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Review

Effect of combined use of cerebral oximetry and electroencephalogram monitoring on the incidence of perioperative neurocognitive disorders in adult cardiac and non-cardiac surgery: A systematic review of randomized and non-randomized trials

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Abstract

Background: **There is insufficient evidence to recommend using either intraoperative cerebral oximetry or (processed) electroencephalogram (EEG) alone for preventing perioperative neurocognitive disorders (PNDs).**
Objective: **: To evaluate the effectiveness of combined use of cerebral oximetry and electroencephalogram-guided anesthesia on the incidence of PNDs in adult patients undergoing cardiac and non-cardiac interventions.**
Methods: **A PICOS - based systematic review of English articles using Pubmed and Embase (from inception to August 2022) was performed. There were no exclusion criteria regarding the type of the study. Abstract proceedings and new study protocols or ongoing studies were not included. Review articles were analyzed in search of eligible references. All possible terms that were illustrative of PNDs were used.**
Results: **Among the 63 full manuscripts that were analyzed in detail, 15 met the inclusion criteria. We found 2 retrospective, 8 prospective observational and 5 randomized controlled trials of which 1 did not evaluate the use of neuromonitoring in the randomization process. The definition and the methods used to diagnose PNDs were very heterogeneous. Only 8 studies used an algorithm to avoid/treat cerebral oxygen desaturation and/or to treat EEG abnormalities. Overall, there was a tendency towards less PNDs in studies where such an algorithm was used.**
Conclusions: **Our results suggest that integrating information obtained from cerebral oximetry and an EEG monitor may reduce the incidence of PNDs whenever an adapted algorithm is used to improve brain function.**

Keywords: **Postoperative delirium, Postoperative cognitive decline, Neurocognitive disorders, Spectroscopy, Near-Infrared, Electroencephalography.**

Introduction

Perioperative neurocognitive disorders (PNDs) associated with anesthesia and surgery and as defined according to the recent nomenclature[1], may occur in up to 60% of the patients[2].

Many predisposing as well as precipitating factors have been identified in the pathophysiology of PNDs, of which some have been advocated as partly modifiable[3,4]. These modifiable factors are on one hand the regional cerebral oxygen saturation ($rScO_2$), and on the other hand the depth of anesthesia (DOA).

Indeed, low $rScO_2$ as measured by oximetry devices has been associated with the occurrence of PNDs in cardiac[5-7], and non-cardiac surgery[8]. However, in 2020 the American Society for enhanced recovery and Perioperative Quality Initiative (PQI) joint consensus statement agreed that although intraoperative use of cerebral oximetry can detect potentially catastrophic malperfusion events, there is no evidence that it will reduce organ-specific morbidity in cardiac as well as non-cardiac surgery[9].

Otherwise, over the last 10 years much research has been performed regarding the perioperative

Presentation: none. Trial registration: none.

neurotoxicity in the elderly10, and the association between an overdose of anesthetic agents and the occurrence of PNDs[11-13]. Nevertheless, pooled data are not conclusive[14] and in 2020 the American Society for enhanced recovery and PQI joint consensus statement concluded that there is insufficient evidence to recommend use of electroencephalogram (EEG) monitoring for preventing PNDs or mortality[15].

Considering that poor cerebral oxygenation as well as anesthetic overdose may each have a distinct but small influence, combining the two monitors may have a synergistic effect and provide information that is not available with each monitor separately, as such affecting the incidence of PNDs.

The aim of this systematic review is to analyze the effect of combined intraoperative use of cerebral oximetry and (processed) EEG monitor on the incidence of PNDs or any neurological complications including stroke.

Methods

This systematic review conforms to PRISMA (Preferred Reported Items for Systematic reviews and Meta-Analyses). A PICOS (Population, Intervention, Comparator, Outcome, Study design) approach was used to formulate the research question.

The search included only adult human data. We identified all articles from inception to August 2022 that analyzed the association of combined intraoperative use of cerebral oximetry and (processed) EEG monitor on the incidence of PNDs or any neurologic complications. In this regard we also encountered for stroke as stroke is a known complication after cardiac surgery and many included studies were performed in cardiac surgery patients. There was no restriction on the type of surgery. Any comparator was included. The search was limited to English-language reports. There were no exclusion criteria regarding the type of study (retrospective, case reports/case series, review articles). Abstract proceedings and new study protocols or ongoing studies were not included. Review articles were analyzed in depth in search of eligible references. Considering that different terms were used to indicate PNDs, before implementation of the new nomenclature of PNDs in 2018,[1] we used all possible terms that were illustrative of PNDs. The new nomenclature refers to PNDs in the short-term including delirium and delayed neurocognitive recovery. The latter was previously known as early postoperative cognitive dysfunction or decline. PNDs in the longer term includes postoperative neurocognitive disorder, previously called postoperative cognitive dysfunction or decline.

