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The effect of intravenous lidocaine on postoperative cognitive dysfunction: a systematic review and meta-analysis



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Abstract

Background Postoperative cognitive dysfunction (POCD) has been reported as a significant complication in elderly patients. Various methods have been proposed for reducing the incidence and severity of POCD. Intravenous lidocaine administration has been reported in the literature to reduce POCD, but the effect of lidocaine remains controversial.

Methods We screened Medline, Embase, Cochrane Library, and China National Knowledge Infrastructure (up to April 2022) databases following a search strategy for intravenous lidocaine on POCD. We also screened related bibliographies on lidocaine for POCD. Ten articles comprising 1517 patients were selected and analyzed. We divided the postoperative follow-up period as follows: short term (<30 days), medium term (30–90 days), and long term (>90 days).

Outcomes We found that lidocaine could attenuate the overall incidence of POCD, especially in the short term. There were no differences between lidocaine and placebo on the overall severity of POCD.

Conclusion Lidocaine administered intravenously could attenuate the overall incidence of POCD and its severity in the short term.

Keywords Lidocaine, Postoperative cognitive dysfunction, Meta-analysis, Intravenous, Elderly

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Introduction

Postoperative cognitive dysfunction (POCD), which reflects a negative change in an individual's cognitive trajectory, has increasingly been recognized as a complication in elderly patients. Cognitive decline lasts for months to years. The incidence of POCD varies from 1.43 to 59% in surgical patients [1-3]. Too many factors contribute to the wide-range incidence, including higher rates of cerebrovascular and myocardial injury, infection and respiratory complications, and diverse surgical populations [4]. In addition, POCD is currently a hypothetical phenomenon for which there is no International Statistical Classification of Disease (ICD-9) code and no Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) code, and nonstandard testing may also amplify the range [5, 6]. The potential pathogenesis of POCD involves neuroinflammation and oxidative stress secondary to anesthesia and surgery [7, 8]. Post-surgery inflammation is characterized by increased levels of inflammatory cytokines and mediators and vascular permeability [9]. Excessive inflammation can disrupt the body's immune system, potentially leading to certain inflammation-related conditions [10].

Lidocaine, a commonly used local anesthetic, crosses the blood-brain barrier (BBB) and exerts anti-inflammatory effects by inhibiting the expression of pro-inflammatory cytokines and the release of histamine [11–13]. Systemic administration of lidocaine has been reported to decrease the occurrence of cognitive dysfunction in the postoperative period [14]. However, Mathew et al. argued that subjects receiving lidocaine were more likely to experience cognitive decline, possibly because of altered lidocaine metabolism [15]. To address the controversies and scant evidence regarding the neuroprotective effect of lidocaine, we conducted the present meta-analysis and systemic review to determine whether the administration of lidocaine could reduce cognitive dysfunction in patients.

Methods

Literature retrieval and research selection

We followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [16] and assessing the methodological quality of systematic reviews (AMSTAR) to report our results. Two investigators independently searched the Medline, China National Knowledge Infrastructure, Embase, and Cochrane Library (up to April 2022) databases for randomized control trials that reported associations between lidocaine and postoperative cognitive dysfunction. The Boolean operator between keyword groups was "AND" and "OR" within the groups. Search terms were created by combing the following medical subject headings (MeSH terms): ("Cognitive Therapy" OR "Cognition Disorders" OR "Cognition" OR "Neuropsychology" OR "Neuropsychological Tests" OR "Cognitive Impairment" OR "delirium" OR "postoperative cognitive dysfunction") AND ("Lidocaine"). The search strategy on Medline is listed in the Appendix, and adjusted slightly in the different databases. To ensure a comprehensive literature search, no languages were restricted, and we also reviewed the bibliography of relevant publications. When the required data were unclear or missing, the author(s) was contacted.

Inclusion and exclusion criteria

The inclusion criteria were as follows: patients were under operation, lidocaine was administered systematically as an intervention, the postoperative cognitive dysfunction was compared before and after operation, the endpoint of the study was postoperative cognitive dysfunction, and studies were randomized control studies. The exclusion criteria were as follows: case reports, comments, reviews, or other types of literature; age less than 18 years; lidocaine was administrated locally or intramuscularly; original data could not be obtained; animal studies; and low-quality studies (Jadad score < 3).

Data extraction and quality assessment

Two authors independently screened the titles and abstracts of the studies and reviewed their full texts of selected studies using structured extraction forms. The characteristics of the included studies were as follows: initial of the first author, publication year, language, geographical location, placebo, participants (sex, age, sample size, history of cognitive dysfunction or psychotropic medication), intravenous lidocaine regimen, cognitive measurement, and follow-up time of assessment. Disagreements were resolved by a third rater, who was approved by a board-certified anesthetist not involved in the initial data extraction.

The occurrence of POCD was defined as at least a 1SD decline in the postoperative score compared with the preoperative score in the included studies. Continuous cognition variables measured using the Mini Mental State Examination (MMSE), information-memory-concentration test (IMCT), and neuropsychological (NP) tests were all included in the meta-analysis. Based on the follow-up assessment, we defined it as short term (<1 month), medium term (1–3 months), and long term (>3 months).

The modified Jadad scale [17] was used to evaluate article quality. Although some have argued that the Jadad score is a simplistic measure that does not characterize all elements of trial quality, it is still perhaps the most common measure of trial quality, and it offers the prospect of objectivity, which is much more efficient than some other subjective methods. The modified Jadad scale

comprises a five-point scale. The scale was defined as follows: (i) was the study described as randomized? "yes or no"; award a bonus point if the method of randomization is appropriate (e.g., computer-generated, score 2), deduct one point if the method of randomization is inappropriate (score 1)-no randomization score was 0; (ii) was the study described as double-blind? "yes or no"; award a bonus point if the method of double blinding is appropriate (e.g., identical placebo, score 2), deduct one point if the method of double blinding is inappropriate (score 1)-no double blinding score was 0; (iii) Was there a description of withdrawals and dropouts? "yes (score 1) or no (score 0)." The scale scores can range from 0 to 5 points, with higher scores indicating better quality. Studies with a score of ≥ 3 were considered high-quality trials, and those with scores of <3 were considered low-quality trials [18].

Statistical analysis

The analyses were conducted on an experiment-to-control basis. A fixed-effects model was used, and a randomeffects model was employed in the case of significant heterogeneity (P-value of chi-square test less than 0.10 and I^2 greater than 50%). This means that variables with a P-value of chi-square test less than 0.10 were considered heterogeneous, the amount of total variance was more than we would expect based on within-study error, and a random effect model was assumed. To provide a more conservative estimation, random rather than fixed effect models were adopted because the former can explain heterogeneity between studies. When the heterogeneity was high, subgroup and sensitivity analyses were conducted to explore the sources of heterogeneity. Potential sources of heterogeneity were identified using sensitivity analyses conducted by omitting one study in each turn and investigating the influence of a single study on the overall pooled estimate. The "risk of bias" according to the Cochrane Handbook was used for quality evaluation of the included literature, including adequate sequence generation, allocation concealment, blinding, incomplete outcome data addressed, free of selective reporting, and other biases. The evaluation grade included three levels of "yes, unclear, and no," and finally, a risk assessment chart of bias was formed. Publication bias was evaluated by using funnel plots. Egger's test was used to evaluate potential publication bias in the case of a few trials included in the meta-analysis. Statistical significance was set at p < 0.05. Data are presented as the mean±standard deviation for continuous variables and as proportions (%) for categorical variables. Dichotomous results were analyzed using the Mantel-Haenszel (MH) method. Risk ratio (RR) and 95% confidence interval (CI) were calculated. The mean difference was calculated for continuous results. All statistical analyses were performed using the Statistical Program for Social Sciences 26.0 (SPSS, Inc., Chicago, IL, USA), and meta-analysis was performed using Review Manager 5 (RevMan, The Cochrane Collaboration, Oxford, United Kingdom). We used the GRADE profiler (GRADEpro, McMaster University and Evidence Prime Inc. Hamilton, Ontario, Canada) to evaluate the quality of the RCT evidence, including the overall risk of bias, inconsistency, indirectness, imprecision, and publication bias. Egger's test was performed using StataMP 17 (Stata Corporation LLC, College Station, TX, USA). Any inconsistencies in the assessment results were resolved through negotiation following the inclusion and exclusion criteria. For a given study, assessed POCD at different follow-up time points, we may divide the study into multiple studies. Because we have to divide the study into subgroups, based on the follow-up time point. Cohen's kappa statistic was used to measure the level of agreement between two researchers who classified items into mutually exclusive categories. The formula for Cohen's kappa was calculated as kappa = (Po-Pe)/(1-Pe), where Po is the relative observed agreement among raters and Pe is the hypothetical probability of chance agreement.

