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A meta-analysis of pharmacological neuroprotection in noncardiac surgery: focus on statins, lidocaine, ketamine, and magnesium sulfate

Z.-W. ZENG, Y.-N. ZHANG, W.-X. LIN, W.-Q. ZHANG, R. LUO

First Anesthesia Department, Meizhou People's Hospital, Guangdong Province, China

Abstract. – OBJECTIVE: Non-cardiac surgery is associated with perioperative cerebral complications (delirium, postoperative cognition dysfunction, stroke). While rare, these complications can lead to disabilities and deaths. Information is ambiguous as to whether pharmacological preoperative treatment exerts neuroprotection. We wished to systematically assess potential modulation by statins, lidocaine, ketamine or magnesium sulfate of the relative risk of cerebral complications in noncardiac surgery. Selection of these pharmacological agents was based on their known neuroprotective abilities.

PATIENTS AND METHODS: By searching Medline, EMBASE and Cochrane databases, we identified 4 suitable publications that collectively enrolled 1358 patients (intent-to-treat population), of which 679 patients were treated preoperatively with statins (404 patients on atorvastatin and 275 on rosuvastatin) and 679 patients with preoperative placebo. The reported cerebral outcome was stroke, assessed either within 30 days (4 publications) or 6 months (2 publications) after surgery.

RESULTS: Episodes of stroke within 30 days and 6 months postoperatively were observed in several publications, enabling aggregate analyses. No modulation by statins of the relative risk of stroke at 30 days was observed (risk ratio 1.59, 95% confidence interval 0.08-30.97; $p = 0.76$). At 6 months, statins showed an insignificant trend toward neuroprotection (risk ratio 0.33, 95% confidence interval 0.05-2.10; $p = 0.24$).

CONCLUSIONS: The available clinical data are still scarce. Our analyses indicate no protective effects by statins against perioperative stroke but some favorable trends toward delayed stroke. Further randomized trials are needed to unequivocally assess the neuroprotective potential of current pharmacological agents in non-cardiac surgery.

Key Words:
Statins, Lidocaine, Ketamine, Magnesium sulfate, Surgery, Non-cardiac, Meta-analysis.

Introduction

In many patients, non-cardiac surgeries are associated with substantial negative perioperative consequences. These include unfavorable cardiovascular (cardiac arrest, myocardial infarction, or congestive heart failure) and cerebral (delirium, postoperative cognitive dysfunction, or stroke) complications. Both cardiovascular and cerebral complications are serious, and can be detrimental and lead to patients' disabilities or deaths. The strong negative impact of these complications fuels recurrent interest to pharmacological interventions that would decrease the incidence of the aforementioned negative consequences. In recent years, substantial appreciation has been achieved with regard to prevention of postoperative cardiovascular events in non-cardiac surgeries. Publications and discussions in the literature[1-9], and recent clinical guidelines[10,11] are helpful for assessing preoperative risk, as well as for introducing proper intraoperative monitoring measures and adequate postoperative management.

In contrast to increasing clarity on prevention of cardiovascular events, much less certainty exists with regard to unfavorable cerebral events after non-cardiac surgeries. The published recommendations on prevention of postoperative stroke[12] provided limited statements on anticipated benefits of pharmacological pre-treatment. These recommendations are much less extensive compared with those on prevention of cardio-

Corresponding Author: Yue-nong Zhang; e-mail: 36856665@qq.com

vascular events. For example, the recommendations on prevention of perioperative stroke[12] only address potential harms of discontinuing the cholesterol-lowering drugs statins before the surgery[12]. Yet the recommendations do not touch upon statin reload prior to the surgery[12], notwithstanding the evidence that statin reload was shown beneficial in preventing stroke in cardiac surgeries[13].

The brevity of clinical recommendations on pharmacological prevention of unfavorable cerebral complications is likely due to the following three problems. The incidence of cerebral complications after non-cardiac surgeries is quite heterogeneous, ranging from the relatively high incidence of delirium through less common postoperative cognitive dysfunction to the least common stroke[14-18]. Similarly, non-cardiac surgeries are also not homogeneous in bearing the relative risk of cerebral complications. Specifically, the relative risk of perioperative stroke is substantially higher with carotid endarterectomy compared with that with general surgery[19-21]. This complicates a quantitative assessment of potentially beneficial pharmacological treatments. Furthermore, reliable literature data on modification of the relative risk of cerebral complications of non-cardiac surgery only recently began to accumulate. The aforementioned recommendations[12] have been published in 2014, and some pertinent clinical studies have been published quite recently[16].

To address the existing knowledge gap on potentially beneficial role of pharmacological neuroprotection, we conducted the present meta-analysis. Pharmacological neuroprotection has deliberately been formulated broad, and encompassed prevention by pharmacological agents of all pertinent unfavorable cerebral complications, including delirium, postoperative cognitive dysfunction, perioperative visual loss, or perioperative stroke. As pharmacological agents, our literature review focused on statins, lidocaine, ketamine, and magnesium sulfate. The rationale for focusing on these pharmacological agents came from the fact that they have previously been described as possessing neuroprotective abilities (e.g., statins[22-24]; lidocaine[24-26], ketamine[24,27-29]; magnesium sulfate[24]).

Notably, the published evidence of anticipated neuroprotective effects of these pharmacological agents is not unequivocal. Indeed, many publications[30-32] underscored the lack of efficacy or even harmful effects of the selected pharmacological agents. In our opinion, this further underscored the need for a thorough and systematic assessment of the literature, hence justifying the present meta-analysis.

