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Pharmacological perioperative brain neuroprotection: a qualitative review of randomized clinical trials

F. Bilotta[1]*, A. W. Gelb[2], E. Stazi[1], L. Titi[1], F. P. Paoloni[3] and G. Rosa[1]

[1] Department of Anesthesiology, Critical Care and Pain Medicine, Section of Neuroanesthesia and Neurocritical Care, 'Sapienza' University of Rome, Rome, Italy
[2] Department of Anesthesia and Perioperative Care, University of California, San Francisco, CA, USA
[3] G.I.M.E.M.A. Onlus, Rome, Italy

* Corresponding author. E-mail: bilotta@tiscali.it

Editor's key points

- This review of 25 randomized controlled clinical trials addresses perioperative pharmacological neuroprotection.
- Effects of various pharmacological agents on neurological and cognitive dysfunctions, and mortality were reviewed.
- Importantly, atorvastatin and magnesium sulphate reduced the incidence of neurological deficit.
- All other agents remain controversial in their role.

Summary. Perioperative cerebral damage may be associated with surgery and anaesthesia. Pharmacological perioperative neuroprotection is associated with conflicting results. In this qualitative review of randomized controlled clinical trials on perioperative pharmacological brain neuroprotection, we report the effects of tested therapies on new postoperative neurological deficit, postoperative cognitive decline (POCD), and mortality rate. Studies were identified from Cochrane Central Register and MEDLINE and by hand-searching. Of 5904 retrieved studies, 25 randomized trials met our inclusion criteria. Tested therapies were: lidocaine, thiopental, *S*(+)-ketamine, propofol, nimodipine, GM1 ganglioside, lexipafant, glutamate/aspartate and xenon remacemide, atorvastatin, magnesium sulphate, erythropoietin, piracetam, rivastigmine, pegorgotein, and 17β-estradiol. The use of atorvastatin and magnesium sulphate was associated with a lower incidence of new postoperative neurological deficit. The use of lidocaine, ketamine, and magnesium sulphate was associated with controversial results on POCD. The POCD did not differ between treated patients and control group for other tested drugs (thiopental, propofol, nimodipine, GM1 ganglioside, lexipafant, glutamate/aspartate, xenon, erythropoietin, remacemide, piracetam, rivastigmine, pegorgotein, and 17β-estradiol). None of the tested drugs was associated with a reduction in mortality rate.

Drugs with various mechanisms of action have been tested over time; current evidence suggests that pharmacological brain neuroprotection might reduce the incidence of new postoperative neurological deficits and POCD, while no benefits on perioperative mortality are described. Of importance from this review is the need for shared methodological approach when clinical studies on pharmacological neuroprotection are designed.

Keywords: brain neuroprotection; ketamine; lidocaine; magnesium sulphate; perioperative cerebral damage; postoperative cognitive decline; perioperative stroke

Perioperative brain damage is among the most serious adverse complications of surgery and anaesthesia, resulting in new postoperative neurological deficits including transient ischaemic attack (TIA), stroke, and postoperative cognitive decline (POCD).[1 2] The incidence of new postoperative neurological deficits ranges from 0.08% after general surgery to 5.2% after cardiac surgery.[3 4] The risk of perioperative stroke is increased in cardiovascular and neurovascular procedures and in patients with predisposing risk factors such as previous stroke, carotid stenosis, patent foramen ovale, atrial fibrillation, infective endocarditis, diabetes, renal failure, and older age (>62).[4–6] The incidence of POCD ranges from 28% to 100% after cardiac surgery and from 7% to 26% after non-cardiac surgical procedures.[7 8] Perioperative brain damage remains a concern because it increases mortality, lengthens hospitalization, impairs postoperative quality of life, and increases perioperative costs.[4 8 9] One unresolved key question is whether pharmacological strategies, independent of mechanism of action, can effectively reduce the clinical impact of perioperative brain damage.

The aim of this review of randomized controlled clinical trials (RCTs) on perioperative pharmacological brain neuroprotection is to assess the effects of the tested therapies on the incidence of new postoperative neurological deficit, POCD, and mortality rate.