The electronic search strategy used the terms cerebral oximetry, cerebral oxygenation, cerebral near-infrared spectroscopy (NIRS) AND terms that were indicative of DOA monitor, processed or frontal EEG. Additionally, the terms combined and multimodal neuromonitoring were used to highlight the combination of the two cerebral monitors. The search was conducted in two main electronic databases (Pubmed, Embase). The studies were first included based on their title and the abstract, which were evaluated by one author (MM). Table I illustrates the exact search strategy. The information on Table I was independently double checked by a second author (AJS). The full paper of eligible papers was then reviewed by one investigator (MM). A standardized form was used to extract data from the included studies. Extracted information included the following items: type of study; year of publication; type of surgery; type of PNDs; sample size; interventions; type of neuromonitoring and use of any algorithms to treat intraoperative cerebral oxygen desaturation and to adapt DOA. All data retrieved from the eligible papers was checked by the other co-authors (QS and AJS). All authors worked independently.

Results

The PRISMA flow diagram is illustrated in Figure 1. In total 62 manuscripts were eligible for complete review based on the title and/or the abstract. Among the 62 manuscripts, one review article revealed one eligible study based on its description. Sixty-three full manuscripts were thus analyzed in detail to evaluate eligibility for inclusion in this systematic review article. Eventually 15 manuscripts met the overall inclusion criteria. Table II shows the characteristics of the included studies. The included studies analyzed patients undergoing cardiac surgery (N = 7)[7,16-21], carotid surgery (N = 2)[22,23], shoulder surgery in beach chair position (N = 3)[24-26] and other non-cardiac interventions (N = 3)[27,28]. Among the 15 included studies, two were retrospective[16,17], eight were prospective[7,18,19,21,22,24,25,28] and five were a randomized controlled trial (RCT)[20,23,26,27,29]. However, the RCT by Meghawry et al.[26] randomized the patients according to a hypotension induced protocol for shoulder surgery in beach chair position. The randomization did thus not evaluate the use of neuromonitoring. The sample size in the studies varied very much, including 20 up to 1513 patients[28,7]. As expected, the definition of PNDs and the methods used to diagnose PNDs were very

Table I. — Search strategies part 1.

Search Terms	Number of hits Embase Search Strategy	Number of hits Pubmed Search Strategy
Combined neuromonitoring	442	305
Combined neuromonitoring AND POCD	1	0
Combined neuromonitoring AND POD	1	1
Combined neuromonitoring AND POD AND POCD	1	0
Combined neuromonitoring AND postoperative cognitive decline	1	1
Combined neuromonitoring AND postoperative cognitive dysfunction	4	2
Combined neuromonitoring AND postoperative delirium	2	3
Combined neuromonitoring AND postoperative delirium AND postoperative cognitive decline	1	0
Combined neuromonitoring AND postoperative delirium AND postoperative cognitive dysfunction	2	0
Combined neuromonitoring AND delayed neurocognitive recovery	0	0
Combined neuromonitoring AND perioperative neurocognitive disorders	1	0
Frontal EEG AND cerebral oximetry	9	8
Frontal EEG AND cerebral oximetry AND POCD	0	0
Frontal EEG AND cerebral oximetry AND POD	0	0
Frontal EEG AND cerebral oximetry AND POD AND POCD	0	0
Frontal EEG AND cerebral oximetry AND postoperative cognitive decline	0	0
Frontal EEG AND cerebral oximetry AND postoperative cognitive dysfunction	0	0
Frontal EEG AND cerebral oximetry AND postoperative delirium	0	0
Frontal EEG AND cerebral oximetry AND postoperative delirium AND postoperative cognitive decline	0	0
Frontal EEG AND cerebral oximetry AND postoperative delirium AND postoperative cognitive dysfunction	0	0
Frontal EEG AND cerebral oximetry AND delayed neurocognitive recovery	0	0
Frontal EEG AND cerebral oximetry AND perioperative neurocognitive disorders	0	0
Processed EEG AND cerebral oximetry	6	26
Processed EEG AND cerebral oximetry AND POCD	0	0
Processed EEG AND cerebral oximetry AND POD	0	0
Processed EEG AND cerebral oximetry AND POD AND POCD	0	0
Processed EEG AND cerebral oximetry AND postoperative cognitive decline	0	2
Processed EEG AND cerebral oximetry AND postoperative cognitive dysfunction	0	3
Processed EEG AND cerebral oximetry AND postoperative delirium	2	1
Processed EEG AND cerebral oximetry AND postoperative delirium AND postoperative cognitive decline	0	1
Processed EEG AND cerebral oximetry AND postoperative delirium AND postoperative cognitive dysfunction	0	1
Processed EEG AND cerebral oximetry AND delayed neurocognitive recovery	0	0
Processed EEG AND cerebral oximetry AND perioperative neurocognitive disorders	0	0
Frontal EEG AND cerebral NIRS	32	118
Frontal EEG AND cerebral NIRS AND POCD	0	0
Frontal EEG AND cerebral NIRS AND POD	0	0
Frontal EEG AND cerebral NIRS AND POD AND POCD	0	0
Frontal EEG AND cerebral NIRS AND postoperative cognitive decline	0	0
Frontal EEG AND cerebral NIRS AND postoperative cognitive dysfunction	0	0
Frontal EEG AND cerebral NIRS AND postoperative delirium	0	0
Frontal EEG AND cerebral NIRS AND postoperative delirium AND postoperative cognitive decline	0	0

Table I. — Search strategies part 2.