Results

Study selection

Cohen's kappa value was 0.997 in this study. Following the search strategy, the study yielded 659 publications and 34 publications from the bibliography of related articles. Sixty-seven full articles were assessed for eligibility after the removing of 117 duplications, and 509 were discarded for the title and abstract. Fifty-seven articles were excluded for animal research, retrospective study, lidocaine used locally, secondary publication, low-quality publication, and other reasons. Ten RCTs [11, 14, 15, 19–25] including 1517 patients, met the inclusion criteria. The details of the PRISMA search strategy are shown in Fig. 1.

Of the 10 included studies, two [20, 25] were published in Chinese with English abstracts and all others in English. Regarding geographical distribution, there were six trials [14, 20, 22–25] from Asia, two [11, 15] from North America, and two [19, 21] from Oceania. Regarding publication quality, four trials [11, 15, 22, 24] had a full score on the Jadad scale, four trials [14, 21, 23, 25] had four points, and two trials [14, 19] had three points.

Characteristics of included studies

A total of 10 RCTs were included in the analysis. The baseline characteristic of included studies were summaried in Table 1. Of all the patients, 754 received lidocaine intravenously, and 763 participants served as controls. In one trial, patients in the comparator arm received placebo treatment with 5% dextrose, and in other trials received 0.9% normal saline. Lidocaine was used as a



Fig. 1 PRISMA diagram showing selection of articles for review of POCD.

bolus around induction of anesthesia or at the opening of the pericardium, followed by continuous pump injection in nine trials [11, 14, 15, 19–21, 23–25]; one trial [22] used a single injection. Bolus doses of lidocaine (0.5, 1.0 or 1.5 mg/kg) followed with different infusion regimens. The serum lidocaine levels varied strongly among the studies.

Studies were conducted in patients undergoing either cardiac surgery [11, 14, 15, 19–21] including CABG with or without CPB; CABG with valve, valve, or supratentorial craniotomy surgery [24]; urologic and orthopedic surgery [22]; spine surgery [23]; or gastrointestinal tumor surgery [25]. The data and conclusion from eligible studies were summarized in Table 2.

The overall age of patients was 62.72 ± 11.56 years, and there were no differences between lidocaine and placebo (62.89 ± 11.02 vs. 62.54 ± 12.08 , p=0.57). The proportion of male patients receiving lidocaine (70.18%) and placebo (69.80%) was not significantly different. The overall education was 12.6 ± 4.0 years from the available studies, and there were also no differences between the lidocaine (12.44 ± 3.9) and placebo (12.76 ± 4.1) groups. The authors addressed the dropout situation in eligible studies, and 70% (7 out of 10) of the studies reported lost patient numbers. We found that 26.0% (340 of 1307) of patients were lost after randomization. There were no differences between the lidocaine and placebo groups (27.5% vs. 24.5%, p=0.19). Because of the different infusion strategies of lidocaine, the serum lidocaine level was difficult to compare between the studies. It can be considered safe and effective with respect to plasma concentration [26, 27].

Of the included studies, six studies [14, 19, 20, 22, 24, 25] assessed the occurrence of POCD, and four studies [22–25] elevated the continuous score via MMSE (or IMCT, HRSD, HAMA), including one trial [25] for base-line only, and another four trials [14, 19, 20, 25] via NP test with different scales.

Incidence of POCD

The overall incidence of POCD was 33.31%, of which 30.12% and 36.40% were for lidocaine and placebo, respectively. Heterogeneity was calculated (Chi^2 =36.35, I^2 =6%). The incidence of POCD in lidocaine was significantly lower than that in the placebo group, with MH RR as 0.84 (95% CI: 0.76 to 0.92).

Table 1 B	aseline cha	racteristic	of included :	studies															
	Mitchell	letal. V	Nang et al.	2002	Mathew et a	I. 2009 I	Mitchell et a	al. 2009	Peng et al.	.2016 (Chen et al	. 2015	Klinger e	tal. H	ashemi e	t Zhue	t al.	Wang e	ital.
	1999												2019	a	. 2013	2015		2004	
	Lid	Con	bi	S	Lid	0	bi	8	Lid	on	Lid	Con	Lid	on	d Con	Lid	Con	Lid	Con
Age*	56.9±8.9	54.4±9.7 5	7.8±9.7	59.3±9.4	61.7±11.9	61.4±13.9 6	1.5±9.6	58.1±11.4	45±9 4	4±10 7	71.3±2.0 7	71.8±1.9	67±9.1 6	7±9.5 60	67±2	71.9±3.8	3 73.1±4.2	58±10	59±9
Male (%)	17 (60.7)	14 (51.9) 4	12 (97.7)	44 (97.8)	83 (72.8)	85 (67) 6	0 (74.1)	63 (81.8)	20 (50) 1	9 (47.5) 2	25 (62.5) 1	3 (57.7)	151 (71.6) 1	60 (76.6) 2: (7	7.1) 28 (80)) 13 (43.3)	13 (43.3)	42 (97.7)	44 (97.8)
Sample size	28	27 4	53	45	133	144	1	77	40 44	7 0	40 4	04	211 2	09 35	35	30	30	43	45
Education*	9.78±3.0	9.81±2.4 9	6±3.5	10.1 ± 3.9	13.3 ± 3.4	12.7±3.3 N	AA A	NA	12.25±3.43 1.	2.75±3.19 N	AA AA	٩N	14.3±2.99 1	5.3±2.99 N	A NA	5.9±2.3	6.2±2.4	10±3	10土4
MMSE score	e NP test	NP test N	VP test, sccurrence	NP test, occurrence	Cognitive index, Occurrence	Cognitive index, C Occurrence	Jccurrence	Occurrence	28.65±0.77 2	9±1.54 2	28.77±1.85	28.19±0.98	Cognitive C index, Oc- ii	ognitive 24 ndex, Oc-	.9±4 25.7±	3.9 27.3±1. NP test,	7, 26.9±1. ² NP test,	, NP test,	NP test,
													currence o	urrence		occur-	occur-	occur-	- 20
																rence	rence	rence	cur-
																			rence
surgery	CABG with valve surge	CPB, C iry	CABG with CPB		CABG with CPB	0	CABG with CPB, '	valve surgery	Supratentorial craniotomy for surgery	tumor	Spine surgery		CABG, CABG valve, valve	with U	ologic and thopedic	Gastroin tumor su	testinal urgery	CABG v CPB	ith
Follow-up	10d, 10wk,	6mo 9	þq		6wk, 1yr				24 h, 1wk, 1mc 6mo	o, 3mo, 3	gd		6mo, 1yr	o le	aving PACU, h, 24 h	2d		9d	
Jadad score	ŝ	4			5	4			5	7	4		5	5		4		m	
*Data are re	sported as n	nean±SD;L	id indicates L	idocaine; Con i	ndicates Control														

Studies have reported an elevated occurrence at various time points. We defined POCD into three segments (short-, medium- and long term) and analyzed its occurrence in three subgroups. Six studies assessed the incidence of POCD in the short term period; the overall incidence of POCD in the short term was 34.50%, of which 27.78% occurred in the lidocaine group, and 41.04% occurred in the placebo group. A meta-analysis of the incidence of POCD revealed a significantly lower occurrence in the lidocaine group than in the placebo group in the short term (MH RR=0.68, 95% CI: 0.57 to 0.80). Five studies assessed the incidence of POCD in the medium term. The overall incidence of POCD was 31.21%; with an incidence of 31.25% in the lidocaine group and an incidence of 31.16% in the placebo group. The meta-analysis did not demonstrate any differences between the groups (MH RR=1, 95% CI: 0.87 1.16). Five studies also assessed the incidence of POCD in the long term. The incidence of POCD was 35.05% in the long term, 31.01% in lidocaine, and 38.73% in placebo. The meta-analysis revealed a significant difference between the groups (MH RR=0.83, 95% CI: 0.71 to 0.97). Figure 2 summarizes the results of the pool analyses.

We compared the weighted mean and standard deviation for short-, medium-, and long term meta-analysis. As a result, we did not find any differences between short term (2.39 ± 0.18) , medium term (2.95 ± 1.08) , and long term (3.73 ± 2.02) with p-value=0.697. Although only six (out of ten included) studies evaluated the incidence of POCD, a battery of data (n=35) was included in the meta-analysis. We demonstrated the publication bias via a funnel plot (Fig. 3); from the figure, we may infer that there were no obvious differences.