Methods

To identify trials for inclusion in this review, a detailed systematic research using Cochrane Central Register of

Controlled Trials and MEDLINE was performed. The terms used are listed in Appendices 1 and 2. Only complete studies were included, not abstracts.

We identified RCTs that met the following criteria: (i) used any pharmacological therapy for perioperative brain neuroprotection; (ii) evaluated neurological status before operation and after operation; (iii) measured the cognitive status before operation and after operation using the same tests; and (iv) included adult patients (at least 18 yr of age with no upper limit) undergoing elective surgery.

Two authors (F.B. and E.S.) independently screened and assessed titles, abstracts, and the full-text papers. Details of study population, interventions, and outcomes were extracted using a standardized data extraction form that includes: eligibility and exclusion criteria, study design, duration of follow-up, randomization, allocation concealment, blinding, number and characteristics of patients, type of surgery, drug dosage, and method of administration.

The outcome measures in this review are:

Primary outcome measure: new postoperative neurological deficit defined as stroke, with the appearance of symptoms and/or focal signs in the physical examination confirmed by computerized tomography (CT) imaging, or as a change in postoperative score from preoperative assessment with neurological scales such as the National Institutes of Health Stroke Scale (NIHSS) and the Western perioperative neurologic scale (WPNS) at short-term ($\leq$2 months) and/or long-term postoperative follow-up ($>$2 months).

Secondary outcome measures: POCD assessed as a 20% or greater deficit from baseline on postoperative testing or as decline $>$1 standard deviation in the postoperative cognitive test scores, compared with the preoperative score, graded with a battery of neuropsychological tests evaluating a broad array of cognitive domains as proposed by each study authors. Some investigators chose to also use other neurocognitive endpoints, in addition and for completeness, we have included these in the Results section as 'neurocognitive performance'.

Mortality.

Results

Five thousand nine hundred and four studies were screened and 5872 excluded as not randomized, duplicate, or irrelevant. Twenty-five RCTs—which included 3274 patients (age range 22–86 yr)—were retrieved and analysed (Fig. 1).[10–34] Characteristics of the studied population are summarized in Table 1. Patients enrolled were of both sex with age ranging from 22 to 86 yr. Twenty-two of the 25 studies were in cardiac surgery patients,[10–18 20 22 24–34] two were in vascular surgery,[19 23] and one was in major abdominal and urological surgery.[21] All studies, but one, provide short-term postoperative follow-up ($\leq$2 months),[10–34] 10 studies provide both short- and long-term ($>$2 months) follow-up,[11 12 16 19 22 25 27 30–32] and one trial provides only long-term ($>$2 months) follow-up data.[24]

New postoperative neurological deficit

New postoperative neurological deficit was reported in 10 RCTs that tested nine drugs: thiopental, GM_1 ganglioside, nimodipine, propofol, pegorgoteine, atorvastatin, magnesium sulphate, 17β-estradiol, and ketamine.[12 14 17 19 22 26 30 31 33 34] The incidence of new postoperative neurological deficit was lower in studies that tested atrovastatin and magnesium sulphate was associated with conflicting results for thiopental and did not differ between treated patients and control group for the other tested drugs (GM_1 ganglioside, nimodipine, propofol, pegorgoteine, 17β-estradiol, and ketamine) (Table 1).

Atorvastatin, administered to 100 vascular surgery patients at a dose of 20 mg day^{-1} for at least 15 days before operation and for a total of 45 days, was associated with a lower incidence of new postoperative neurological deficits detected clinically daily, until discharge, and monthly, until the 6th month, and confirmed by neuroimaging.[19]

Magnesium sulphate was tested in one RCT. One hundred and seventy-four cardiac surgery patients received a 780 mg bolus dose during anaesthesia induction followed by 3169 mg in a continuous infusion for 24 h. Assessment at 96 h after operation with WPNS showed a better composite primary endpoint when compared with the 176 patients who served as the control group.[31]

Thiopental, administered by continuous infusion titrated to EEG isoelectricity, was tested in 482 patients undergoing cardiac surgery in two RCTs.[26 34] Both trials found no reduction in the incidence of new postoperative neurological deficits. However, one of these trials, Nussmeier and colleagues,[26] found at 10 days that when data on new neurological and psychiatric dysfunction were pooled for the 182 treated patients, the incidence was significantly reduced ($P<0.025$).