Frontal EEG AND cerebral NIRS AND postoperative delirium AND postoperative cognitive dysfunction	0	0
Frontal EEG AND cerebral NIRS AND delayed neurocognitive recovery	0	0
Frontal EEG AND cerebral NIRS AND perioperative neurocognitive disorders	0	0
Processed EEG AND cerebral NIRS	14	267
Processed EEG AND cerebral NIRS AND POCD	0	0
Processed EEG AND cerebral NIRS AND POD	2	1
Processed EEG AND cerebral NIRS AND POD AND POCD	0	0
Processed EEG AND cerebral NIRS AND postoperative cognitive decline	0	4
Processed EEG AND cerebral NIRS AND postoperative cognitive dysfunction	3	4
Processed EEG AND cerebral NIRS AND postoperative delirium	5	5
Processed EEG AND cerebral NIRS AND postoperative delirium AND postoperative cognitive decline	0	3
Processed EEG AND cerebral NIRS AND postoperative delirium AND postoperative cognitive dysfunction	1	3
Processed EEG AND cerebral NIRS AND delayed neurocognitive recovery	0	0
Processed EEG AND cerebral NIRS AND perioperative neurocognitive disorders	0	1
Depth-of-anesthesia monitor AND cerebral oximetry	7	9
Depth-of-anesthesia monitor AND cerebral oximetry AND POCD	3	2
Depth-of-anesthesia monitor AND cerebral oximetry AND POD	1	1
Depth-of-anesthesia monitor AND cerebral oximetry AND POD AND POCD	1	1
Depth-of-anesthesia monitor AND cerebral oximetry AND postoperative cognitive decline	2	2
Depth-of-anesthesia monitor AND cerebral oximetry AND postoperative cognitive dysfunction	3	3
Depth-of-anesthesia monitor AND cerebral oximetry AND postoperative delirium	1	2
Depth-of-anesthesia monitor AND cerebral oximetry AND postoperative delirium AND postoperative cognitive decline	1	2
Depth-of-anesthesia monitor AND cerebral oximetry AND postoperative delirium AND postoperative cognitive dysfunction	1	2
Depth-of-anesthesia monitor AND cerebral oximetry AND delayed neurocognitive recovery	0	0
Depth-of-anesthesia monitor AND cerebral oximetry AND perioperative neurocognitive disorders	0	0
Depth-of-anesthesia monitor AND cerebral NIRS	1	10
Depth-of-anesthesia monitor AND cerebral NIRS AND POCD	1	2
Depth-of-anesthesia monitor AND cerebral NIRS AND POD	1	2
Depth-of-anesthesia monitor AND cerebral NIRS AND POD AND POCD	0	1
Depth-of-anesthesia monitor AND cerebral NIRS AND postoperative cognitive decline	0	3
Depth-of-anesthesia monitor AND cerebral NIRS AND postoperative cognitive dysfunction	1	4
Depth-of-anesthesia monitor AND cerebral NIRS AND postoperative delirium	0	3
Depth-of-anesthesia monitor AND cerebral NIRS AND postoperative delirium AND postoperative cognitive decline	0	3
Depth-of-anesthesia monitor AND cerebral NIRS AND postoperative delirium AND postoperative cognitive dysfunction	0	3
Depth-of-anesthesia monitor AND cerebral NIRS AND delayed neurocognitive recovery	0	0
Depth-of-anesthesia monitor AND cerebral NIRS AND perioperative neurocognitive disorders	0	1
BIS AND cerebral oximetry	54	28
BIS AND cerebral oximetry AND POCD	0	0
BIS AND cerebral oximetry AND POD	0	0
BIS AND cerebral oximetry AND POD AND POCD	0	0
BIS AND cerebral oximetry AND postoperative cognitive decline	2	1
BIS AND cerebral oximetry AND postoperative cognitive dysfunction	3	2

Table I. — Search strategies part 3.