We performed sensitivity analysis by omitting one study. We removed the study conducted by Mathew et al. [15], as the overall loss to follow-up of the study was up to 37.91% and even to 41.35% for the lidocaine group. MH RR decreased from 0.84 to 0.83, which means that the significant association between lidocaine and POCD was not confounded by the study.

The GRADEpro assessed the overall quality of the eligible studies in the incidence of POCD and deduced a moderate-quality grade.

The severity of POCD

Three studies assessed the severity of POCD using continuous cognitive variables, including MMSE, IMCT, and NP tests. As the meta-analysis demonstrated, there were no differences between the lidocaine and placebo groups (p=0.21). The overall Standardized mean difference was -0.07 (95% CI: -0.29 to 0.04). However, in the subgroup analysis, lidocaine could attenuate the severity of POCD in the short term with a Standardized mean difference of -0.18 (95%CI: -0.34 to -0.01), but not in the medium

Studies	Design	placebo	Trial medication	Plasma concentration	Test battery	Drop out	conclu- sion
Mitchell et al. 1999	RCT	5% dextrose	Began at the induction, 1 mg/kg bolus over 5 min, 240 mg for the first hour, 120 mg for the second hour, 60 mg/h for 46 h	6–12 (µmol/L)	6 tests with 11 subscales	9 (14.06%) patients lost after randomization, 4 (12.5%) in lidocaine and 5 (15.63) in placebo	No dif- ference
Wang et al. 2002	RCT	Saline	1.5 mg/kg bolus over 5 min at the opening of pericardium, 4 mg/ min till the end of surgery; 4 mg/ kg to the priming solution of CPB	5.52±1.18 (µg/ml)	7 tests with 9 subscales	30 patients (25.42%) lost, 16 (26.23%) in placebo, and 14 (24.56%) in lidocaine	Decline
Mathew et al. 2009	RCT	Saline	1 mg/kg bolus, 4 mg/min for first hour, 2 mg/min for second hour, 1 mg/min for 46 h	2.45±0.93(mg/mL)	5 tests	105 (37.91%) patients lost after randomization, 50 (34.72%) in placebo and 55 (41.35%) in lidocaine	No dif- ference
Mitchell et al. 2009	RCT	Saline	1 mg/kg bolus over 5 min at in- duction, 2 mg/min for 2 h, 1 mg/ min for 12 h.	6–12 (µmol/L)	7 tests and self-rating	51 (32.28%) patients lost, 24 (31.17%) in placebo and 27 (33.33%) in lidocaine	No dif- ference
Peng et al. 2016	RCT	Saline	1.5 mg/kg bolus after induction, 2 mg/kg/h till the end of surgery	NA	MMSE, IMCT	14 patients (14.89%) lost, 6 (13.04%) in lidocaine and 8 (16.67%) in placebo	No dif- ference
Chen et al. 2015	RCT	Saline	1 mg/kg bolus over 5 min after induction, 1.5 mg/h till the end of surgery	NA	MMSE	No patients lost after randomization	Improve cogni- tion
Klinger et al. 2019	RCT	Saline	1 mg/kg bolus after induction, 48 μg/kg/min for the first hour, 24 μg/kg/min for the second hour, 10 μg/kg/min for 46 h	Less than 5 µg/ml	5 tests	101 (21.13%) patients lost, 45 (18.99%) in placebo and 56 (23.24%) in lidocaine	No dif- ference
Hash- emi et al. 2013	RCT	Saline	1.5 mg/kg before extubation	NA	MMSE	No patients lost after randomization	No dif- ference
Zhu et al. 2015	RCT	Saline	0.5 mg/kg bolus after induction, 0.5 mg/kg/h till to the end of surgery	NA	5 tests	No patients lost after randomization	Decline
Wang et al. 2004	RCT	Saline	1.5 mg/kg bolus at opening the pericardium, 4 mg/min till the end of surgery; 4 mg/kg to the prim- ing solution of CPB	5.54±1.23 (μg/ml)	9 tests	30 (25.42%) patients lost, 16 (26.23%) in placebo and 14 (24.56%) in lidocaine	Decline

MMSE indicates Mini-Mental State Examination; IMCT, information-memory-concentration test; NA, not available

and long term (-0.03 [95% CI: -0.2 to 0.14] and 0.02 [95% CI: -0.29 to 0.33], respectively). Figure 4 shows the pool analysis. We compared the weighted mean and standard deviation among the short term (3.31 ± 0.03) , medium term (3.71 ± 0.23) , and long term (3.92 ± 0.38) . The results revealed no significant differences between the groups (p=0.119). Publication bias was demonstrated using a funnel plot (Fig. 5). It can be inferred that the difference was not obvious from Fig. 5.

A sensitivity analysis was conducted by omitting one study. A battery of data from the study conducted by Hashemi et al. [22] had the highest standard error (4.93 and 4.76 for lidocaine and placebo, respectively) among RCTs. The Standardized mean difference remained at -0.07, and the scope of 95% CI changed from (-0.19 to 0.04) to (-0.19 to 0.05). The overall effect of lidocaine remained even after exclusion from the study.

The GRADEpro assessed the overall quality of the eligible studies in terms of the severity of POCD and deduced the quality grade as high.

Three studies compared the influence of lidocaine versus placebo on POCD using the NP test with different scales in the short term, including digit symbol, accumulation, digit span forward, digit span backward, trail making A, pegboard favored hand, pegboard unfavored hand, visual retention, and paired associated verbal learning. We classified the scales into subgroups and performed a meta-analysis. As the results demonstrated, lidocaine could attenuate the severity of POCD in the short term with an overall Standardized mean difference of -2.4 (95%CI: -3.31 to -1.49), especially at trail making A (-12.07 [95% CI: -20.07 to -4.06]) and pegboard unfavored hand (-4.22 [-8.31 to -0.14]) (Fig. 6). Publication bias for the NP test could not be assessed by a funnel plot because there were only three studies included for metaanalysis. It is not recommended to assess publication