Postoperative cognitive deficits

The POCD was evaluated in 24 RCTs that tested 16 drugs: lidocaine in four studies, magnesium sulphate, thiopental, *S*(+)-ketamine, propofol, nimodipine in two studies each, while GM1 ganglioside, lexipafant, glutamate/aspartate, xenon, erythropoietin, remacemide, piracetam, rivastigmine, pegorgotein, and 17β-estradiol were tested in one study.[10–18 20–34] The incidence of POCD did not differ between treated patients and control group for tested drugs [thiopental, *S*(+)-ketamine, propofol, nimodipine, GM1 ganglioside, lexipafant, glutamate/aspartate, xenon, erythropoietin, remacemide, piracetam, rivastigmine, pegorgotein, and 17β-estradiol], and was associated with conflicting results for lidocaine, ketamine, and magnesium sulphate.

Lidocaine was evaluated in four studies that enrolled a total of 571 cardiac patients.[16 24 28 32] Three evaluated POCD at short-term postoperative follow-up (9, 10 days, 6 weeks) and two at long-term postoperative follow-up (25 weeks and 6 months). The trials differ in time and dosing of the lidocaine infusion. In two studies, lidocaine was administered as a 48 h continuous infusion, in one study as a 12 h

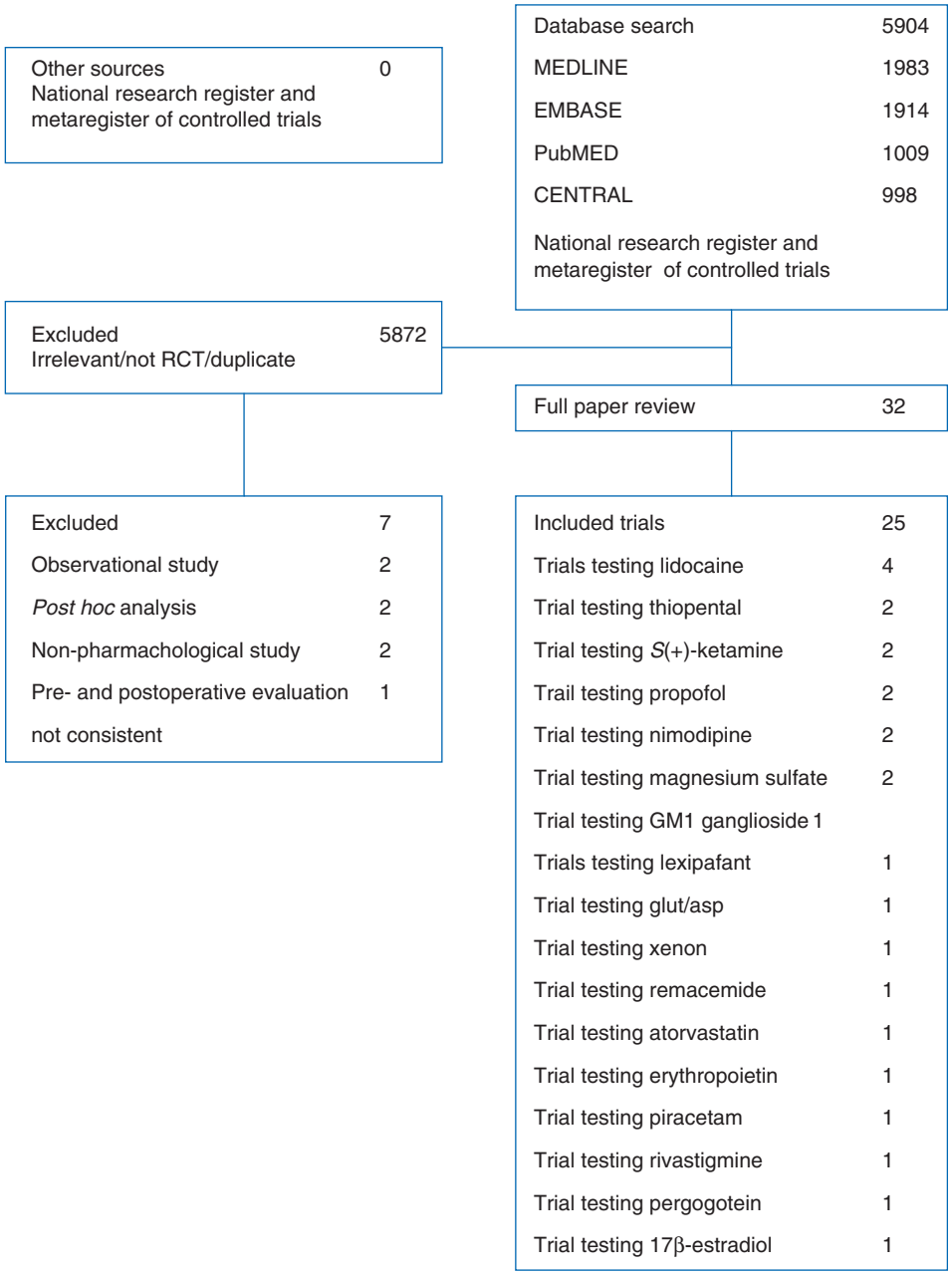

Fig 1 Study selection for inclusion in meta-analysis.