BIS AND cerebral oximetry AND postoperative delirium	4	1
BIS AND cerebral oximetry AND postoperative delirium AND postoperative cognitive decline	1	1
BIS AND cerebral oximetry AND postoperative delirium AND postoperative cognitive dysfunction	1	1
BIS AND cerebral oximetry AND delayed neurocognitive recovery	0	0
BIS AND cerebral oximetry AND perioperative neurocognitive disorders	0	0
BIS AND cerebral NIRS	32	40
BIS AND cerebral NIRS AND POCD	0	1
BIS AND cerebral NIRS AND POD	1	0
BIS AND cerebral NIRS AND POD AND POCD	0	0
BIS AND cerebral NIRS AND postoperative cognitive decline	0	2
BIS AND cerebral NIRS AND postoperative cognitive dysfunction	1	2
BIS AND cerebral NIRS AND postoperative delirium	4	3
BIS AND cerebral NIRS AND postoperative delirium AND postoperative cognitive decline	0	1
BIS AND cerebral NIRS AND postoperative delirium AND postoperative cognitive dysfunction	0	1
BIS AND cerebral oximetry AND delayed neurocognitive recovery	0	0
BIS AND cerebral oximetry AND perioperative neurocognitive disorders	0	0
NeuroSENSE AND cerebral oximetry	2	1
NeuroSENSE AND cerebral oximetry AND POCD	1	1
NeuroSENSE AND cerebral oximetry AND POD	1	1
NeuroSENSE AND cerebral oximetry AND POD AND POCD	1	1
NeuroSENSE AND cerebral oximetry AND postoperative cognitive decline	1	1
NeuroSENSE AND cerebral oximetry AND postoperative cognitive dysfunction	1	1
NeuroSENSE AND cerebral oximetry AND postoperative delirium	1	1
NeuroSENSE AND cerebral oximetry AND postoperative delirium AND postoperative cognitive decline	1	1
NeuroSENSE AND cerebral oximetry AND postoperative delirium AND postoperative cognitive dysfunction	1	1
NeuroSENSE AND cerebral oximetry AND delayed neurocognitive recovery	0	0
NeuroSENSE AND cerebral oximetry AND perioperative neurocognitive disorders	0	0
NeuroSENSE AND cerebral NIRS	0	2
NeuroSENSE AND cerebral NIRS AND POCD	0	1
NeuroSENSE AND cerebral NIRS AND POD	0	1
NeuroSENSE AND cerebral NIRS AND POD AND POCD	0	1
NeuroSENSE AND cerebral NIRS AND postoperative cognitive decline	0	1
NeuroSENSE AND cerebral NIRS AND postoperative cognitive dysfunction	0	1
NeuroSENSE AND cerebral NIRS AND postoperative delirium	0	1
NeuroSENSE AND cerebral NIRS AND postoperative delirium AND postoperative cognitive decline	0	1
NeuroSENSE AND cerebral NIRS AND postoperative delirium AND postoperative cognitive dysfunction	0	1
NeuroSENSE AND cerebral NIRS AND delayed neurocognitive recovery	0	0
NeuroSENSE AND cerebral NIRS AND perioperative neurocognitive disorders	0	0
Narcotrend AND cerebral oximetry	2	0
Narcotrend AND cerebral oximetry AND POCD	1	0
Narcotrend AND cerebral oximetry AND POD	0	0
Narcotrend AND cerebral oximetry AND POD AND POCD	0	0
Narcotrend AND cerebral oximetry AND postoperative cognitive decline	0	0
Narcotrend AND cerebral oximetry AND postoperative cognitive dysfunction	1	0

Table I. — Search strategies part 4.

Narcotrend AND cerebral oximetry AND postoperative delirium	0	0
Narcotrend AND cerebral oximetry AND postoperative delirium AND postoperative cognitive decline	0	0
Narcotrend AND cerebral oximetry AND postoperative delirium AND postoperative cognitive dysfunction	0	0
Narcotrend AND cerebral oximetry AND delayed neurocognitive recovery	0	0
Narcotrend AND cerebral oximetry AND perioperative neurocognitive disorders	0	0
Narcotrend AND cerebral NIRS	1	1
Narcotrend AND cerebral NIRS AND POCD	0	0
Narcotrend AND cerebral NIRS AND POD	0	0
Narcotrend AND cerebral NIRS AND POD AND POCD	0	0
Narcotrend AND cerebral NIRS AND postoperative cognitive decline	0	1
Narcotrend AND cerebral NIRS AND postoperative cognitive dysfunction	1	1
Narcotrend AND cerebral NIRS AND postoperative delirium	1	1
Narcotrend AND cerebral NIRS AND postoperative delirium AND postoperative cognitive decline	0	1
Narcotrend AND cerebral NIRS AND postoperative delirium AND postoperative cognitive dysfunction	0	1
Narcotrend AND cerebral NIRS AND delayed neurocognitive recovery	0	0
Narcotrend AND cerebral NIRS AND perioperative neurocognitive disorders	0	0
Sedline AND cerebral oximetry	6	1
Sedline AND cerebral oximetry AND POCD	0	0
Sedline AND cerebral oximetry AND POD	0	0
Sedline AND cerebral oximetry AND POD AND POCD	0	0
Sedline AND cerebral oximetry AND postoperative cognitive decline	0	0
Sedline AND cerebral oximetry AND postoperative cognitive dysfunction	0	0
Sedline AND cerebral oximetry AND postoperative delirium	0	0
Sedline AND cerebral oximetry AND postoperative delirium AND postoperative cognitive decline	0	0
Sedline AND cerebral oximetry AND postoperative delirium AND postoperative cognitive dysfunction	0	0
Sedline AND cerebral oximetry AND delayed neurocognitive recovery	0	0
Sedline AND cerebral oximetry AND perioperative neurocognitive disorders	0	0
Sedline AND cerebral NIRS	6	1
Sedline AND cerebral NIRS AND POCD	0	0
Sedline AND cerebral NIRS AND POD	1	0
Sedline AND cerebral NIRS AND POD AND POCD	0	0
Sedline AND cerebral NIRS AND postoperative cognitive decline	0	0
Sedline AND cerebral NIRS AND postoperative cognitive dysfunction	0	0
Sedline AND cerebral NIRS AND postoperative delirium	3	1
Sedline AND cerebral NIRS AND postoperative delirium AND postoperative cognitive decline	0	0
Sedline AND cerebral NIRS AND postoperative delirium AND postoperative cognitive dysfunction	0	0
Sedline AND cerebral NIRS AND delayed neurocognitive recovery	0	0
Sedline AND cerebral NIRS AND perioperative neurocognitive disorders	0	0
Entropy AND cerebral oximetry	5	4
Entropy AND cerebral oximetry AND POCD	1	0
Entropy AND cerebral oximetry AND POD	0	0
Entropy AND cerebral oximetry AND POD AND POCD	0	0
Entropy AND cerebral oximetry AND postoperative cognitive decline	1	0

Table I. — Search strategies part 5.