Study or Subarous Forents Total Venents Total Venents Total Venents M.H. Fixed. 95% CL M.H. Fixed. 95% CL Hashemi 2013 19 35 22 35 35% 0.86 (0.58, 1.28) + Hashemi 2013 10 35 9 35 1.4% 1.11 (0.51, 2.40) + Hashemi 2016 10 29 16 31 2.5% 0.67 (0.36, 1.23) + Peng-2016 10 29 16 31 2.5% 0.67 (0.36, 1.23) + Peng-2016 7 29 12 31 1.9% 0.52 (0.29, 1.36) + Peng-2016 7 40 15 40 2.4% 0.47 (0.21, 0.21 + Peng-2016 5 40 14 40 2.2% 0.50 (0.24, 0.21 + Vang 2002 8 43 19 45 0.20 (0.50, 0.81 + Vang 2004 9.43 19 45 0.20 (0.50, 0.81 +		Lidocaine Control			Risk Ratio	Risk Ratio		
4.1.1 short.term Hashemi 2 2013 17 35 15 35 2.4% 1.13 [0.68, 1.98] Hashemi 2 2013 17 35 15 35 2.4% 1.13 [0.68, 1.98] Hashemi 2 2013 10 35 1.8 2.4% 1.13 [0.68, 1.98] Hichell 1999 10 25 18 2.4 9.5 0.53 [0.31, 0.81] Peng-21016 16 2.9 1.6 31 2.5% 0.67 [0.05, 1.26] Peng-2016 7 28 1.2 1.9% 0.62 [0.24, 1.02] Peng-2016 7 28 1.2 1.9% 0.52 [0.24, 1.02] Peng-2016 7 40 15 0.20 [0.24, 1.02] 1.9% Vang 2002 8 43 18 45 3.0% 0.20 [0.25, 0.87] Total events 1.45 2.00 1.6% 0.00 [0.7, 0.80] 1.0% Vang 2002 8 43 9.4 6.7% 0.99 [0.24, 1.32] 1.0% Vang 2016 7 4.0 5.40 0.20 [0.8, 0.87] 0.88 [0.57, 0.80] 1.01 [0.023, 2.76]	Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% Cl	M-H, Fixed, 95% Cl
Hashemi 2013 19 35 22 35 3.5% 0.86 [0.58, 1.28] Hashemi 2013 17 35 15 32 2.4% 1.13 [0.68, 1.89] Hashemi 2013 10 35 9 35 1.4% 1.13 [0.68, 1.89] Peng 2016 10 29 16 31 2.5% 0.53 [0.31, 0.91] Peng 2016 7 29 7 31 1.9% 0.53 [0.31, 0.91] Peng 2016 7 29 7 31 1.9% 0.52 [0.31, 1.39] Peng 2016 7 29 7 31 1.9% 0.52 [0.31, 1.39] Peng 2016 7 29 7 31 1.9% 0.52 [0.31, 1.39] Peng 2016 7 29 7 31 1.9% 0.52 [0.31, 1.39] Peng 2016 7 40 15 40 2.4% 0.52 [0.31, 1.39] Peng 2016 7 40 15 40 2.4% 0.52 [0.31, 1.39] Peng 2016 7 40 15 40 2.4% 0.59 [0.47, 1.32] Peng 2016 7 40 15 40 2.4% 0.59 [0.47, 1.32] Peng 2016 7 40 15 40 2.4% 0.59 [0.47, 1.32] Peng 2016 7 40 15 40 2.4% 0.59 [0.27, 0.80] Subtotal (95% Ch) 522 538 34.9% 0.68 [0.57, 0.80] 4.12 median-term Kinger 2019 6 7 211 83 209 13.4% 1.04 [0.82, 1.31] Heterogeneity: Ch ² 2142, df = 14 (P = 0.93); P = 35% Test for overall effect Z = 4.62 (P < 0.0001) 4.12 median-term Kinger 2016 7 40 6 40 1.9% 0.59 [0.27, 0.80] Peng 2016 7 40 6 40 1.9% 0.59 [0.27, 0.80] Peng 2016 7 40 6 40 1.9% 0.57 (0.80] Peng 2016 7 40 6 40 1.9% 0.57 (0.80, 0.99] Peng 2016 7 40 6 40 1.9% 0.57 (0.52, 1.37] Heterogeneity: Ch ² = 21.42, df = 14 (P = 0.98); P = 35% Test for overall effect Z = 4.62 (P < 0.0001) 4.12 median-term Kinger 2016 7 40 6 40 1.9% 0.57 (0.52, 1.37] Heterogeneity: Ch ² = 5.38, df = 34 (P = 0.38); P = 0% Test for overall effect Z = 2.32 (P = 0.02) Total events 220 50 47 91 5.4% 0.77 (0.52, 1.52] Heterogeneity: Ch ² = 5.33, df = 31 (P = 0.88); P = 0% Test for overall effect Z = 2.32 (P = 0.02) Total events 41 7 (P = 0.89); P = 0% Test for overall effect Z = 2.37 (P = 0.001) Total events 512 40 41 90.0% 1.30 (0.21, 2.378] Peng 2.2016 7 40 7.0 1761 100.0% 0.84 [0.57, 0.52] Peng 2.2016 7 40 7.0 1761 100.0% 0.84 [0.57, 0.52] Peng 2.2016 7 40 7.0 1761 100.0% 0.84 [0.57, 0.52] Peng 2.2016 7 40 7.0 1761 100.0% 0.84 [0.57, 0.52] Peng 2.2016 7 40 7.0 1761 100.0% 0.84 [0.57, 0.52] Peng 2.2016 7 40 7.0 1761 100.0% 0.84 [0.57, 0.52] Peng 2.2016 7 40 7.4 7 9.10 3.30; P	4.1.1 short-term							
Hashemi-2 2013 17 35 15 26 24% 1.13 [0.68, 1.89] Mitchell 1989 10 25 18 24 29% 0.53 [0.31, 0.91] Peng-2016 10 29 16 31 2.5% 0.67 [0.36, 1.3] Peng-2 2016 16 29 16 31 2.5% 0.67 [0.36, 1.3] Peng-2 2016 7 29 7 31 11% 0.02 [0.37, 1.2] Peng-2 2016 7 29 7 31 11% 0.02 [0.38, 1.36] Peng-2 2016 7 40 15 40 2.4% 0.47 [0.21, 1.02] Peng-2 2016 15 40 13 40 3.1% 0.79 [0.47, 1.32] Peng-2 2016 15 40 14 40 2.2% 0.36 [0.14, 0.00] Peng-2 2016 5 40 14 40 2.2% 0.50 [0.24, 1.02] Peng-2 2016 5 40 14 40 2.2% 0.50 [0.24, 0.02] Pung-2 2016 5 2 30 10 30 1.6% 0.20 [0.05, 0.84] Zhu 2015 2 30 10 30 1.6% 0.20 [0.05, 0.84] Zhu 2015 2 30 10 30 1.6% 0.20 [0.05, 0.84] Zhu 2015 2 30 10 30 1.6% 0.20 [0.05, 0.84] Zhu 2015 2 46 22 ($F < 0.00001$) 4.12 median-term Kitchell 2009 40 88 43 94 6.7% 0.99 [0.72, 1.37] Mitchell 2009 40 88 43 94 6.7% 0.99 [0.72, 1.37] Mitchell 2009 40 88 43 94 6.7% 0.99 [0.72, 1.37] Mitchell 2009 40 88 43 94 6.7% 0.99 [0.72, 1.37] Mitchell 2009 40 88 44 0 54 0.08% 0.80 [0.23, 0.26] Peng-2 2016 7 40 6 40 1.0% 1.17 [0.43, 3.77] Peng-4 2016 7 40 8 40 1.3% 1.38 [0.62, 0.99] Peng-2016 7 40 8 40 1.3% 1.38 [0.62, 0.69] Peng-2016 7 40 8 40 1.3% 1.38 [0.62, 0.69] Peng-2016 7 40 8 40 1.3% 1.38 [0.62, 0.69] Peng-2016 15 40 14 40 2.2% 1.07 [0.60, 1.92] Peng-2016 15 40 14 40 2.2% 1.07 [0.60, 1.92] Peng-2016 7 40 8 40 1.3% 1.38 [0.62, 0.69] Peng-2016 7 40 8 40 1.3% 1.38 [0.62, 0.69] Peng-2016 15 40 14 40 2.3% 1.38 [0.62, 0.69] Peng-2016 7 40 7 06 35.3% 1.00 [0.27, 1.6] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.16] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.16] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.16] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.16] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.16] Mathew 2009 20 50 47 91 5.4% 0.07 [0.52, 1.16] Mathew 2009 20 50 47 91 5.4% 0.07 [0.52, 1.16] Mathew 2009 20 50 47 91 5.4% 0.07 [0.52, 1.16] Mathew 2009 20 50 47 91 5.4% 0.07 [0.5, 7.6] Peng-2016 2 40 2 40 0.3% 0.69 [0.7, 1.6] Peng-2016 5 2.4 ($F = 0.02$) Total events 147 7 ($F = 0.03$); $F = 0\%$ Sat	Hashemi 2013	19	35	22	35	3.5%	0.86 [0.58, 1.28]	