Materials and Methods

Database Searches and Data Extraction

The methodology for this meta-analysis was conform to international recommendations[33]. The protocol of this meta-analysis has been published on the PROSPERO website[34] (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=75252).

Specifically, the primary objective of electronic database searches was to determine whether pharmacological treatment with statins, lidocaine, ketamine, or magnesium sulfate would provide neuroprotection in noncardiac surgery. The searches involved Medline (both via PubMed and Ovid), EMBASE, and Cochrane databases, and have been sequentially for each pharmacological agent. We used pre-specified key words and MeSH terms, appropriately combined with Boolean operators "AND" or "OR", to identify the publications of interest. The search algorithms and steps, along with the number of identified publications, are shown in Tables I-IV.

In addition, bibliography of each suitable original, review or meta-analysis article was cross-checked for potentially suitable publications. The searches were limited to the time frame between June 1992 and June 2017 (25 years). This was due to the fact that statins gained popularity around 1994.

The inclusion criteria were the following. We intended to include all clinical trials that had used statins (both hydro- and lipophilic), lidocaine, ketamine, and magnesium sulfate as preoperative intervention in noncardiac surgery. Neuroprotective effects of each of the aforementioned pharmacological agents were to be evaluated separately. The timing of pharmacological pre-treatment was expected to vary from hours before the surgery (bolus treatment) to up to 30 days before the surgery.

Another inclusion criterion was based on study design. To be included, clinical trials were to have experimental and quasi-experimental study design (that is, were to be randomized controlled trials, non-randomized trials, or case report series) and had to enroll at least 10 patients in each study arm.

Table I. Statin searches and number of identified publications.

	Search step	Key words and Boolean operators	Number of identified publications
Medline (PubMed) search	1	Statins OR hmg coa statins [MeSH Terms]	45233
	2	Surgery	4187792
	3	Non-cardiac OR noncardiac	9930
	4	"1992/06/01"[Date - MeSH]: "2017/06/30"[Date - MeSH]	17503054
	5	(statins OR hmg coa statins[MeSH Terms]) AND surgery AND ("1992/06/01"[Date - MeSH]: "2017/06/30"[Date - MeSH])) AND (non-cardiac OR noncardiac)	**154**
Medline (OVID) search	1	Statins.mp OR Hydroxymethylglutaryl-CoA Reductase Inhibitors/	41093
	2	Surgery.mp OR General Surgery/	1225019
	3	Limit 2 to yr="1992 – 2017"	917192
	4	Non-cardiac.mp	4766
	5	1 and 2 and 3 and 4	**58**
EMBASE search	1	Statins.mp OR Hydroxymethylglutaryl-CoA Reductase Inhibitors/	85810
	2	Surgery.mp OR General Surgery/	3202204
	3	Limit 2 to yr="1992 – 2017"	2603929
	4	Non-cardiac.mp	8305
	5	1 and 2 and 3 and 4	**171**
Cochrane search	1	MeSH descriptor: [Hydroxymethylglutaryl-CoA Reductase Inhibitors] explode all trees	3452
	2	MeSH descriptor: [General Surgery] explode all trees	381
	3	#2 Publication Year from 1992 to 2017	364
	4	"non-cardiac surgeries": ti,ab,kw (Word variations have been searched)	163
	5	1 and 3 and 4	**0**

Footnote: 383 total references were included for subsequent screening.

Table II. Lidocaine searches and number of identified publications.

	Search step	Key words and Boolean operators	Number of identified publications
Medline (PubMed) search	1	Lidocaine OR lidocaine [MeSH Terms]	30117
	2	Surgery	4187792
	3	Non-cardiac OR noncardiac	9930
	4	"1992/06/01"[Date - MeSH]: "2017/06/30"[Date - MeSH]	17503054
	5	(lidocaine OR lidocaine[MeSH Terms]) AND surgery AND ("1992/06/01"[Date - MeSH]: "2017/06/30"[Date - MeSH])) AND (non-cardiac OR noncardiac)	**13**
Medline (OVID) search	1	Lidocaine.mp OR Lidocaine	32566
	2	Surgery.mp OR General Surgery	1225019
	3	Limit 2 to yr="1992 – 2017"	917192
	4	Non-cardiac.mp	4766
	5	1 and 2 and 3 and 4	**7**
EMBASE search	1	Lidocaine.mp OR Lidocaine	68442
	2	Surgery.mp OR General Surgery	3202204
	3	Limit 2 to yr="1992 – 2017"	2603929
	4	Non-cardiac.mp	8305
	5	1 and 2 and 3 and 4	**26**
Cochrane search	1	MeSH descriptor: [Lidocaine] explode all trees	4335
	2	MeSH descriptor: [General Surgery] explode all trees	381
	3	#2 Publication Year from 1992 to 2017	364
	4	"Non-cardiac surgeries": ti, ab, kw (Word variations have been searched)	163
	5	1 and 3 and 4	**1**

Footnote: 47 total references were included for subsequent screening.

Table III. Ketamine searches and number of identified publications.