Entropy AND cerebral oximetry AND postoperative cognitive dysfunction	2	1
Entropy AND cerebral oximetry AND postoperative delirium	0	0
Entropy AND cerebral oximetry AND postoperative delirium AND postoperative cognitive decline	0	0
Entropy AND cerebral oximetry AND postoperative delirium AND postoperative cognitive dysfunction	0	0
Entropy AND cerebral oximetry AND delayed neurocognitive recovery	0	0
Entropy AND cerebral oximetry AND perioperative neurocognitive disorders	0	0
Entropy AND cerebral NIRS	9	47
Entropy AND cerebral NIRS AND POCD	0	0
Entropy AND cerebral NIRS AND POD	0	0
Entropy AND cerebral NIRS AND POD AND POCD	0	0
Entropy AND cerebral NIRS AND postoperative cognitive decline	0	1
Entropy AND cerebral NIRS AND postoperative cognitive dysfunction	1	1
Entropy AND cerebral NIRS AND postoperative delirium	1	1
Entropy AND cerebral NIRS AND postoperative delirium AND postoperative cognitive decline	1	1
Entropy AND cerebral NIRS AND postoperative delirium AND postoperative cognitive dysfunction	1	1
Entropy AND cerebral NIRS AND delayed neurocognitive recovery	0	0
Entropy AND cerebral NIRS AND perioperative neurocognitive disorders	0	0
Multimodal neuromonitoring	580	376
Multimodal neuromonitoring AND POCD	0	0
Multimodal neuromonitoring AND POD	2	1
Multimodal neuromonitoring AND POD AND POCD	0	0
Multimodal neuromonitoring AND postoperative cognitive decline	3	2
Multimodal neuromonitoring AND postoperative cognitive dysfunction	6	2
Multimodal neuromonitoring AND postoperative delirium	5	3
Multimodal neuromonitoring AND postoperative delirium AND postoperative cognitive decline	2	1
Multimodal neuromonitoring AND postoperative delirium AND postoperative cognitive dysfunction	2	1
Multimodal neuromonitoring AND delayed neurocognitive recovery	0	1
Multimodal neuromonitoring AND perioperative neurocognitive disorders	1	0

heterogeneous. Postoperative delirium (POD) alone was the primary endpoint in 4 studies[18,21,23,28]. Five studies analyzed postoperative cognitive function as primary endpoint[24-27,29]. Two studies evaluated postoperative cognitive function as well as POD[7,20]. Stroke was the outcome of interest in 3 studies[17,19,22]. Interestingly, one retrospective study used the old nomenclature of neurological complications with focal injury, stupor or coma belonging to type 1 injury and deterioration in intellectual function, memory deficit or seizures belonging to type 2 injuries[17]. The second retrospective study did not precise the definition of neurologic complications that were analyzed[16]. Among the included studies, 7 used one- or two-sided transcranial doppler (TCD) in addition to cerebral oximetry and EEG/processed EEG monitoring[16-18,21-24]. Except in two studies where one-sided cerebral NIRS was used[18,28], in all other studies the two hemispheres were monitored with a frontal oximeter. One-sided or bilateral Bispectral Index (BIS) was the DOA monitor in 8 studies[18,20,21,24-28]. The BIS value was here the studied parameter. Two studies used the Patient State Index (PSI) and the EEG based Density Spectral Analysis (DSA)[23,29]. In one study the authors analyzed bilateral raw EEG and the corresponding DSA provided by the NeuroSENSE® DOA monitor[7]. In 4 studies the raw channel EEG was the used monitor[16,17,19,22]. Only 8 studies used an algorithm to avoid/treat cerebral oxygen desaturation and/or to treat EEG abnormalities, EEG suppression or abnormally low BIS values[7,16,17,20,23,25,27,29].

The double-blind RCT by Xu et al. analyzed whether a processed EEG-guided anesthesia management, including PSI combined with DSA monitoring could reduce the incidence of POD in

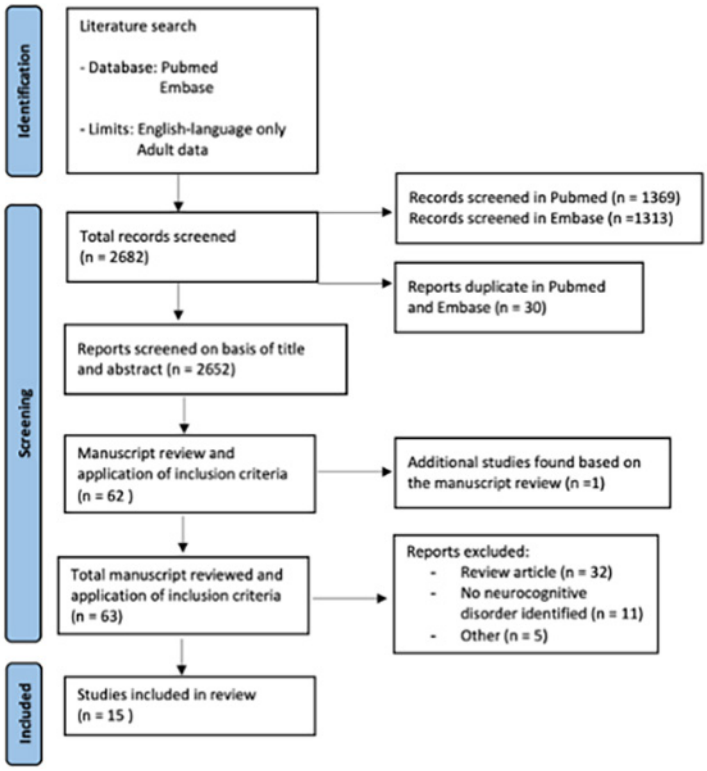

Fig. 1 — PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow diagram.