Hashemi-3 2013 10 35 9 36 1.4% 1.11 [0.51, 2.40] Hitchell 1999 10 25 18 24 2.9% 0.53 [0.31, 0.31] Peng-2016 10 29 16 31 2.5% 0.57 [0.36, 1.23] Peng-3 2016 7 28 12 31 1.9% 0.52 [0.24, 1.02] Peng-5 2016 7 40 10 40 1.6% 0.30 [0.09, 101] Peng-5 2016 7 40 15 40 2.4% 0.47 [0.21, 1.02] Peng-5 2016 15 40 14 40 2.2% 0.56 [0.14, 0.60] Wang 2002 8 43 18 42 2.7% 0.56 [0.14, 0.60] Wang 2004 9 43 19 45 3.0% 0.50 [0.24, 1.02] Peng-7 2016 15 40 19 40 3.1% 0.79 [0.47, 1.2] Peng-7 2016 15 40 19 40 3.1% 0.79 [0.47, 1.2] Peng-7 2016 15 40 19 40 3.1% 0.79 [0.47, 1.2] Peng-7 2016 15 40 19 40 3.1% 0.79 [0.47, 1.2] Peng-7 2016 5 40 14 40 2.2% 0.56 [0.24, 1.02] Vang 2004 9 43 19 45 3.0% 0.50 [0.24, 1.02] Vang 2004 9 43 19 45 3.0% 0.50 [0.24, 1.02] Heterogenethy: Ch ² = 21.42, df = 14 (P = 0.09); P = 35%. Test for overall effect Z = 4.62 (P < 0.0001) 4.12 median-term Kinger 2019 67 211 83 209 13.4% 1.04 [0.82, 1.31] Mathew 2009 40 88 43 94 6.7% 0.99 [0.72, 1.37] Mitchell 1999 12 26 18 24 3.0% 0.62 [0.33, 0.99] Peng-2016 2 40 3 40 0.5% 0.67 [0.12, 3.78] Peng-2016 15 40 14 40 2.2% 1.07 [0.60, 1.92] Peng-2016 15 40 14 40 2.2% 1.07 [0.60, 1.92] Peng-2016 15 40 14 40 2.3% 1.13 [0.74, 1.76] Peng-2016 15 40 14 40 2.3% 1.38 [0.62, 3.26] Peng-2016 15 40 0.8% 0.67 [0.12, 3.78] Peng-2016 15 40 0.8% 0.63 [0.27, 1.56] Heterogenethy: Ch ² = 3.87 (P = 0.007); P = 0% Test for overall effect Z = 3.07 (P = 0.007); P = 0% Test for overall effect Z = 3.37 (P = 0.0001) Events 160-2 = 0.02 (P = 0.02) Total events 147 201 Heterogenethy: Ch ² = 3.87 (P = 0.0001) Events 160-2 = 0.03 (P = 0.0001) Events 160-2 = 0.04 (P = 0.9%) Total events 147 201 Heterogenethy: Ch ² = 3.87 (P = 0.0001) Events 160-2 = 0.04 (P = 0.02); P	Hashemi-2 2013	17	35	15	35	2.4%	1.13 [0.68, 1.89]	
$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	Hashemi-3 2013	10	35	9	35	1.4%	1.11 [0.51, 2.40]	
Peng-2016 10 29 16 31 2.5% 0.67 [0.36, 1.23] Peng-2016 7 29 7 31 1.1% 1.07 [0.43, 2.67] Peng-32016 7 29 7 31 1.1% 1.07 [0.43, 2.67] Peng-52016 3 40 10 40 1.6% 0.30 [0.09, 1.01] Peng-52016 7 40 15 40 2.4% 0.47 [0.21, 1.02] Peng-52016 5 40 14 40 2.2% 0.56 [0.24, 1.02] Peng-62016 7 40 15 40 2.4% 0.47 [0.21, 1.02] Peng-62016 5 40 14 40 2.2% 0.56 [0.24, 1.02] Vang 2002 8 43 18 46 2.7% 0.56 [0.24, 1.02] Vang 2004 9 43 19 45 3.0% 0.56 [0.25, 0.97] Total events 145 220 Heterogeneity: Ch ² = 21.42, df = 14 (P = 0.09); P = 35% Test for overall effect Z = 4.52 (P < 0.0001) Hitchell 2009 40 88 43 94 6.7% 0.99 [0.72, 1.37] Heterogeneity: Ch ² = 21.42, df = 14 (P = 0.09); P = 35% Test for overall effect Z = 4.62 (P < 0.0001); Heterogeneity: Ch ² = 21.42, df = 14 (P = 0.09); P = 25% Test for overall effect Z = 4.62 (P < 0.0001); Heterogeneity: Ch ² = 21.42, df = 14 (P = 0.09); P = 25% Test for overall effect Z = 4.62 (P < 0.0001); Heterogeneity: Ch ² = 21.42, df = 14 (P = 0.09); P = 25% Test for overall effect Z = 4.62 (P < 0.0001); Heterogeneity: Ch ² = 21.42, df = 14 (P = 0.09); P = 25% Test for overall effect Z = 4.62 (P < 0.0001); Heterogeneity: Ch ² = 5.23, df = 11 (P = 0.80); P = 0.5% Total events 200 20 54 76 91 54 00 0.5% 0.67 (0.1, 23, 76] Peng-52016 15 40 14 40 2.25% Hoterogeneity: Ch ² = 5.33, df = 11 (P = 0.80); P = 0.% Test for overall effect Z = 0.04 (P = 0.96); Heterogeneity: Ch ² = 5.33, df = 11 (P = 0.80); P = 0.% Test for overall effect Z = 3.27 (P = 0.097); P = 0.% Test for overall effect Z = 3.37 (P = 0.001); Peng-22016 2 40 40 0.6% 0.50 [0.10, 256] Peng-22016 2 40 2 40 0.3% 1.00 [0.15, 6.76] Peng-22016 2 40 2 40 0.3% 1.00 [0.12, 1.66] Peng-22016 2 40 4 40 0.6% 0.50 [0.10, 2.56] Heterogeneity: Ch ² = 5.33, df = 14 (P = 0.36); P = 0.% Test for overall effect Z = 3.37 (P = 0.001) Favours Hodecale E Favours control	Mitchell 1999	10	25	18	24	2.9%	0.53 [0.31, 0.91]	
Peng-3 2016 16 29 16 31 2.5% 1.07 [0.67, 1.72] Peng-3 2016 7 29 12 31 1.9% 0.62 [0.29, 1.36] Peng-4 2016 7 29 12 31 1.9% 0.62 [0.29, 1.36] Peng-5 2016 7 40 15 40 2.4% 0.47 [0.21, 1.02] Peng-7 2016 15 40 19 40 3.1% 0.79 [0.47, 1.32] Peng-7 2016 5 40 14 40 2.2% 0.36 [0.14, 0.90] Wang 2002 8 43 18 48 2.7% 0.50 [0.24, 1.02] Wang 2004 9 43 19 45 3.0% 0.50 [0.25, 0.97] Zhu 2015 2 30 10 30 1.6% 0.20 [0.05, 0.80] Total events 145 220 Heterogenetic chi= 21.42 ($P < 0.00001$) 4.12 median-term Kinger 2019 87 211 83 209 13.4% 1.04 [0.82, 1.31] Mitchell 2009 27 59 24 59 3.9% 1.13 [0.74, 1.70] Peng-2016 4 40 5 40 0.9% 0.80 [0.27, 1.37] Mitchell 2009 27 59 24 59 3.9% 1.13 [0.74, 1.70] Peng-2016 4 40 5 40 0.9% 0.80 [0.23, 2.76] Peng-2016 2 40 3 40 0.5% 0.67 [0.12, 3.78] Peng-2016 1 40 6 40 1.3% 1.17 [0.43, 3.17] Peng-2016 2 40 3 40 0.5% 0.67 [0.12, 3.78] Peng-2016 1 4 00 5 40 0.8% 0.80 [0.32, 2.76] Peng-2016 1 1 40 8 40 1.3% 1.13 [0.62, 3.06] Peng-2016 1 1 40 8 40 1.3% 1.33 [0.62, 3.06] Peng-2016 1 1 40 5 40 0.8% 0.80 [0.23, 2.76] Peng-2016 1 1 40 5 40 0.8% 0.80 [0.23, 2.76] Peng-2016 1 1 40 5 40 0.8% 0.80 [0.23, 2.76] Peng-2016 1 1 40 5 40 0.9% 0.80 [0.23, 2.76] Peng-2016 1 1 40 5 40 0.8% 0.80 [0.23, 2.76] Peng-2016 1 1 40 5 40 0.8% 0.80 [0.23, 2.76] Peng-2016 1 1 40 5 40 0.8% 0.80 [0.23, 2.76] Peng-2016 1 1 40 5 40 0.8% 0.80 [0.23, 2.76] Peng-2016 1 1 40 5 40 0.8% 0.80 [0.23, 2.76] Peng-2016 1 1 40 5 40 0.8% 0.80 [0.23, 2.76] Peng-2016 2 40 2 40 1.3% 1.13 [0.42, 2.62] Peng-2016 2 40 2 40 0.8% 0.50 [0.70, 1.03] Heterogenetic, Chi=21.42 ($T (P = 0.80), P = 0\%$ Total events 220 220 Heterogenetic, Chi=2.53, df = 11 ($P = 0.80), P = 0\%$ Test for overall effect Z = 2.32 ($P = 0.001$) Total events 147 7 201 Heterogenetic, Chi=2.3, df = 7 ($P = 0.30$; $P = 0\%$ Test for overall effect Z = 3.37 ($P = 0.0001$) Total events 147 7 201 Heterogenetic, Chi=2.3, df = 7 ($P = 0.30$; $P = 0\%$ Test for overall effect Z = 2.32 ($P = 0.001$) Total events 147 7 201 Heterogenetic, Chi=2.53, df = 3 ($A $	Peng 2016	10	29	16	31	2.5%	0.67 [0.36, 1.23]	
