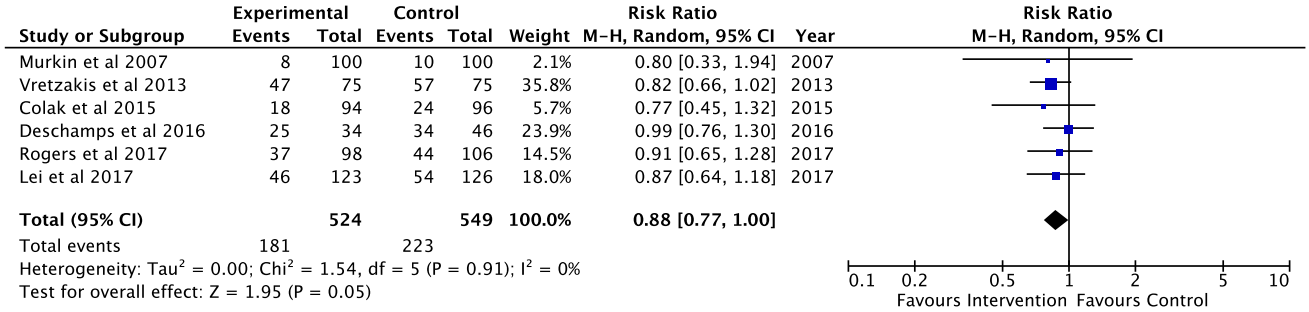

Fig. 6 Pooled effect of cerebral-oximetry guided management on incidence of postoperative delirium

and reduction in POCD (five RCTs; RR 0.6; 95% CI, 0.50 to 0.94; $P = 0.02$; $I^2 = 72\%$). The use of cerebral oximetry-driven interventions was not associated with a statistically higher MMSE at one week (Fig. 2B; SMD, 0.39; 95% CI, −0.03 to 0.80; $P = 0.07$; $I^2 = 79\%$) compared with controls. There was no evidence of publication bias in our analyses (Egger's test bias = −0.05; $P = 0.96$). Sensitivity analysis revealed no significant differences in the overall analysis for either endpoint.

Secondary outcomes

The ICU LOS was examined in eight trials, all of which were conducted in cardiac surgery. Our results suggest that patients in the intervention group have significantly shorter lengths of ICU stay compared with the control group (Fig. 3; SMD, −0.21 hr; 95% CI, −0.37 to −0.05; $P = 0.009$; $I^2 = 48\%$). In subgroup analysis, we found that among the studies that followed the Denault *et al.* algorithm, there was a significant association with a reduction in ICU stay (five RCTs; RR, −0.31 hr; 95% CI, −0.46 to −0.16; $P < 0.001$; $I^2 = 0\%$). In contrast, there was no significant association among the studies that did not follow the Denault *et al.* algorithm (four RCTs; RR, −0.11 hr; 95% CI, −0.38 to 0.15; $P = 0.40$; $I^2 = 63\%$). Among the eight trials that reported on hospital LOS, pooled analysis found no significant difference between the groups (Fig. 4; SMD, −0.06 days; 95% CI, −0.18 to 0.06; $P = 0.29$; $I^2 = 0\%$).

Transfusion was examined in six trials, all of which were conducted in cardiac surgery. Patients monitored with intraoperative cerebral oximetry tended to have fewer

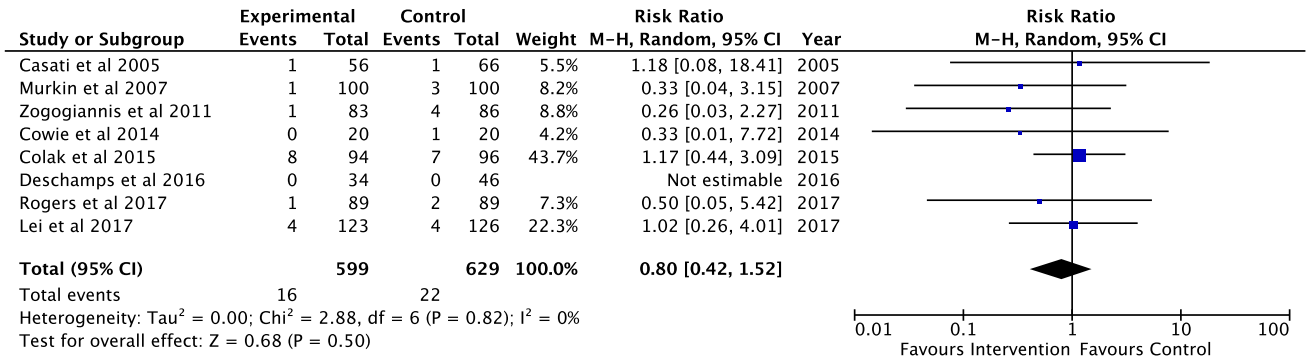

Fig. 7 Pooled effect of cerebral oximetry-guided management on incidence of postoperative myocardial infarction