high-risk patients undergoing carotid surgery[23]. They randomized 255 patients into a standardized care group where the information provided by bilateral cerebral oximetry and TCD was used to avoid cerebral hypo- or hyperperfusion. The anesthesiologists were blinded to EEG data and spectrograms, and only PSI values were displayed that were kept between 25-50. In the intervention group EEG data and spectrograms together with PSI were available to the anesthesiologists. The parameters demonstrated by the Sedline® DOA monitor were integrated together with the information provided by cerebral oximetry and TCD in order to avoid EEG suppression. No episodes of cerebral hypo- or hyperperfusion were observed in either group. However, in the intervention group the total time spent in EEG suppression was significantly shorter. The incidence of POD based on Confusion Assessment Method was significantly lower in the intervention group.

In the RCT conducted by Kunst et al.[82] elderly patients undergoing coronary artery bypass graft surgery received either a BIS and cerebral oximetry blinded anesthesia or a BIS and cerebral oximetry guided anesthesia[20]. The primary endpoint being cognitive function evaluated by Mini Mental State Examination was not significantly different between both groups. The authors however observed a significant reduction in the secondary outcome being POD evaluated by the Confusion Assessment Method (2.4% in the intervention group vs 20% in the control group).

The small sample sized RCT of Yang et al. divided 26 patients undergoing spinal surgery into an intervention group where a multimodal brain management strategy involved EEG-based PSI and DSA together with Analgesia Nociception Index and cerebral oximetry[29]. In the control group the DOA was based on BIS. No other brain monitoring was used. There was no significant difference in the incidence of PNDs between both groups. One RCT was nested within a prospective longitudinal cohort study in elderly[27]. The longitudinal cohort study showed that there is a significant increased frequency of cognitive impairment in patients > 60 years undergoing non-cardiac surgery compared to a non-surgical control group. The nested RCT showed that a pragmatic intervention to optimize anesthetic depth and cerebral oxygenation resulted in better postoperative cognitive outcome. The intervention group strikingly presented similar incidence of postoperative cognitive dysfunction as the non-surgical cohort, demonstrating that implementation of algorithms to improve global cerebral oxygenation and to avoid anesthetic overdose may reduce the incidence of PNDs.

Interestingly, the two retrospective studies in cardiac surgery that were conducted more than 15 years ago, showed that multimodal neuromonitoring in cardiac surgery is feasible and effective in

Table II. — Included studies for the systematic review part 1.

First author	Type of study	Year of publication	Type of surgery	Type of PND	Sample size	Type of neuromonitoring	Algorithms used	Interventions
Momeni[7]	Prospective, Observational	2019	Cardiac interventions	- POCD - POD	1513	- Bilateral cerebral NIRS - NeuroSENSEâ with bilateral raw EEG and DSA	Yes	Avoidance of cerebral O_2 desaturation (>25% compared to baseline values) as well as EEG suppression in all patients
Edmonds[16]	Retrospective	2002	Cardiac surgery	Not precised	78	- Bilateral cerebral NIRS - 4 Channel EEG - Single channel TCD	Yes	Standardized intervention algorithm to correct physiological imbalances
Edmonds[17]	Retrospective	2005	CABG and OPCAB	Type I and type II neurologic injury *	332	- Bilateral cerebral NIRS - 4 Channel EEG - Single channel TCD	Yes	In all patients: Avoidance of cerebral O_2 desaturation (>20% compared to baseline values); avoidance of respectively cerebral hypoperfusion or hyperperfusion by middle cerebral artery blood flow velocity of <20% or >200% compared to baseline; avoidance of cerebral cortical synaptic decrease of >50% compared to baseline
Thudium[18]	Prospective, Observational	2018	Cardiac surgery	POD	30	- Right cerebral NIRS - BIS - Single channel TCD	No	No intervention
Stewart[19]	Prospective, Observational	2020	Thoracic aortic surgery	Stroke Including death	30	- 7 Channel EEG - Bil cerebral NIRS	No	No intervention
Kunst[20]	RCT	2020	CABG	- Postop Cognitive function - POD as secondary outcome	82	- Bilateral cerebral NIRS - Bilateral BIS	Yes (in the intervention group)	-Intervention group: Avoidance of cerebral O_2 desaturation (>15% compared to baseline values or values <50%) and BIS targeted at 50±10 -Control group: Anesthesiologists blinded to neuromonitoring data
Liu[21]	Prospective, Observational	2021	Cardiac surgery	POD	79	- Bilateral cerebral NIRS - Bilateral TCD - One-sided BIS	No	No intervention
Pennekamp[22]	Prospective, Observational	2013	Carotid surgery	Stroke as secondary outcome	151	- 16 Channel EEG - Bilateral cerebral NIRS - Two channel TCD	No	Shunt placement based on EEG changes

Table II. — Included studies for the systematic review part 2.