Peng-3 2016 7 29 7 31 1.1% 1.07 (0.43, 267) Peng-5 2016 7 29 12 31 1.9% 0.02(0.23, 136) Peng-5 2016 7 40 15 40 2.4% 0.47 (0.21, 102) Peng-6 2016 5 40 14 40 2.2% 0.36 [0.14, 0.90] Peng-6 2016 5 40 14 40 2.2% 0.36 [0.14, 0.90] Peng-8 2016 5 40 14 40 2.2% 0.56 [0.24, 102] Wang 2002 8 43 18 48 2.7% 0.56 [0.24, 102] Wang 2004 9 43 19 45 3.0% 0.56 [0.25, 0.97] Zhu 2015 2 30 10 30 1.6% 0.20 [0.05, 0.84] Subtotal (95% C1) 522 536 34.9% 0.68 [0.57, 0.80] 4.12 median-term Kilnger 2019 87 211 83 209 13.4% 1.04 [0.82, 1.31] Mathew 2009 40 88 43 94 6.7% 0.99 [0.72, 1.37] Hitchell 1999 12 26 18 24 3.0% 0.68 [0.37, 0.80] Peng-2016 2 40 3 40 0.5% 0.67 [0.12, 376] Peng-2016 7 40 6 40 1.0% 1.17 [0.43, 317] Peng-2016 7 40 6 40 1.0% 1.17 [0.43, 317] Peng-2016 1 40 5 40 0.8% 0.067 [0.12, 376] Peng-2016 15 40 14 40 2.2% 1.07 [0.56, 1.27] Peng-2016 15 40 14 40 2.2% 1.07 [0.56, 1.27] Peng-2016 15 40 14 40 2.2% 1.07 [0.50, 1.23] Peng-2016 15 40 14 40 2.2% 1.07 [0.50, 1.23] Peng-2016 15 40 14 40 2.2% 1.07 [0.50, 1.2] Peng-2016 11 40 8 40 1.3% 1.31 [0.46, 2.62] Peng-2016 15 40 14 40 2.2% 1.07 [0.50, 1.2] Peng-2016 11 40 8 40 1.3% 1.31 [0.46, 2.62] Peng-2016 11 40 8 40 1.3% 1.31 [0.46, 2.62] Peng-2016 11 40 8 40 1.3% 1.31 [0.46, 2.62] Peng-2016 12 40 2.40 0.8% 0.00 [0.23, 2.76] Peng-2016 14 40 5 40 0.8% 0.00 [0.23, 2.76] Peng-2016 14 40 5 40 0.8% 0.00 [0.32, 2.76] Peng-2016 14 40 5 40 0.8% 0.00 [0.32, 2.76] Peng-2016 14 40 5 40 0.8% 0.00 [0.32, 2.76] Peng-2016 14 40 5 40 0.8% 0.00 [0.33, 2.76] Peng-2016 14 40 5 40 0.8% 0.50 [0.10, 2.51] Peng-2016 2 40 2.40 0.3% 1.00 [0.31, 319] Peng-2016 3 40 3 40 0.5% 0.50 [0.10, 2.56] Peng-2016 2 40 2 40 0.3% 1.00 [0.21, 4.66] Peng-2016 2 40 4 40 0.6% 0.56 [0.70, 1.03] Total (95% C1) 700 1761 100.0% 0.84 [0.76, 0.92] Total (95% C1) 1700 1761 100.0% 0.84 [0.76, 0.	Peng-2 2016	16	29	16	31	2.5%	1.07 [0.67, 1.72]	
Preng-4 2016 7 29 12 31 19% 0.02 [0.29, 1.36] Preng-5 2016 7 40 15 40 24% 0.47 [0.21, 1.02] Preng-8 2016 7 40 14 40 22% 0.36 [0.14, 0.90] Preng-7 2016 15 40 19 40 31% 0.79 [0.47, 1.32] Preng-8 2016 5 40 14 40 22% 0.36 [0.14, 0.90] Vang 2002 8 43 18 48 2.27% 0.56 [0.24, 1.02] Vang 2004 9 43 19 45 3.0% 0.50 [0.25, 0.97] Zhu 2015 2 30 10 30 1.6% 0.20 [0.05, 0.84] Preng-7 2016 522 536 34.9% 0.68 [0.57, 0.80] Total events 145 220 Preng-2016 7 40 6 40 1.9% Preng-2016 15 40 14 40 22% 0.67 [0.12, 378] Preng-2016 7 40 6 40 1.9% Preng-2016 15 40 14 40 22% Preng-2016 15 40 14 40 2.2% Preng-2016 11 40 8 40 1.3% 1.33 [0.62, 3.06] Preng-2016 11 40 8 40 1.3% 1.33 [0.62, 3.06] Preng-2016 11 40 8 40 1.3% Preng-2016 15 40 14 40 2.2% Preng-2016 11 40 8 40 1.3% 1.33 [0.62, 3.06] Preng-2016 11 40 8 40 1.3% 1.30 [0.62, 7.16] Preng-2016 12 40 2.40 0.3% 1.00 [0.87, 1.16] Preng-2016 14 40 5 40 0.8% Preng-2016 2.40 2.40 0.3% 1.00 [0.16, 7.16] Preng-2016 2.40 2.40 0.3% 1.00 [0.16, 6.76] Preng-2016 2.40 2.40 0.3% 1.00 [0.16, 7.16] Preng-2016 2.40 2.40 0.3% 1.00 [0.16, 6.76] Preng-2016 2.40 2.40 0.3% Preng-2016 2.40 2.4	Peng-3 2016	ſ	29	10	31	1.1%	1.07 [0.43, 2.67]	
Peng-6 2016 3 40 10 40 1.6% 0.30 [0.08, 101] Peng-5 2016 7 40 15 40 2.4% 0.47 (0.21, 1.02] Peng-7 2016 15 40 14 40 2.2% 0.36 [0.14, 0.90] Wang 2002 8 43 18 48 2.7% 0.50 [0.24, 1.02] Wang 2004 9 43 19 45 3.0% 0.50 [0.26, 0.81] Yuang 2004 9 43 19 45 3.0% 0.50 [0.26, 0.84] Subtotal (5% CI) 5.22 55 3.4.9% 0.68 [0.57, 0.80] 4.12 median-term Kilinger 2019 87 211 43 220 Heterogeneity: Ch ⁺ = 21.42, df = 14 ($P = 0.09$); $P = 35\%$ Test for overall effect Z = 4.62 ($P < 0.0001$) 4.1.2 median-term Kilinger 2019 87 211 83 209 13.4% 1.04 [0.82, 1.31] Mathew 2009 40 88 43 94 6.7% 0.99 [0.72, 1.37] Peng-2 2016 4 40 5 40 0.8% 0.80 [0.23, 2.76] Peng-2 2016 2 40 3 40 0.5% 0.67 [0.12, 3.78] Peng-3 2016 7 40 6 40 1.0% 1.17 [0.43, 3.17] Peng-3 2016 7 40 6 40 1.0% 0.80 [0.23, 2.76] Peng-2 2016 1 40 8 40 1.3% 1.38 [0.62, 3.06] Peng-2 2016 1 5 40 14 40 2.2% 1.07 [0.60, 1.92] Peng-2 2016 1 14 0 8 40 1.3% 1.38 [0.62, 3.06] Peng-2 2016 1 14 0 8 40 1.3% 1.38 [0.62, 3.06] Peng-2 2016 1 14 0 8 40 1.3% 1.38 [0.62, 3.06] Peng-2 2016 1 14 0 8 40 1.3% 1.38 [0.62, 3.06] Peng-2 2016 1 14 0 8 40 1.3% 1.38 [0.62, 3.06] Peng-2 2016 1 14 0 8 40 1.3% 1.38 [0.62, 3.06] Peng-2 2016 1 14 0 8 40 1.3% 1.38 [0.62, 3.06] Peng-2 2016 1 14 0 8 40 1.3% 1.38 [0.62, 3.06] Peng-2 2016 1 14 0 8 40 1.3% 1.38 [0.62, 3.06] Peng-2 2016 1 14 0 8 40 1.3% 1.38 [0.62, 3.06] Peng-2 2016 1 14 0 8 40 1.3% 1.38 [0.62, 3.06] Peng-2 2016 1 14 0 8 40 1.3% 1.38 [0.62, 3.06] Peng-2 2016 1 14 0 8 40 1.3% 1.38 [0.58 [0.70, 1.03] Mathew 2009 19 54 20 53 3.2% 0.39 [0.57, 1.54] Michell 2009 19 54 20 53 3.2% 0.39 [0.27, 1.25] Peng-2 2016 2 40 2 40 0.3% 1.00 [0.31, 3.18] Peng-4 2016 2 40 2 40 0.3% 1.00 [0.37, 1.09] Total (95% CI) 170 1761 100.0% 0.84 [0.76, 0.92] Total (95% CI) 1700 1761 100.0% 0.84 [0.	Peng-4 2016 Bawa 5 2046		29	12	31	1.9%	0.62 [0.29, 1.36]	