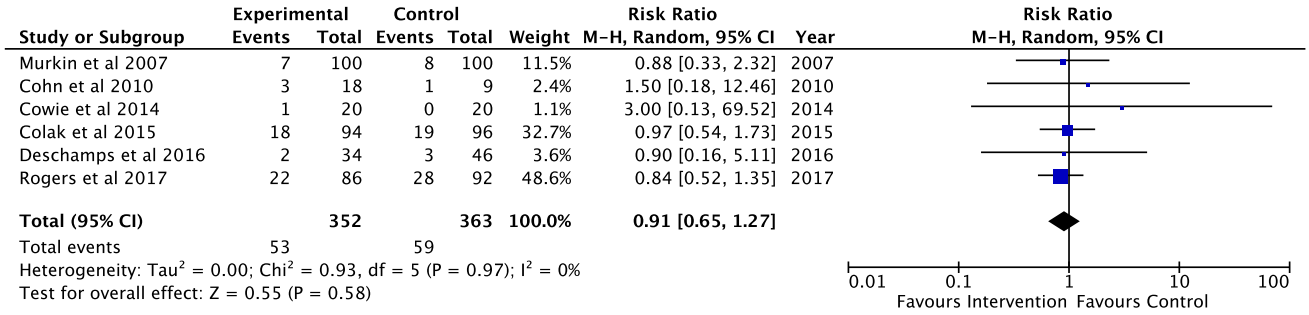

Fig. 8 Pooled effect of cerebral oximetry-guided management on incidence of postoperative surgical site infection

blood transfusions but this did not reach significance compared with the control group (Fig. 4; RR, 0.88; 95% CI, 0.77 to 1.10; $P = 0.05$; $I^2 = 0\%$) (Fig. 5).

Four RCTs specifically assessed for postoperative delirium. There was no significant difference between groups in the incidence of postoperative delirium (Fig. 6; RR, 0.90; 95 % CI, 0.63 to 1.29; $P = 0.57$; $I^2 = 0\%$).

The results of pooled analysis in the eight trials that reported on myocardial infarction suggested no significant difference between groups (Fig. 7; RR, 0.80; 95% CI, 0.42 to 1.52; $P = 0.50$; $I^2 = 0\%$). Subgroup analysis specific to cardiac (RR, 0.98; 95% CI, 0.46-2.06; $P = 0.95$; $I^2 = 0\%$) and non-cardiac (RR, 0.68; 95% CI, 0.09 to 5.40; $P = 0.72$; $I^2 = 0\%$) surgery yielded similar results.

Six RCTs compared the surgical site infection rates between the groups. We found no difference in the rate of infection (Fig. 8; RR, 0.91; 95% CI, 0.65 to 1.27; $P = 0.58$; $I^2 = 0\%$) between groups. Mortality within 30 days of surgery was comparable between the intervention and control group (RR, 0.73; 95% CI, 0.34 to 1.58; $P = 0.42$; $I^2 = 0\%$) (Fig. 9).

Methodologic quality assessment

The electronic supplemental material (ESM) shows the assessment of study quality (ESM Table) and the funnel plots are shown in the ESM figures. We found no evidence of significant asymmetry or publication bias based upon Begg's test (for POCD, $P = 0.36$; for delirium, $P = 0.99$; for mortality, $P = 0.29$; for surgical site infection, $P = 0.99$). Overall, 12 studies were classified at moderate risk and two at high risk of bias.[17,39] Given these results, further sensitivity analysis was not performed based upon risk of bias assessment.

Discussion

This meta-analysis assessed the effects of intraoperative cerebral oximetry-guided management on select postoperative outcomes. The results of this study suggest that interventions associated with intraoperative cerebral oximetry monitoring reduce the incidence of POCD resulting in higher MMSE scores at one week compared with a control population. Similarly we found a significant association with shorter ICU LOS in the oximetry-guided intervention group. Nevertheless, the results of our pooled analysis do not suggest a significant difference in hospital LOS or in the incidence of postoperative delirium, transfusion, surgical site infection, or myocardial infarction.