Xu[23]	RCT	2021	Carotid surgery	POD	255	- PSI with DSA - Bilateral cerebral NIRS - TCD	Yes	-NIRS and TCD in all patients to avoid cerebral hypo- or hyperperfusion -Intervention group: EEG, DSA and PSI available -Control group :Only PSI available; to be maintained between 25-50
Aguirré[24]	Prospective, Observational, Assesser blinded	2019	Shoulder surgery in beach chair position	Postop Cognitive function	40	- Bilateral cerebral NIRS - Bilateral BIS - Single channel TCD	No	-BIS targeted at 40-60 for all patients -Anesthesiologists blinded to cerebral NIRS data in all patients
Jing[25]	Prospective, Interventional trial	2021	Shoulder surgery in beach chair position	POCD	60	- Bilateral cerebral NIRS - Bilateral BIS	Yes (in the intervention group)	-Intervention group: Avoidance of cerebral O_2 desaturation (>20% compared to baseline values or values <50%) and BIS targeted at 40-60 -Control group: Cerebral NIRS recorded but not applied in the hemodynamic management. Bis targeted at 40 - 60
Meghawry[26]	RCT	2015	Shoulder surgery in beach chair position	POCD	50	- Bilateral cerebral NIRS - One-sided BIS	No	Avoidance of cerebral O_2 desaturation (>25% compared to baseline values)
Ballard[27]	- Prospective longitudinal cohort study - Nested RCT	2012	Abdominal and Orthopedic surgery	POCD	72	- Bilateral cerebral NIRS - Bilateral BIS	Yes (in the intervention group)	-Intervention group: Avoidance of cerebral O_2 desaturation (>15% compared to baseline values or values <50%) and BIS targeted at 40-60 (±5) -Control group: Anesthesiologists blinded to neuromonitoring data
Morimoto[28]	Prospective, Observational	2009	Abdominal surgery	POD	20	- Right-sided BIS - Left-sided cerebral NIRS	No	No intervention
Yang[29]	RCT	2021	Spinal surgery	Postop cognitive function	26	- PSI with DSA or BIS - Bilateral cerebral NIRS - Analgesia nociception index	Yes (in the intervention group)	-Intervention group: Avoidance of cerebral O_2 desaturation (>20% compared to baseline values or values <50%) and PSI targeted at 25-50 and analgesia adapted on the analgesia nociception index -Control group: BIS targeted at 40-60; no cerebral NIRS

BIS: Bispectral Index; CABG: Coronary artery bypass graft; DSA: Density Spectral Analysis; EEG: electroencephalogram; OPCAB: Off pump coronary artery bypass; NIRS: Near-infrared spectroscopy; PND: Perioperative neurocognitive disorder; POCD: Postoperative cognitive dysfunction; POD: Postoperative delirium; PSI: Patient State Index; RCT: Randomized controlled trial; TCD: Transcranial doppler.
* Type I neurologic injury: Focal injury, stupor or coma; Type II neurologic injury: Deterioration in intellectual function, memory deficit or seizures.

significantly reduce neurologic complications compared to a cohort in whom neuromonitoring was not applied[16,17].

Discussion

Our study is the first systematic review evaluating the combined effect of cerebral oximetry and (processed) EEG monitor on the incidence of PNDs. Numerous systematic reviews and meta-analyses have evaluated the evidence regarding the use of either cerebral oximetry[30-35] or processed EEG alone[14,36,37] in the reduction of PNDs. Only few review articles have discussed the use of both monitors in the same setting and this without any focus on their combined use[38,39].

Overall, our results showed a tendency towards less PNDs in studies where an algorithm was used to improve regional cerebral oxygen saturation and to avoid anesthetic overdose or EEG abnormalities. However, most of the included studies were not designed as a RCT and the few RCTs included were not powered to demonstrate a reduction in PNDs. More importantly no algorithms were used to simultaneously adapt the information from the cerebral oximetry and from the processed EEG. Integrating information provided by two monitors can indeed be helpful in the perioperative hemodynamic management of patients[40-42]. Figure 2 illustrates such an algorithm used in the authors' institution. This is important as the underlying mechanisms of PNDs are complex and multifactorial. Perioperative alteration in brain perfusion, reperfusion injury, thromboembolic phenomena, neuroinflammation, possible iatrogenic neurotoxicity from anesthetic agents and altered neurotransmission or neuronal metabolism have all been associated with the occurrence of PNDs[43-46].

From the current study it is not possible to conclude in what extent the combined use of cerebral oximetry and (processed) EEG is more effective than use of one or none of these monitors. A meta-analysis looking at the effects of electroencephalography and regional cerebral oximetry on PNDs showed that EEG-guided anesthesia reduced the incidence of POD in non-cardiac surgery but had no effect on the incidence of early postoperative cognitive decline, whereas cerebral oximetry monitoring decreased the incidence of postoperative cognitive decline but had no impact on the incidence of POD[39]. It is therefore plausible that the impact of these monitors is only minimal and can be observed in specific patient population. Nevertheless, this meta-analysis only analyzed the use of each of these monitors separately.