Peng-2016 1 4 40 19 40 3 40 24% 0.47 $[0.21, 10.2]$ Peng-8 2016 5 40 14 40 2.2% 0.36 $[0.14, 0.90]$ Peng-8 2016 5 40 14 40 2.2% 0.36 $[0.24, 10.2]$ Viang 2004 9 43 19 45 3.0% 0.50 $[0.24, 10.2]$ Zhu 2015 2 30 10 30 1.8% 0.20 $[0.57, 0.80]$ Zhu 2015 2 30 10 30 1.8% 0.20 $[0.57, 0.80]$ Total events 145 220 Heterogeneity: Ch ² = 21.42, df = 14 ($P = 0.00$); P= 35% Test for overall effect Z = 4.62 ($P < 0.00001$) 4.12 median-term Kinger 2019 87 211 83 209 13.4% 1.04 $[0.82, 1.31]$ Mitchell 2009 27 59 24 59 3.9% 1.13 $[0.74, 1.70]$ Peng-2016 2 40 3 40 0.5% 0.80 $[0.23, 2.76]$ Peng-2016 2 40 3 40 0.5% 0.87 $[0.12, 3.78]$ Peng-2016 7 40 6 40 1.3% 1.38 $[0.62, 3.06]$ Peng-2016 1 5 40 14 40 2.2% 1.07 $[0.6, 1.92]$ Peng-2016 7 40 6 40 1.3% 1.38 $[0.62, 3.06]$ Peng-2016 1 5 40 14 40 2.2% 1.07 $[0.6, 1.92]$ Peng-2016 1 5 40 14 40 2.2% 1.07 $[0.6, 1.92]$ Peng-2016 1 5 40 14 40 2.3% $[0.77, 1.60, 1.92]$ Peng-2016 1 5 40 14 40 2.3% $[0.70, 1.03, 3.17]$ Peng-2016 1 5 40 14 40 2.3% $[0.70, 1.03, 3.17]$ Peng-2016 1 5 40 14 40 2.3% $[0.70, 1.03, 3.17]$ Peng-2016 1 5 40 14 40 2.3% $[0.70, 1.03, 3.17]$ Peng-2016 1 5 40 14 40 2.3% $[0.70, 1.03, 3.17]$ Peng-2016 1 5 40 14 40 2.3% $[0.23, 2.76]$ Peng-2016 1 5 40 14 40 2.3% $[0.23, 2.76]$ Peng-2016 1 5 40 14 40 2.3% $[0.70, 1.03]$ Peng-2016 1 40 8 40 1.3% $[0.23, 2.76]$ Peng-2016 2 40 3 40 0.5% $[0.70, 1.03]$ Mathew 2009 20 50 47 9 15 2.4% $[0.70, 1.03]$ Mathew 2009 20 50 47 9 15 2.4% $[0.70, 1.03]$ Mathew 2009 20 50 47 9 15 2.3% $[0.00, 0.87, 1.16]$ Total events 220 220 Heterogeneity: Ch ² = 5.93, df = 11 ($P = 0.80$); $P = 0\%$ Test for overall effect Z = 0.04 ($P = 0.80$); $P = 0\%$ Total events 147 201 Heterogeneity: Ch ² = 5.37 ($P = 0.000$) Total events 147 7 201 Heterogeneity: Ch ² = 3.37 ($P = 0.0001$) Total events 512 641 Heterogeneity: Ch ² = 3.37 ($P = 0.0001$) Favours lidocaine Favours control Favours lidocaine Favours control	Perig-5 2016 Dong 6 2016	37	40	10	40	1.0%	0.30 [0.09, 1.01]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Perig-bi2016 Bong 7 2016	15	40	10	40	2.4%	0.47 [0.21, 1.02]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Peng 9 2016	10	40	19	40	0.170 0.000	0.79 [0.47, 1.32]	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $	Feng-o 2010 Wang 2002	о 0	40	14	40	2.270	0.50 [0.14, 0.90]	
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$\begin{array}{c c c c c c c c c c c c c c c c c c c $	7bu 2015	3	40	10	30	1.6%	0.00 [0.20, 0.97]	
$\begin{array}{c} Lat. point (b) for the left of th$	Subtotal (95% CI)	2	522	10	536	34.9%	0.68 [0.57, 0.80]	•
Heterogeneity: $Ch^{\mu} = 21.42$, $df = 14$ ($P = 0.00$); $P = 35\%$ Test for overall effect: $Z = 4.62$ ($P < 0.00001$) 4.12 median-term Kinger 2019 87 211 83 209 13.4% 1.04 [0.82, 1.31] Mathew 2009 27 59 24 59 3.9% 1.13 [0.74, 1.70] Peng 2016 2 40 3 40 0.8% 0.80 [0.23, 2.76] Peng 2016 7 40 6 40 1.0% 1.17 [0.43, 3.17] Peng 2016 7 40 6 40 1.0% 1.17 [0.43, 3.17] Peng 2016 7 40 6 40 1.0% 1.17 [0.43, 3.17] Peng 2016 15 40 14 40 2.2% 1.07 [0.60, 1.92] Peng 2016 15 40 14 40 2.2% 1.07 [0.60, 1.92] Peng 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng 2016 2 40 2.40 Peng 2016 2 40 4.40 Peng 2016 Peng 2016 2 40 4.40 Peng 2016 Peng 2016	Total events	145	JLL	220	000	011070	0.00 [0.01, 0.00]	
The theorem is the transformed and the transformation of tr	Heterogeneity: Chi ² =	140 ch 17:	= 14 (E	220 = 0.09):	E= 359	¥.		
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4.1.2 median-term Kinger 2019 87 211 83 209 13.4% 1.04 [0.82, 1.31] Mathew 2009 40 88 43 94 6.7% 0.99 [0.72, 1.37] Michell 2009 27 59 24 59 3.9% 1.13 [0.74, 1.70] Michell 1999 12 26 18 24 3.0% 0.62 [0.38, 0.99] Peng 2016 2 40 3 40 0.5% 0.80 [0.23, 2.76] Peng-2016 2 40 3 40 0.5% 0.67 [0.12, 3.78] Peng-5 2016 15 40 14 40 2.2% 1.07 [0.60, 1.92] Peng-5 2016 15 40 1.3% 1.38 [0.62, 3.06] 1.38 Peng-5 2016 14 40 5.3% 1.00 [0.87, 1.16] 1.04 [0.87, 1.16] Subtotal (95% CI) 704 706 35.3% 1.00 [0.87, 1.5] 1.04 [0.24, 3.262] Peng-5 2016 2 0.47 91 5.4% 0.77 [0.52, 1.16] 1.04 [0.27, 1.56] Michell 2009 19 54 20 <td< td=""><td></td><td></td><td></td><td>,</td><td></td><td></td><td></td><td></td></td<>				,				
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$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Klinger 2019	87	211	83	209	13.4%	1.04 [0.82, 1.31]	+
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	Mathew 2009	40	88	43	94	6.7%	0.99 [0.72, 1.37]	+
Mitchell 1999 12 26 18 24 3.0% $0.62 [0.38, 0.39]$ Peng 2016 4 40 5 40 0.8% $0.80 [0.23, 2.76]$ Peng-2016 2 40 3 40 0.5% $0.67 [0.12, 3.78]$ Peng-2016 2 40 3 40 0.5% $0.67 [0.12, 3.78]$ Peng-2016 15 40 14 0.2% $1.07 [0.60, 1.92]$ Peng-52016 15 40 40 2.2% $1.07 [0.60, 1.92]$ Peng-52016 14 40 2.2\% $1.07 [0.60, 1.92]$ Peng-52016 4 40 5 40 0.8% $0.80 [0.23, 2.76]$ Peng-82016 4 40 5 40 0.8% $0.80 [0.23, 2.76]$ Subtotal (95% CI) 704 706 35.3% $1.00 [0.87, 1.16]$ Total events 220 220 220 Heterogeneity: Chi ² = 5.93, df = 11 (P = 0.80); P = 0\% 1.00 [0.27, 1.55] $0.85 [0.70, 1.03]$ Mitchell 2009 19 54 20 53 3.2% $0.03 [0.57, 1.54]$	Michell 2009	27	59	24	59	3.9%	1.13 [0.74, 1.70]	-
Peng 2016 4 40 5 40 0.8% 0.80 [0.23, 2.76] Peng-2 2016 2 40 3 40 0.5% 0.67 [0.12, 3.78] Peng-3 2016 7 40 6 40 1.0% 1.17 [0.43, 3.17] Peng-4 2016 2 40 3 40 0.5% 0.67 [0.12, 3.78] Peng-5 2016 15 40 14 40 2.2% 1.07 [0.60, 1.92] Peng-6 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng-7 2016 9 40 8 40 1.3% 1.38 [0.62, 3.06] Peng-7 2016 9 40 8 40 1.3% 1.31 [0.48, 2.62] Peng-8 2016 4 40 5 40 0.8% 0.80 [0.23, 2.76] Subtotal (95% CI) 704 706 35.3% 1.00 [0.87, 1.16] Total events 220 220 Heterogeneity: Chi ² = 5.93, df = 11 (P = 0.88); I ² = 0% Test for overall effect: $Z = 0.04$ (P = 0.96) 4.1.3 long-term Klinger 2019 89 185 109 192 17.2% 0.85 [0.70, 1.03] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Michell 2009 19 54 20 53 3.2% 0.93 [0.57, 1.54] Michell 999 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng-2016 3 40 3 40 0.5% 1.00 [0.21, 4.66] Peng-2 2016 2 40 2 40 0.3% 1.00 [0.15, 6.76] Peng-2 2016 2 40 4 40 0.6% 0.50 [0.10, 2.58] Subtotal (95% CI) 474 519 29.9% 0.83 [0.71, 0.97] Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); I ² = 0% Test for overall effect: $Z = 2.32$ (P = 0.02) Total events 512 641 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); I ² = 0% Test for overall effect: $Z = 2.32$ (P = 0.02) Total events 512 641 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); I ² = 0% Test for overall effect: $Z = 2.32$ (P = 0.02) Total events 512 641 Heterogeneity: Chi ² = 3.6.35, df = 34 (P = 0.36); I ² = 6% Test for overall effect: $Z = 3.87$ (P = 0.001) Test for suborous differences: Not apolicable	Mitchell 1999	12	26	18	24	3.0%	0.62 [0.38, 0.99]	