continuous infusion, while in one study, lidocaine infusion was stopped at the end of surgery. The first two studies showed a significant benefit in treated patients, while the latter failed to confirm a neuroprotective benefit.[16 24 28 32] Furthermore, the authors of the latter comment that the failure may be related to a too short an infusion period, an excessively high dose, or having included diabetic patients who might be at increased risk of neurological injury or a different sensitivity to lidocaine.[32]

Ketamine was evaluated in two trials that enrolled a total of 172 patients undergoing cardiac surgery.[14 25] The trials differ in timing and dosing of ketamine. In one trial, ketamine was injected as an i.v. bolus (0.5 mg kg^{-1}) during anesthesia induction, while in the other, it was given as bolus (2.5 mg kg^{-1}) during anesthesia induction followed by continuous infusion (125 μg kg^{-1} min^{-1}) until the end of the surgical procedure. Benefits in terms of reduction of POCD at 1 week after surgery were limited to the trial that tested the lower dose of ketamine bolus injection (0.5 mg kg^{-1}) during anesthesia induction.[14]

Magnesium sulphate was tested for the prevention of POCD in two RCTs with conflicting results.[23 31] In a trial of 350 cardiac patients randomized to control or to receive a 780 mg bolus dose during anaesthesia induction followed

Table 1 Characteristics of randomized controlled trials included in the qualitative review