	Search step	Key words and Boolean operators	Number of identified publications
Medline (PubMed) search	1	Ketamine OR ketamine [MeSH Terms]	17215
	2	Surgery	4187792
	3	Non-cardiac OR noncardiac	9930
	4	"1992/06/01"[Date - MeSH]: "2017/06/30"[Date - MeSH]	17503054
	5	(Ketamine OR ketamine [MeSH Terms]) AND surgery AND ("1992/06/01"[Date - MeSH]: "2017/06/30"[Date - MeSH] AND (non-cardiac OR noncardiac)	**13**
Medline (OVID) search	1	Ketamine.mp OR Ketamine	18871
	2	Surgery.mp OR General Surgery	1225019
	3	Limit 2 to yr="1992 – 2017"	917192
	4	Non-cardiac.mp	4766
	5	1 and 2 and 3 and 4	**7**
EMBASE search	1	Ketamine.mp OR Ketamine	37063
	2	Surgery.mp OR General Surgery	3202204
	3	Limit 2 to yr="1992 – 2017"	2603929
	4	Non-cardiac.mp	8305
	5	1 and 2 and 3 and 4	**30**
Cochrane search	1	MeSH descriptor: [Ketamine] explode all trees	1288
	2	MeSH descriptor: [General Surgery] explode all trees	381
	3	#2 Publication Year from 1992 to 2017	364
	4	"non-cardiac surgeries":ti, ab, kw (Word variations have been searched)	163
	5	1 and 3 and 4	**0**

Footnote: 55 total references were included for subsequent screening.

Table IV. Magnesium sulfate searches and number of identified publications.

	Search step	Key words and Boolean operators	Number of identified publications
Medline (PubMed) search	1	Magnesium sulfate OR magnesium sulfate [MeSH Terms]	9144
	2	Surgery	4187792
	3	Non-cardiac OR noncardiac	9930
	4	"1992/06/01"[Date - MeSH]: "2017/06/30"[Date - MeSH]	17503054
	5	(Magnesium sulfate OR magnesium sulfate[MeSH Terms]) AND surgery AND ("1992/06/01"[Date - MeSH]: "2017/06/30" [Date - MeSH])) AND (non-cardiac OR noncardiac)	**5**
Medline (OVID) search	1	Magnesium sulfate.mp OR Magnesium Sulfate	6743
	2	Surgery.mp OR General Surgery	1225019
	3	Limit 2 to yr="1992 – 2017"	917192
	4	Non-cardiac.mp	4766
	5	1 and 2 and 3 and 4	**4**
EMBASE search	1	Magnesium sulfate.mp OR Magnesium Sulfate	15424
	2	Surgery.mp OR General Surgery	3202204
	3	Limit 2 to yr="1992 – 2017"	2603929
	4	Non-cardiac.mp	8305
	5	1 and 2 and 3 and 4	**9**
Cochrane search	1	MeSH descriptor: [Magnesium Sulfate] explode all trees.	712
	2	MeSH descriptor: [General Surgery] explode all trees.	381
	3	#2 Publication Year from 1992 to 2017	364
	4	"Non-cardiac surgeries": ti, ab, kw (Word variations have been searched).	163
	5	1 and 3 and 4	**0**

Footnote: 55 total references were included for subsequent screening.

As a comparator, the included trials were to have a placebo control or no intervention study arm. No limitations were set for age, gender or disease/type of surgery. If possible, though, we wanted to conduct sub-analyses for the underlying disease and the type of surgery. This is because some types of non-cardiac surgeries have been associated with elevated relative risk of cerebral complications (for example, carotid endarterectomy and stroke[19-21]).

Exclusion criteria were pharmacological treatments in non-cardiac surgery other than statins, lidocaine, ketamine or magnesium sulfate, or any interventions in cardiac surgery. Furthermore, long-term treatment with statins (for more than 30 days prior to the surgery) was an exclusion factor, unless statin reload shortly before the surgery was employed. Retrospective studies, registry or chart reviews, and studies without the aforementioned comparators were also to be excluded.

We intended to analyze all neuroprotection-related outcomes. No specific outcome has been set as the principal outcome to allow for broader inclusion of the literature. No secondary outcomes have been planned.

Database searches were conducted by two investigators (Y.-N. Zhang and W.-X. Lin) in parallel and independently from one another. The lead investigator (Z.-W. Zeng) served as an arbitrary for potential disagreements between these investigators. Independent screening was done at each subsequent step (that is, at title, abstract, and full-text screenings). At the step of full-text screening, consultations have been held with two other co-authors (Zhang and Luo) with regard to reference cross-checking ("snowballing"). To ensure higher comparability of the screening, we used a pre-defined questionnaire. The questionnaire was developed during a pilot literature screening conducted prior to registration of the study protocol at the PROSPERO. These steps warranted excellent inter-investigator agreement.

Meta-analysis

Our study was meant to be an aggregate assessment of efficacy of pharmacological neuroprotection. No evaluations of the strength of evidence and/or risk of bias (apart from potential publication bias) have been planned. For calculations, we used RevMan (Review Manager) version 5.3 (computer program; Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Because the intervention has been expected to be heterogeneous (four different pharmacological treatments, different underlying medical conditions, and different types of non-cardiac surgery), a random effect model was used.

Based on our pilot searches, we expected the majority of publications to present the data (for example, incidence of stroke) as categorical data. These data were to be assessed by calculation of the relative risk. If continuous data needed to be analyzed, standardized mean differences were to be calculated. The reporting bias was to be assessed by the funnel plot if the number of publications exceeded 10. We further intended to rank the data heterogeneity using the I^2-test. The semi-quantitative ranking of heterogeneity was to be based on recommendations[35] related to I^2 values, with thresholds set to less than 25%, less than 50%, and less than 75% to respectively indicate low, moderate, and high heterogeneity.