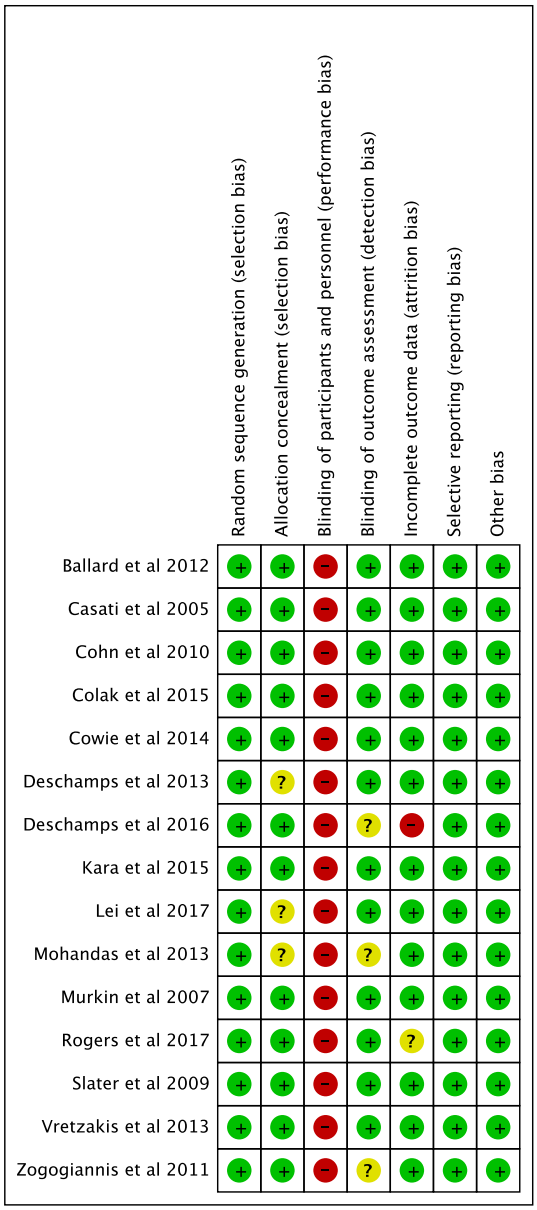

Fig. 9 Summary of the risk of bias assessment of each study

Others have performed meta-analyses to assess the effect of cerebral oximetry monitoring on outcomes after cardiac arrest as well as in extremely low birth weight infants.[52-54] Cournoyer *et al.*[52] included 20 non-randomized studies in a meta-analysis assessing the effects of cerebral oximetry after cardiac arrest and concluded that higher regional cerebral saturation is associated with improved resuscitation outcomes, especially the return to spontaneous circulation.[48] Sorensen et al. concluded that cerebral oximetry monitoring seems important for predicting neurologic complications associated with liver transplantion.[54] Although these prior efforts may provide insight into the potential interventions that might stem from the use of cerebral oximetry, it is worth noting that these populations provided only limited information regarding the surrogacy of cerebral oximetry in an operative cohort.[55,56]

Though not meta-analyses, prior studies designed to illustrate the impact of cerebral oximetry-guided management have qualitatively evaluated the methodology in several populations. At least four systematic reviews have alluded to the potential benefit of cerebral oximetry monitoring in the cardiac surgery population.[9,53,57,58] These reviews concluded that despite a limited amount of high-level clinical evidence, the majority of the literature supports the link of cerebral oximetry monitoring to the prevention of POCD. Indeed, Taillefer *et al.* published a systematic review regarding the use of cerebral oximetry in cardiac surgery, though the authors included only a single RCT,[36] and rightfully concluded that this topic had not yet been sufficiently investigated with the rigour necessary to make a more definitive statement regarding the role of cerebral oximetry in adult cardiac surgery.[53] It is worth mentioning that the review article of Taillefer *et al.* was conducted before the publication of the first RCT in cerebral oximetry.[40] Our analysis was designed to address this limitation through the inclusion of only RCTs that incorporated interventions guided by the use of cerebral oximetry. Furthermore, we primarily investigated the cognitive impact of these interventions.