Study ID	Surgery	Drug studied	Dose of drug studied	No. of pts receiving drug	No. of pts receiving placebo	Postoperative follow-up	New postoperative neurological deficit	POCD
Mitchell and colleagues[16]	Cardiac	Lidocaine	1 mg kg^{-1} in bolus; 4 mg min^{-1} for 1 h; 2 mg min^{-1} for 2 h; 1 mg min^{-1} for 46 h	32	32	10 days; 10 weeks; 6 months	NA	P=0.025 at short-term follow-up; P=NS at long-term follow-up
Wang and colleagues[28]	Cardiac	Lidocaine	1.5 mg kg^{-1} in bolus; 4 mg min^{-1} until the end of operation	57	61	9 days	NA	P=0.028
Mitchell and colleagues[24]	Cardiac	Lidocaine	1 mg kg^{-1} bolus; 2 mg min^{-1} for 2 h; 1 mg min^{-1} for 10 h	81	77	10; 25 weeks	NA	P=NS at early and long-term follow-up
Mathew and colleagues[32]	Cardiac	Lidocaine	1 mg kg^{-1} in bolus; 4 mg min^{-1} for 1 h; 2 mg min^{-1} for 46 h	114	127	6 weeks; 1 yr	NA	P=NS at early and long-term follow-up
Nussmeier and colleagues[26]	Cardiac	Thiopental	50–100 mg until EEG became isolelectric	89	93	5 days	P=NS	P=NS; $P>0.025$ for neurological and neuropsychological complications
Zaidan and colleagues[34]	Cardiac	Thiopental	To create burst suppression	149	151	2; 5 days	P=NS	P=NS
Nagels and colleagues[25]	Cardiac	Ketamine	2.5 mg kg^{-1} bolus; 125 μg kg^{-1} min^{-1}	58	62	1; 10 week	NA	P=NS
Hudetz and colleagues[14]	Cardiac	Ketamine	0.5 mg kg^{-1} in bolus	26	26	1 week	NA	$P<0.01$
Roach and colleagues[33]	Cardiac	Propofol	Infusion just burst suppression	109	116	1–2; 5–7; 50–70 days	P=NS	P=NS at early and long-term follow-up
Kanbak and colleagues[15]	Cardiac	Propofol	6; 3 mg kg^{-1} h^{-1}	10	10	3; 6 days	NA	P=NS
Forsman and colleagues[11]	Cardiac	Nimodipine	0.5 μg kg^{-1} min^{-1}	20	19	5 days; 6 months	NA	P=NS
Legault and colleagues[22]	Cardiac	Nimodipine	60 mg before surgery; 30 mg every 6 h for 5 days after surgery	75	74	1 week; 1; 6 months	P=NS	P=NS
Bhudia and colleagues[31]	Cardiac	Magnesium sulphate	780 mg over 15 min; 3160 mg over 24 h	174	176	1; 4 days; 3 months	P=NS; better composite primary endpoint at 96 h evaluated with WPNS	Magnesium sulphate did not influence neuropsychological function 3 months after operation
Mack and colleagues[23]	Vascular	Magnesium sulphate	(I) 10 g 500 ml^{-1}; (II) 18 g 500 ml^{-1}; (III) 20 g 500 ml^{-1}	55	53	1 day	NA	Low-dose group (I–II): P=0.01; high-dose group (III): P=NS
Grieco and colleagues[12]	Cardiac	GM1 ganglioside	300 mg × 2	19	11	1 week; 6 months	P=NS	P=NS
Taggart and colleagues[27]	Cardiac	Lexipafant	0.4; 4 mg h^{-1}	100	50	5 days; 3 months	NA	P=NS
Erol and colleagues[10]	Cardiac	Glutamate/aspartate-enriched crystalloid cardioplegia	15 mmol $litre^{-1}$	35	35	3 days	NA	P=NS
Höcker and colleagues[21]	Major non cardiac	Xenon	60% in O_2	56	58	1; 6; 30 days	NA	P=NS

Arrowsmith and colleagues[18]	Cardiac	Remacemide	25–50–100–150 mg 1° day; 150 ×4/day	87	84	8 weeks	NA	*P*=NS; the remacemide group showed significantly superior performance in three tests over the control group
Durazzo and colleagues[19]	Vascular	Atorvastatine	20 mg day^{-1} for 45 days	50	50	Until the discharge; 6 months	*P*=0.18; treated patients had a significant decrease in the rate of cardiac events	NA
Haljan and colleagues[13]	Cardiac	Erythropoietin	375; 750; 1500 units kg^{-1}	24	8	On day of discharge; 2 months	NA	*P*=NS at early and long-term follow-up
Holinski and colleagues[20]	Cardiac	Piracetam	12 g in bolus	60	60	3 days	NA	*P*>0.0005 cognitive decline was less in all subtests of the treated patients except attention
Gamberini and colleagues[29]	Cardiac	Rivastigmine	Three 1.5 mg doses per day every 8 h starting on the evening preceding the operation and continuing until the evening of the 6th postoperative day	59	61	Daily for 6 days	NA	*P*=NS
Butterworth and colleagues[17]	Cardiac	Pegorgotein	5000 UI kg^{-1} i.v. bolus; 2000 UI kg^{-1} i.v. bolus	45	22	5–7 days; 4–6 weeks	*P*=NS. No patients demonstrated a periopertaive stroke	*P*=NS at early and long-term follow-up
Hogue and colleagues[30]	Cardiac	17β-estradiol	7.6 mg in transdermal patch; 0.08 ng kg^{-1} min^{-1} infusion during surgery	86	88	4–6 weeks; 6 months	*P*=NS	*P*=NS at early and long-term follow-up