As mentioned above, analyses were to be conducted separately for each tested pharmacological agent.

Results

Selecting Publications for a Quantitative Reference Pool

The search of Medline (via Pubmed and OVID), EMBASE and Cochrane electronic databases led to identification of 383 potentially suitable publications on preoperative treatment with statins, and of 47, 55 and 18 potentially suitable publications respectively on lidocaine, ketamine and magnesium sulfate pre-treatments (Tables I-IV). These publications were included in further screening (Figure 1). Redundant publications were eliminated, leading to the remaining 269, 36, 38, and 8 publications (Figure 1). We then defined the suitability of the remaining publications by reading titles and abstracts, and, where justified, pertinent sections of the text. Thereby, the number of publications selected for the full-text reading was reduced to, respectively, 59, 20, 22, and 2 publications (Figure 1). Thereby, our initial reference pool comprised 103 publications (Figure 1).

During the full-text reading, we eliminated 100 publications (Figure 1). Initially, based on the inclusion and exclusion criteria defined in the Materials and Methods section, we excluded 90 publications from quantitative analysis. The reasons for exclusion were study design deviant from inclusion criteria (such as, a retrospective study,

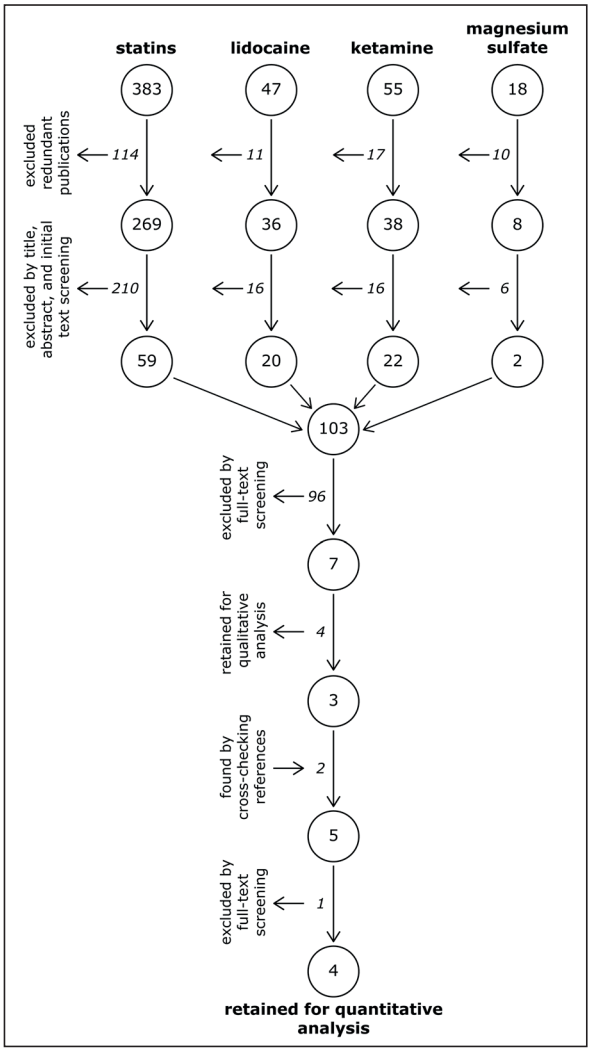

Figure 1. Flow chart of electronic database screening following PRISMA recommendations[33].

or chart review, or case report with < 10 patients; 41 total publications), being a commentary, review, meta-analysis or a clinical guidelines article (11 publications), not reporting relevant outcomes (25 publications), and publications irrelevant for various other reasons (13 publications).

An additional reason to exclude publications has not been foreseen by us upon planning this investigation. As it turned out, many publications (mostly on beta-blockers, but some involving statins as well) came from the discredited Dutch cardiology group led by Don Poldermans. Because validity of conclusions in publications from this Dutch group have been put under questioning[36,37], we decided to exclude from our reference pool all publications co-authored by Don Poldermans. This led to exclusion of 6 additional publications.

Additional four publications (Figure 1) have been excluded from quantitative analysis but retained for qualitative analysis. The first two publications kept for qualitative analysis dealt with ketamine[38,39]. Avidan et al[38] studied potential beneficial effects of ketamine (bolus sub-anesthetic dose of 0.5 or 1.0 mg/kg during anesthesia before cardiac or non-cardiac surgery) to prevent perioperative delirium. This study has not been included in the quantitative analysis because of no clear distinction between cardiac and non-cardiac surgeries. The other study was by Lee et al[39]. This work tested whether ketamine (bolus sub-anesthetic dose of 0.5 mg/kg during anesthesia before orthopedic surgery) beneficially modulates the incidence of postoperative cognitive dysfunction. While formally eligible for inclusion in our meta-analysis, this investigation was not matched by similar studies in the remaining publication pool, precluding quantitative analysis. For this reason, the study by Lee et al[39] was retained for qualitative analysis only. The third study (Hashemi et al[40]) tested the effects of lidocaine (bolus dose of 1.5 mg/kg) on postoperative cognitive dysfunction. The intervention was administered right before the end of the surgery, which was not conforming to our definition of preoperative treatment. Thereby, this study has been kept for qualitative analysis only. Finally, the fourth study (Wong et al[41]) put forward the objective of assessing early postoperative cognitive function following noncardiac surgeries. Even though this research evaluated lidocaine, the drug was part of a drug cocktail for epidural analgesia. Moreover, this work provided unclear indications of an administered dose of lidocaine. Due to these limitations, this study was only used for a qualitative analysis.