There are several possible explanations for the association between cerebral oximetry monitoring during surgery and reduction in POCD. Certainly, it is logical to conclude that the reduction in the incidence of low intraoperative cerebral saturation levels (i.e., indicative of potential cerebral hypoxia) might lead to a subsequent reduction in POCD. This is further supported to be a simple mechanism for benefit by other observational studies. A more nuanced interpretation is that POCD is likely secondary to a relative decrease in effective cerebral perfusion. This may be the downstream result of inadequate arterial blood pressure, cerebral autoregulation impairment, or other unidentified hemodynamic indices.[59] While our analysis is unable to specifically evaluate each of these players, cerebral oximetry may represent a useful final common pathway for interpretation of a low perfusion state. Therefore, interventions designed to address one (or all) of these potential variables may provide benefit in reducing the incidence of POCD.

Although our analysis supports the benefit of cerebral oximetry-guided management on the incidence of POCD and a shorter length of ICU stay, it does not show similar impact among a number of other secondary clinical outcomes. Observational studies have previously shown an association between low cerebral oxygen saturation and postoperative delirium.[3,60] Others have shown that the severity or duration of postoperative delirium may ultimately be related to subsequent POCD.[61] While our

analysis did not confirm these results, it is quite possible our pooled analysis included too few patients to adequately assess for postoperative delirium. Furthermore, it is equally plausible that patients may develop POCD without showing signs of early postoperative delirium.

There are several potential implications of these study results. First, they suggest that intraoperative management guided by cerebral oximetry may have applications in the postoperative period. Interventions designed to maintain baseline cerebral perfusion and/or oxygen saturation may prevent POCD and even reduce the length of ICU stay. Second, the interventions described among the included studies are relatively simple and largely include modifications to ventilation strategies, supplementation of additional oxygen, or application of vasopressor support. These do not represent particularly invasive strategies, and therefore it would not be difficult or particularly controversial to begin to develop goal-directed cerebral perfusion protocols based upon the interventions associated with these included trials.

Several important limitations are associated with our meta-analysis. First, the results of our primary analysis were associated with a significant degree of heterogeneity probably due to the different types of cerebral oximetry-based interventions as well as variations in the definition of cerebral oxygen desaturation, the different combinations of cognitive tests that were used to define POCD among the studies, varying surgical case mixes, and other potential differences in individual study-specific patient populations. A number of strategies were utilized to attempt to determine the cause of this level of heterogeneity, including the use of a random effects model, assessment for publication bias, employment of subgroup analysis, and risk of bias assessment. Second, the relatively short time frame that POCD was assessed (i.e., one week postoperatively) could limit the clinical significance of our findings; however it is important to note that only two trials assessed this outcome at three months and both showed significant reduction of POCD in the intervention group.[44,48] Another limitation of this meta-analysis is the small sample size of the included RCTs. This highlights the need for further large randomized trials designed to investigate similar intervention strategies surrounding the use of intraoperative cerebral oximetry. Although our analysis failed to show a significant association between the use of cerebral oximetry and other secondary outcomes, this may in part be a function of either a low overall incidence of complications or a lack of adequate patient numbers to detect meaningful differences. After searching the databases and international registries of RCTs, we found two completed but not published RCTs (NCT02155868, ISRCTN23557269) and an ongoing RCT (NCT01707446). Similar future initiatives are likely to add substantial clarity to a rapidly evolving field.

In conclusion, intraoperative cerebral oximetry-guided management is associated with significant reduction in the incidence of POCD. Providers may consider the application of cerebral oximetry to inform specific interventions geared towards minimizing cerebral desaturation and hypoperfusion. Although further large high-quality trials are necessary to elucidate which interventions are most effective and how they directly impact cognitive dysfunction, our findings suggest that simple intraoperative maneuvers based upon cerebral oximetry may provide clear benefit.

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Author contributions *Andres Zorrilla-Vaca* contributed to the study conception and design, drafting the manuscript, acquisition of data, and analysis and interpretation of data. *Ryan Healy* was involved in drafting the manuscript and literature search. *Michael C. Grant* was involved in drafting the manuscript and revising it for important intellectual content. *Brijen Joshi* was involved in drafting the manuscript and revising it for important intellectual content. *Lucia Rivera-Lara* was involved in drafting the manuscript and revising it for important intellectual content. *Charles Brown* was involved in drafting the manuscript and revising it for important intellectual content. *Marek A. Mirski* was involved in drafting the manuscript and revising it for important intellectual content.

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