by 3169 mg in a continuous infusion for 24 h, no reduction in POCD was found.[31] Magnesium sulphate given to 49 vascular surgery patients treated with a bolus during anaesthesia induction, dose range 2–4 g, and followed by a continuous 24 h infusion, dose range 8–16 g, when compared with the 43 control patients, was associated with a lower incidence of POCD at the first postoperative day in the 13 patients who received less than a total of 10 g of magnesium sulphate (bolus+infusion).[23]

Finally, the use of remacemide and piracetam, although not effective in reducing POCD, yielded a better postoperative 'neurocognitive performance'.[18 20]

Mortality

Mortality was evaluated in 16 RCTs that tested 12 drugs: lidocaine, thiopental, propofol, ketamine, remacemide, nimodipine, atorvastatin, magnesium sulphate, xenon, rivastigmine, pegorgotein, and 17β-estradiol.[11 16–19 21 22 24 25 28–34] No statistically significant differences in the mortality rate among treated and untreated patients were found.

Of interest, one RCT that tested nimodipine was prematurely suspended because of a higher mortality rate in patients randomized to receive nimodipine compared with those in the placebo group.[22]

Discussion

The main finding of this review is that in some experimental paradigms, a few drugs appear to potentially have a neuroprotective effect. However, the methodological inconsistencies and weakness, and the small number of studies do not allow any firm conclusions.

The studies we analysed have many methodological discrepancies: rationale for drug selection, dosing, timing, length of administration, type of surgery, and type and timing of neurocognitive testing. The drugs tested for pharmacological brain neuroprotection have many differing mechanisms of action and their dosing and timing were selected according to preclinical studies associated with positive results.[35–41] However, in animal studies, neurological outcome is usually based on fairly simple tasks, whereas in humans, neurocognitive testing evaluates complex neuronal functions and tasks.[35–37 42–45] These difference might, in part, explain the lack of positive effects when pharmacological brain neuroprotection clinical trials are designed based on animal studies. A retrospective analysis on the effects of statin and β-blockers in patients who had undergone coronary artery bypass graft, not included in this review because of the study design, demonstrates protective effects on postoperative stroke and provides interesting insights on methodological criteria for drug selection.[46]

Although our review was not intended to focus primarily on neuroprotection in cardiac surgery, the majority of selected studies (22 out of the 25) were accomplished in this clinical setting. It is controversial if the perioperative brain damage that takes place during cardiac surgery represents an appropriate study model for other types of surgery.[2 43 47] These patients have a markedly higher incidence of perioperative brain damage than other high-risk patients. Perioperative neurological deficits have been detected in up to 80% of in-hospital patients after cardiac surgery and it is still present in as many as 42% 3–5 yr later. In non-cardiac surgery, perioperative neurological deficit/cognitive decline is much less frequent and can be detected in 26% of patients in short-term follow-up and in 10% in long-term follow-up.[1 4 5] The higher incidence probably reflects specific factors unique to cardiac surgery, so that neuroprotective strategies pertinent to those patients may not be appropriate for other high-risk patients.[42 48] Studies in cardiac surgery should be viewed as hypothesis generating but needing to be confirmed in the different surgical settings.

No consensus exists on the best neuropsychometric tests for detecting and quantifying neurological damage and POCD. Neither is there agreement on the optimal timing for postoperative testing, both for research and for day-to-day clinical use.[49–51] Cognition is the result of activities in multiple complex, distributed, and interacting neuronal circuits that underlie specific information processing functions. Therefore, comprehensive neuropsychological assessment requires a battery of tests assessing a variety of cognitive domains.[1] In this review, we included only studies that used consistent pre- and postoperative evaluation methods for the neurological and cognitive status in order to minimize the risk of bias related to matching patients. For the same reason, we also excluded patients with acute brain damage (i.e. trauma or acute subarachnoid haemorrhage).[17 20] The study that tested rivastigmine for perioperative neuroprotection was included in this meta-analysis, despite having postoperative delirium as primary endpoint because it presented cognitive dysfunction evaluated before and after operation according to our inclusion criteria as secondary endpoint.[29]