Thereby, our literature searches yielded three suitable publications (Figure 1): Berwanger et al[42], Xia et al[43], and Neilipovitz et al[17]. Cross-checking the references in bibliographies of 103 excluded publications revealed two additional, potentially suitable publications (Figure 1). These publications have been added to the reference pool for quantitative analysis (Figure 1). The first publication (Chopra et al[44]) was a systematic review and meta-analysis, and has, therefore, been removed from the reference pool (Figure 1). The other publication (Durazzo et al[45]) has been considered suitable and has been added to the reference pool for quantitative analysis (Figure 1), increasing the number of included publications to four.

Characteristics of Publications in the Quantitative Reference Pool

All four publications[17,42,43,45] in the quantitative reference pool studied how statins modulated cardiovascular and cerebral complications following non-cardiac surgeries (Table V). There were no publications on neurological protection by lidocaine, ketamine, or magnesium sulfate, which would be suitable for quantitative analysis.

All four publications in the quantitative reference pool described observations from randomized controlled trials (Table V). Collectively, these publications presented data from 1358 patients (intent-to-treat population), of which 679 patients were treated preoperatively with statins (404 patients: with atorvastatin [lipophilic statin]; 275 patients: with rosuvastatin [hydrophilic statin]), whereas the remaining 679 patients were treated preoperatively with placebo.

The study designs differed among publications. For instance, Berwanger et al[42] and Durazzo et al[45] utilized a parallel study design (Table V) to compare outcomes in patients who were pre- and postoperatively treated with atorvastatin with outcomes in patients on pre- and postoperative placebo. In contrast, the remaining two publications (Xia et al[43] and Neilipovitz et al[17]) utilized a partly crossover study design (Table V), both without a washout period. Specifically, Xia et al[43] had patients in the statin study arm pre- and postoperatively on rosuvastatin, while patients in the control study arm receive placebo only preoperatively and were switched to rosuvastatin after the surgery (Table V). An even more complex study design was seen in the work by Neilipovitz et al[17] who had three study arms. In particular, two study arms (atorvastatin and placebo) were run in a parallel study design, whereas patients in the third study arm received placebo prior to surgery and were switched to atorvastatin (Table V). Neither Xia et al[43] nor Neilipovitz et al[17] addressed the rationale for this partly crossover study design.

The doses of administered statins also differed. Specifically, the doses ranged from conventional (20 mg of atorvastatin[45] or rosuvastatin[43]; Table V) to high doses (80 mg of atorvastatin[17,42]; Table V). The duration of preoperative statins was also quite variable, ranging from 2 hours[43] to more than 2 weeks[45] before the surgery.

The included publications differed in the time frames of postoperative surveillance. These ranged from 30 days to 6 months postoperatively (Table V), with studies by Xia et al[43] and Durazzo at al[45] assessing the outcomes at both 30 days and 6 months following the surgery (Table V).

The types of non-cardiac surgeries included general and vascular surgeries (Table V). Among the patients enrolled by these studies, there were both those with pre-existing cardiovascular and cerebrovascular diseases, and those without. Specifically, Berwanger et al[42] reported 60 patients with cardiovascular disease and 25 patients with cerebrovascular disease in the intervention arm, and, respectively, 57 and 22 patients in control arm. Xia et al[43] had 105 and 15 patients with, respectively, cardiovascular and cerebrovascular disease in the intervention arm and, respectively, 112 and 18 patients in control arm. Neilipovitz et al[17] comprised two control arms. The intervention arm had 17 patients with cardiovascular disease and 1 patient with cerebrovascular disease. In control arms 1 and 2, these numbers were, respectively, 4, 3, 8 and 4. Finally, Durazzo at al[45] reported 37 patients with cardiovascular disease and 0 patients with cerebrovascular disease in the intervention arm, and, respectively, 32 and 0 patients in control arm. The majority of patients in all four publications were reported as having hypertension. The aforementioned data indicate the majority of patients in both intervention and placebo arms of all included publications had risk factors to develop perioperative cerebral complications, such as stroke.

Aggregate Analysis of Publications in the Quantitative Reference Pool

We next evaluated the outcome of interest. All four studies reported stroke as an outcome, and did not assess other cerebral complications (such as delirium) of non-cardiac surgeries. For this reason, we quantitatively analyzed how preoperative statins modified the relative risk of perioperative stroke.

It is important to underscore that literature indicates that reported incidence of perioperative stroke may be determined by how stroke is defined in a particular study. For instance, Mrkobrada et al[46] demonstrated that covert episodes of stroke do not always fall under established criteria[12] and will remain under-diagnosed, unless specialized methods (such as magnetic resonance imaging) are employed. Thereby, the true incidence of stroke may be higher than currently assumed.

Importantly, clinical recommendations on stroke following non-cardiac surgery[12] encompass both ischemic and hemorrhagic mechanisms of a brain

Table V. Characteristics of publications included in the quantitative reference pool.