It should be noted that although these monitors are non-invasive and rather easy to use, their correct interpretation may be challenging and requires expertise. The raw EEG is very much influenced by age[47]. Frontal alpha waves are considered as the most prominent feature of EEG during general anesthesia maintained either with propofol or sevoflurane[48,49]. However, studies have shown a decrease of frontal alpha waves in patients with baseline cognitive impairment[50]. Moreover, propofol- and sevoflurane-induced alpha power declines with age even when used in an age-adjusted manner[51]. This makes the interpretation of raw EEG very difficult in some patients. Additionally, the index value generated by the processed EEG monitors, and very often used as an index of adequate level of unconsciousness, may be influenced by many factors such as electromyographic activity, environmental artifacts, use of drugs such as N-Methyl-D-Aspartate receptor antagonists and alpha-two adrenergic receptor agonists[48,52]. To complicate the situation lower intraoperative alpha power has been associated with a higher propensity of EEG burst suppression[53,54]. On the other hand, there are many limitations with the use of cerebral oximeter devices that have been discussed in several review articles, where solutions and alternatives have been proposed in order to avoid them[55,56]. The use of cerebral oximetry and EEG monitor can therefore reduce the incidence of PNDs only if they are properly interpreted and adapted to the clinical situation.

This systematic review study has some limitations. First, in some of the included studies TCD ultrasonography was part of the multimodal neuromonitoring. Its use adds paramount information particularly in cardiac surgery as it provides an indirect measurement of cerebral blood flow as well as a quantitative description of embolic processes. It is therefore possible that in these studies the neurologic outcome was positively influenced. Second, we considered any neurologic outcome including stroke. PNDs were obviously the outcome of interest in this systematic review. However, stroke may be the result of cerebral hypoperfusion in specific patients, which can be possibly detected by cerebral oximetry and EEG monitor.

In conclusion, the results of this systematic review suggest that integrating information obtained from cerebral oximetry and (processed) EEG may reduce the incidence of PNDs whenever an algorithm is used to improve $rScO_2$ and/or to avoid anesthetic overdose or EEG abnormalities. Future studies using the new nomenclature of PNDs and the adapted methods to diagnose these complications are needed to show the benefit of combined cerebral oximetry and EEG monitoring.

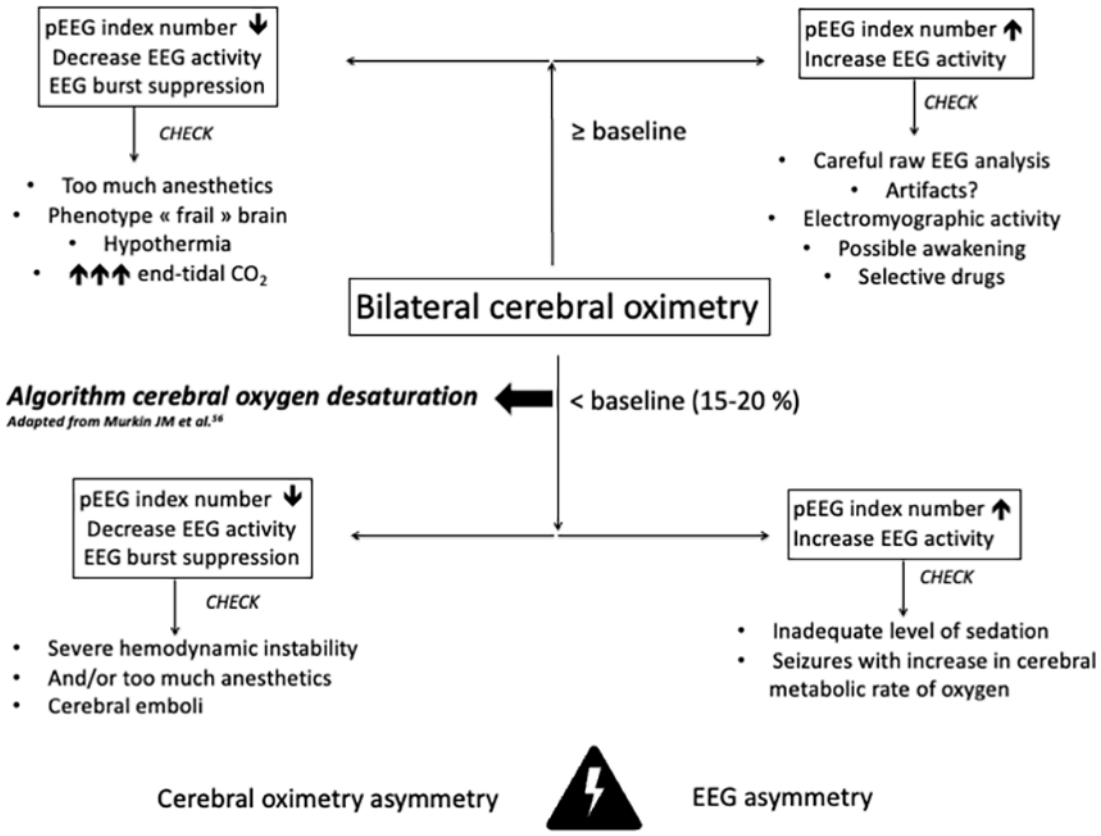

Fig. 2 — Simplistic approach to combined use of cerebral oximetry and processed electroencephalogram.

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