A potential limitation of this review is related to the separate analysis for new postoperative neurological deficits and POCD. We decided to independently analyse these two complications because current research practice categorizes new focal neurological deficits (type 1 outcome) separately from POCD, confusion, agitation, memory loss, and seizures when they are without evidence of focal injury (type 2 outcome).[2 52] A second limitation is the heterogeneity of surgical procedures studied. Of interest when the same drug, magnesium sulphate, was tested in cardiac and non-cardiac patients, both studies reported a neuroprotective effect.[23 31] This single example though does not validate the extrapolation of results from cardiac surgery to other types of surgery.

In conclusion, based on single studies, pharmacological neuroprotection might provide benefits in terms of a reduction in new postoperative neurological deficits or POCD, but no effects on mortality were reported. Almost all studies to date have been done in cardiac surgery patients, where the more general applicability is unclear. Future studies need to include a broader range of relevant clinical scenarios using a wider consensus on the methodological approaches, including timing and dosing of drug administration, patient selection, and perioperative neurological and cognitive testing.

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Appendix 1: CENTRAL, The Cochrane Library

#1 MeSH descriptor Neuroprotective Agents explode all trees
#2 ((cerebral or brain) near protect*) or neuroprotect*
#3 (#1 OR #2)
#4 MeSH descriptor Endarterectomy, Carotid explode all trees
#5 MeSH descriptor Cardiac Surgical Procedures explode all trees
#6 MeSH descriptor Neurosurgery explode all trees
#7 MeSH descriptor Foramen Ovale, Patent explode all trees
#8 MeSH descriptor Extracorporeal Circulation explode all trees
#9 MeSH descriptor Atrial Fibrillation explode all trees
#10 MeSH descriptor Endocarditis explode all trees
#11 MeSH descriptor Carotid Stenosis explode all trees
#12 MeSH descriptor Anesthesia, General, this term only
#13 MeSH descriptor Anesthesia, Local explode all trees
#14 MeSH descriptor Anesthetics, Local, this term only
#15 Barbiturat* or Propofol or Isoflurane or Lidocaine or Lignocaine or Nimodipine or GM1 ganglioside or Remacemide or (adrenergic receptor antagonist*) or ketamine or Thiopental or Thiopentone or Carotid endoarterectom* or [(Cardi* or Open heart) near Surg*] or Coronary artery bypass or Neurosurg* or Patent Foramen Ovale or Extracorporeal circulation or Atrial fibrillation or Infective endocarditis or Carotid stenosis
#16 (#4 OR #5 OR #6 OR #7 OR # OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15)
#17 (#3 AND #16)

Appendix 2: MEDLINE

(1) {[(cerebral or brain) protect*] or neuro?protect*}.mp.
(2) Neuroprotective Agents/
(3) 1 or 2
(4) {(An?esthetic* adj3 Drug*) or Barbiturat* or Propofol or Isoflurane or Lidocaine or Lignocaine or Nimodipine or GM1 ganglioside or Remacemide or (adrenergic receptor antagonist* or ketamine) or Thiopental or Thiopentone or Carotid endoarterectom* or [(Cardi* or Open heart) adj3 Surg*] or Coronary artery bypass or Neurosurg* or Patent Foramen Ovale or Extracorporeal circulation or Atrial fibrillation or Infective endocarditis or Carotid stenosis}.mp.
(5) exp Endarterectomy, Carotid/ or exp Cardiac Surgical Procedures/ or exp Neurosurgery/ or exp Foramen Ovale, Patent/ or exp Extracorporeal Circulation/ or exp Atrial Fibrillation/ or exp Endocarditis/ or exp Carotid Stenosis/ or exp Anesthesia, General/ or exp Anesthesia, Local/ or exp Anesthetics, Local/
(6) 4 or 5
(7) 3 and 6
(8) [(randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.] not [animals not (humans and animals)].sh.
(9) 7 and 8

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