Publication	Study design	Total study population; prior statin use; age (mean ± SD) years, intervention *vs.* control arm	Patient number, intervention *vs.* control arm	Type of surgery, (number intervention *vs.* control arm)	Medication, dose, duration	Outcome
Berwanger et al[42]	Placebo-controlled RCT (parallel study design)	648 patients (ITT); statin-naïve; 66.8 ± 13 *vs.* 66.7 ± 12.6	328 *vs.* 320	Intraperitonial (83 *vs.* 69), orthopaedic (89 *vs.* 104), gynaecologic (30 *vs.* 24), vascular (21 *vs.* 21), urologic (27 *vs.* 19), neurosurgery (12 *vs.* 16), mastectomy (7 *vs.* 8), thoracic (8 *vs.* 8), other types (6 *vs.* 6), did not undergo surgery (12 *vs.* 15)	Intervention arm: atorvastatin, 80 mg preoperatively (18 hours before the surgery; if surgery was postponed, then again 80 mg) + 40 mg 12 hours postoperatively + 40 mg once daily for 7 days postoperatively. Control arm: placebo pre- and postoperatively	Incidence of stroke (within 30 days postoperatively)
Xia et al[43]	Placebo-controlled RCT (partly crossover study design)	550 patients (ITT); chronic statin use*; 67.0 ±10 *vs.* 68 ± 11	275 *vs.* 275	Acute suppurative appendicitis (93 *vs.* 96), acute cholecystitis (56 *vs.* 50), acute cholangitis (45 *vs.* 51), acute pancreatis (42 *vs.* 38), peptic ulcer perforation (23 *vs.* 21), urinary calculi (16 *vs.* 19)	Intervention arm: rosuvastatin, 20 mg preoperatively (2 h before the surgery) + 10 mg for 6 months postoperatively. Control arm: placebo preoperatively + 10 mg rosuvastatin for 6 months postoperatively	Incidence of stroke (within 30 days and 6 months postoperatively)
Neilipovitz et al[17]	Placebo-controlled RCT (partly crossover study design)	60 patients (ITT); statin-naïve; 71.0 ± 10 *vs.* 67 ± 11 *vs.* 69 ± 11[#]	26 *vs.* 17 *vs.* 17[#]	Aortic surgery (9 *vs.* 5 *vs.* 5[#]), infralinguinal revascularization (7 *vs.* 8 *vs.* 9[#]), nonvascular surgery (10 *vs.* 3 *vs.* 3[#])	Intervention arm: atorvastatin, 80 mg preoperatively (the day of surgery) + 80 mg for 7 days postoperatively. Control 1 arm: placebo preoperatively + 80 mg for 7 days postoperatively. Control 2 arm: placebo pre- and postoperatively	Incidence of stroke (within 30 days postoperatively)
Durazzo et al[45]	Placebo-controlled RCT (parallel study design)	100 patients (ITT); statin-naïve; 65.9 ± 9.9 *vs.* 68.4 ± 9.5	50 *vs.* 50	Aortic repair (28 *vs.* 28), infralingual arterial bypass (9 *vs.* 11), carotid endarterectomy (6 *vs.* 5), amputation (1 *vs.* 2), no operation (6 *vs.* 4)	Intervention arm: atorvastatin, 20 mg preoperatively (at least 14 days before the surgery) + 20 mg for at 30 days postoperatively. Control arm: placebo pre- and postoperatively	Incidence of stroke (within 30 days and 6 months postoperatively)

Footnote: RCT, randomized controlled trial; ITT, intent-to-treat; *Statin reload prior to surgery; [#]Intervention *vs.* control 1 *vs.* control 2 arm.

infarction that underlie stroke. Furthermore, the time frame for perioperative stroke is limited to an episode occurring within 30 postoperative days[12].

Based on these considerations, we first studied the definitions of stroke in publications in the quantitative reference pool. One study (Xia et al[43]) defined stroke as brain hemorrhage, diagnosed neurologically and confirmed by magnetic resonance imaging. Another one (Durazzo et al[45]) identified stroke as ischemic injury revealed by neurologic examination, and confirmed by imaging and through a neurologist. The two other publications either defined stroke as a focal neurological deficit lasting for at least one week [17] or did not provide a definition[42].

Three out four selected publications[17,42,45] tested the anti-stroke effects of statins in statin-naïve patients (that is, those without statin treatment for 30 days preceding the surgery). The remaining publication[43] employed a statin reloading design. Thereby, all four publications (Table V) met our inclusion criteria. The aggregate quantitative analysis of these publications yielded the following. First, two[42,45] out of four publications reported episodes of stroke within 30 days post surgery (Figure 2). Therefore, while all four publications have been included in the aggregate analysis, only two of them[42,45] provided data to compare the relative risk of stroke in patients treated preoperatively with statins or placebo. Our analysis demonstrated that the relative risk of perioperative stroke has not been beneficially modified by preoperative statins (Figure 2). Specifically, the aforementioned two publications reported a total of 3 episodes of stroke per 677 statin-pretreated patients and 1 episode of stroke per 658 placebo-pretreated patients (Figure 2). This yielded the risk ratio of 1.59 (95% confidence interval: 0.08-30.97; $p = 0.76$; Figure 2).

Durazzo et al[45] and Xia et al[43] reported episodes of stroke within 6 months following the surgery. While not strictly falling under the definition of "perioperative stroke"[12], an episode of stroke occurring later in life may still lead to devastating consequences. Therefore, beneficial pharmacological modulation of the relative risk of delayed stroke incidence would also be advantageous. Moreover, in both aforementioned publications, patients continued receiving statins for considerable amount of time (for at least one month[45] or for 6 months[43] postoperatively) following the surgery. Therefore, potential stroke preventing effects of statins may have extended beyond 30 days after surgery. For this reason, we conducted an assessment of the relative risk of delayed stroke (that is, occurring for more than 30 days after the surgery) using the data from the aforementioned two publications.

We observed a trend to beneficial modulation of the relative risk of delayed stroke by statins administered preoperatively and for long-term postoperatively (Figure 3). While not reaching significance, the trend indicated a nearly 70% reduction in the relative risk of delayed stroke by statins (Figure 3). Specifically, the risk ratio was 0.33 (95% confidence interval 0.05-2.10; $p = 0.24$) in statin-treated patients (Figure 3).

Neither the 30-day nor the 6-months analysis had sufficient number of studies to check for publication bias. Therefore, we abstained from this analysis.

Analysis of Publications in the Qualitative Reference Pool

Finally, we qualitatively assessed the four publications[38-41] that had not been included in the quantitative analysis. The reasons for not including them in the quantitative analysis have been

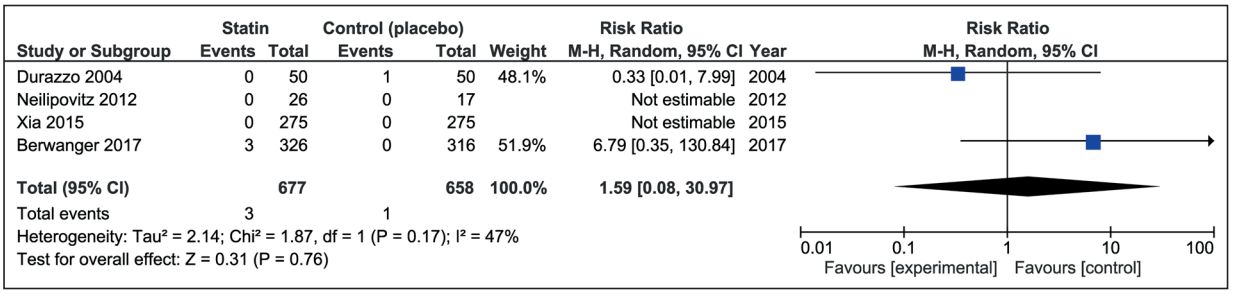

Figure 2. Forest plot of risk ratio of stroke (= "events") within 30 days after noncardiac surgery in patients preoperatively treated with statins or placebo. From the work of Neilipovitz et al[17], we compared the data from statin-pretreated patients vs. the data from patients treated pre- and postoperatively with placebo. This publication also presented a third study arm (preoperative placebo treatment followed by postoperative statin treatment). Adding these data to placebo data on Figure 2 did not change the results.

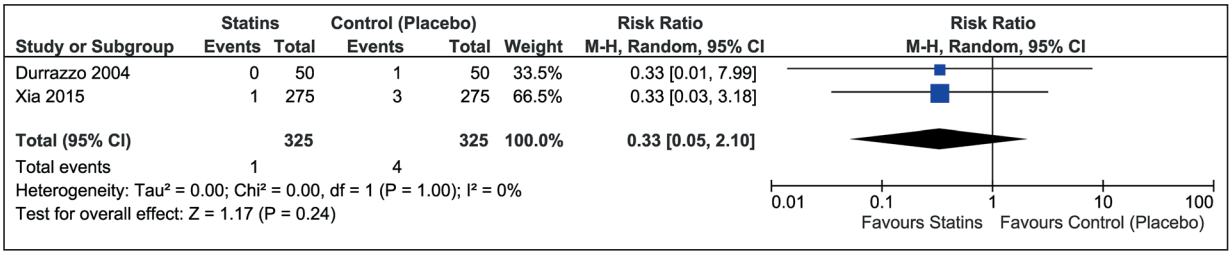

Figure 3. Forest plot of risk ratio of stroke (= "events") within 6 months after noncardiac surgery in patients preoperatively treated with statins or placebo.

described above. Ketamine and lidocaine were the pharmacological agents whose neuroprotective effects have been evaluated in these four publications.

These publications demonstrated that, for instance, subanesthetic doses of ketamine do not diminish the incidence of perioperative delirium[38]. While the publication reporting this did not present the data separately for cardiac and non-cardiac surgeries, the reported trend was discouraging. A similar lack of neuroprotective effect has been reported for both ketamine[39] lidocaine[40], with regard to postoperative cognition disorder. Lidocaine has also been a pharmacological agent tested in the fourth publication[41] in relationship to postoperative cognition disorder. The fact that this publication tested lidocaine as part of a drug cocktail limits the conclusiveness of its observations. Still, this publication, too, did not report beneficial neuroprotective effects of lidocaine. Thereby, none of the four, qualitatively analysed publications reported neuroprotective effects of ketamine or lidocaine.

Discussion

Our meta-analysis aimed to quantitatively assess beneficial modulation of cerebral complications of non-cardiac surgeries by statins, lidocaine, ketamine and magnesium sulfate. This modulation was assessed by calculation of the relative risk of unfavorable cerebral events during perioperative period (within 30 days after surgery) and beyond (up to 6 months). Out of four pharmacological agents of interest, publications suitable for quantitative analysis have been found only on statins, and only with regard to incidence of stroke[17,42,43,45]. Our analyses indicate an apparent lack of neuroprotective effects of preoperative statins on the relative risk of stroke during the perioperative period, and a trend toward beneficial effects of pre- and postoperative statins on delayed (that is, beyond the time frame of 30 days) relative risk of stroke. Thereby, the evidence of a protective role of preoperative statins is not conclusive yet, in our view. As mentioned above, several factors complicate an assessment of pharmacological neuroprotection in non-cardiac surgery. First, some surgical interventions are especially prone to lead to neurological complications[19-21], while this is not applicable to other non-cardiac surgeries. Second, the incidence of neurological complications varies, depending on the type of complication, with more frequent delirium and the least frequent stroke[14-18]. Third, there are current indications that many of these complications are under-diagnosed[46], necessitating the use of newest diagnostic methods for adequate recognition. This specifically concerns the perceived rarity of perioperative stroke in non-cardiac surgeries, and raises the question of whether the more common neurological complications (such as delirium) are, in fact, manifestations of under-recognized stroke[47]. Fourth, there is substantial complexity within each of the reported neurological complications. For example, perioperative stroke may be caused by ischemia, thrombosis, anemia-associated hypoxia, embolism, or haemorrhages[47]. This aggravates the assessment of individual preoperative risk and development of successful therapies for pharmacological attenuation of the risk of neurological complications following non-cardiac surgeries. Finally, pharmacological agents whose neuroprotective effects are currently tested in clinical trials are quite heterogeneous. Even within statins, there are substantial differences based on their chemical composition. For instance, lipophilic statins cross the blood-brain barrier more easily than hydrophilic statins[48]. On the other hand, lipophilic statins may be more prone to causing side effects[49]. This chemical and functional heterogeneity compounds the analysis. Side effects

associated with pharmacological neuroprotection deserve a dedicated publication. In particular, statins have well-known side effects, including hepatotoxicity, rhabdomyolysis, and cardiac arrest. Therefore, benefits and risks of pharmacological neuroprotection need to be thoroughly weighed against each other. Statins are not the only drugs tested for potential neuroprotective effects. As described above, there are studies addressing similar effects by ketamine or lidocaine. The publications[38-41] found by us as part of the literature screening for this meta-analysis indicate a lack of protective effects by ketamine or lidocaine toward perioperative delirium or postoperative cognition disorder subsequent to non-cardiac surgeries.

In the absence of hard evidence from clinical trials, it is wise to assess other available resources, such as patient registries or large patient cohorts. So far, the data from studies assessing these resources have not been conclusive, though. For instance, some studies appear to support preoperative use of statins[50], whereas others do not[16,51]. An important limitation of such studies is that they rely on the assumption that a cerebral perioperative complication, such as stroke, has been properly diagnosed and coded in patient registry. It is likely, though, that many minor or covert episodes are not recognized without specific diagnostic approaches, such as discussed above with regard to cover stroke. In addition, data mining of patient registries or cohorts suffers from an inherent limitation of pharmacological pre-treatment being quite heterogeneous, similar to what is described above with regard to statins. In addition, patients may be prescribed different doses of pharmacological agents, adding to data heterogeneity. In addition, patient adherence to treatment can only be assumed when registry or cohort data are analyzed. Given the limitations of the clinical evidence available to date, we, similar to other researchers[42], advocate the need for a large randomized controlled trial to unequivocally confirm or dispel the belief about pharmacological neuroprotection in non-cardiac disease. Based on what we learned from the above literature review and meta-analysis, the following recommendations can be expressed with regard to future clinical trials.

First and foremost, these trials should include substantial number of patients. This is important, given that the incidence of cerebral complications after non-cardiac surgeries is lower than after cardiac surgeries[47]. Second, adequate diagnosing cerebral complications likely requires application of newest and sophisticated diagnostic methods to enable catching minor or cover abnormalities[46]. Third, patients absolutely need to be pre-stratified based on the type of non-cardiac surgery. Specifically, vascular surgery causes cerebral complications more frequently than general surgery. Fourth, considerable thought should be given to selection, dose, and timing of administration of a pharmacological agent of interest. For instance, if statins are to be tested, ideally statin-naïve patients should be enrolled. However, many patients receive statins chronically, and current recommendations advise against discontinuing statins prior to non-cardiac surgery[12]. In such cases, statin reload may be considered while planning a clinical trial. Statin reload may better approximate the clinical setting in real life and may help avoid excessive patient selection to enroll only statin-naïve patients. Finally, we need to understand better the complex pathophysiology that leads to development of preoperative cerebral complications in non-cardiac surgeries. However rare, cerebral complications can often be devastating and deadly. Once we have a better understanding of which factors cause these complications, we will be able to better assess individual risks and develop specific interventions. Therefore, further translational studies are urgently needed in this field.

Conclusions

Perioperative cerebral complications of non-cardiac surgeries, such as stroke, are rare yet devastating. Pharmacological agents may provide neuroprotection. In the present meta-analysis, we analyzed the literature on potential neuroprotective effects of statins, lidocaine, ketamine and magnesium sulfate. Reliable clinical trials on this neuroprotection are still rare, enabling quantitative analysis only on statins and stroke. Our assessment does not show protection by statins against perioperative stroke but a trend toward decreased relative risk of delayed incidence of stroke. Prospective clinical and translational studies are urgently needed to better assess individual patient risk for perioperative cerebral complications, to provide unequivocal evidence on the current pharmacological agents, and to develop future, more effective and safe, therapeutic interventions.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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