Peng-2 2016 2 40 3 40 0.5% 0.67 [0.12, 3.78] Peng-3 2016 7 40 6 40 1.0% 1.17 [0.43, 3.7] Peng-4 2016 2 40 3 40 0.5% 0.67 [0.12, 3.78] Peng-5 2016 15 40 14 40 2.2% 1.07 [0.60, 1.92] Peng-6 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng-7 2016 9 40 8 40 1.3% 0.83 [0.62, 3.06] Peng-7 2016 9 40 8 40 1.3% 1.08 [0.23, 2.76] Subtrat (95% C1) 704 706 35.3% 1.00 [0.87, 1.16] Total events 220 220 Heterogeneity: $Ch^{P} = 5.93$, $df = 11 (P = 0.88)$; $P = 0\%$ Test for overall effect $Z = 0.04$ (P = 0.96) 4.1.3 long-term Kinger 2019 89 185 109 192 17.2% 0.85 [0.70, 1.03] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Michell 2009 19 54 20 53 3.2% 0.93 [0.57, 1.54] Mitchell 1999 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng-2 2016 2 40 2 40 0.3% 1.00 [0.21, 4.66] Peng-2 2016 2 40 2 40 0.3% 1.00 [0.10, 15, 6.76] Peng-3 2016 5 40 5 40 0.8% 0.83 [0.71, 0.97] Total events 512 641 Heterogeneity: $Ch^{P} = 1.74$, $df = 7$ (P = 0.97); $P = 0\%$ Test for overall effect $Z = 3.87$ (P = 0.001) Total events 512 641 Heterogeneity: $Ch^{P} = 1.74$, $df = 7$ (P = 0.36); $P = 6\%$ Test for overall effect $Z = 3.87$ (P = 0.001) Test for subroup differences: Not applicable	Peng 2016	4	40	5	40	0.8%	0.80 [0.23, 2.76]	
Peng-3 2016 7 40 6 40 1.0% 1.17 [0.43, 317] Peng-4 2016 2 40 3 40 0.5% 0.67 [0.12, 3.78] Peng-5 2016 15 40 14 40 2.2% 1.07 [0.60, 1.92] Peng-6 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng-7 2016 9 40 8 40 1.3% 1.38 [0.62, 3.06] Peng-8 2016 4 40 5 40 0.8% 0.80 [0.23, 2.76] Subtotal (95% CI) 704 706 35.3% 1.00 [0.87, 1.16] Total events 220 220 Heterogeneity: Chi ² = 5.93, df = 11 (P = 0.88); I ² = 0% Test for overall effect: $Z = 0.04$ (P = 0.96) 4.1.3 long-term Klinger 2019 89 185 109 192 17.2% 0.85 [0.70, 1.03] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Mitchell 2009 19 54 20 53 3.2% 0.93 [0.57, 1.54] Mitchell 1999 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng-2016 3 40 3 40 0.5% 1.00 [0.31, 319] Peng-4 2016 5 40 5 40 0.8% 1.00 [0.31, 319] Peng-4 2016 2 40 2 40 2.4% 0.38% 1.00 [0.31, 319] Peng-4 2016 2 40 4 40 0.6% 0.50 [0.10, 2.58] Subtotal (95% CI) 1700 1761 100.0% 0.84 [0.76, 0.92] Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); I ² = 0% Test for overall effect: $Z = 3.87$ (P = 0.001) Test for subroup differences: Not applicable	Peng-2 2016	2	40	3	40	0.5%	0.67 [0.12, 3.78]	
Peng-4 2016 2 40 3 40 0.5% 0.67 [0.12, 3.78] Peng-5 2016 15 40 14 40 2.2% 1.07 [0.60, 1.92] Peng-6 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng-7 2016 9 40 8 40 1.3% 1.38 [0.62, 3.06] Peng-7 2016 4 40 5 40 0.8% 0.80 [0.23, 2.76] Subtotal (95% CI) 704 706 35.3% 1.00 [0.87, 1.16] Total events 220 220 Heterogeneity: Chi ² = 5.93, df = 11 (P = 0.88); I ² = 0% Test for overall effect: $Z = 0.04$ (P = 0.96) 4.1.3 long-term Klinger 2019 89 185 109 192 17.2% 0.85 [0.70, 1.03] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Michell 2009 19 54 20 53 3.2% 0.39 [0.57, 1.54] Mitchell 2009 19 54 20 53 3.2% 0.39 [0.57, 1.54] Mitchell 399 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng-2016 2 40 2 40 0.3% 1.00 [0.21, 4.66] Peng-2 2016 2 40 5 40 0.8% 1.00 [0.31, 3.19] Peng-4 2016 2 40 5 40 0.8% 1.00 [0.31, 3.19] Peng-4 2016 2 40 4 40 0.6% 0.50 [0.10, 2.58] Subtotal (95% CI) 474 519 29.9% 0.83 [0.71, 0.97] Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); I ² = 0% Test for overall effect: $Z = 3.23$ (P = 0.02) Total events 512 641 Heterogeneity: Chi ² = 38.35, df = 34 (P = 0.36); I ² = 6% Test for overall effect: $Z = 3.87$ (P = 0.001) Test for subgroup differences: Not applicable	Peng-3 2016	7	40	6	40	1.0%	1.17 [0.43, 3.17]	
Peng-5 2016 15 40 14 40 2.2% 1.07 [0.60, 1.92] Peng-6 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng-7 2016 9 40 8 40 1.3% 1.38 [0.62, 3.06] Peng-8 2016 4 40 5 40 0.8% 0.80 [0.23, 2.76] Subtotal (95% CI) 704 706 35.3% 1.00 [0.87, 1.16] Total events 220 220 Heterogeneity: Chi ^P = 5.93, df = 11 (P = 0.88); I ^P = 0% Test for overall effect $Z = 0.04$ (P = 0.98) 4.1.3 long-term Klinger 2019 89 185 108 192 17.2% 0.85 [0.70, 1.03] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Michell 2009 19 54 20 53 3.2% 0.93 [0.57, 1.54] Mitchell 1999 7 25 11 23 1.8% 0.58 [0.27, 1.25] Peng 2016 3 40 3 40 0.3% 1.00 [0.15, 6.76] Peng-2 2016 2 40 2 40 0.3% 1.00 [0.15, 6.76] Peng-3 2016 5 40 5 40 0.8% 1.00 [0.31, 3.19] Peng-4 2016 2 40 4 40 0.6% 0.50 [0.10, 2.58] Subtotal (95% CI) 474 519 29.9% 0.83 [0.71, 0.97] Total events 147 201 Heterogeneity: Chi ^P = 1.74, df = 7 (P = 0.97); I ^P = 0% Test for overall effect: $Z = 2.32$ (P = 0.02) Total events 512 641 Heterogeneity: Chi ^P = 1.74, df = 3 (4P = 0.36); I ^P = 6% Test for overall effect: $Z = 3.87$ (P = 0.001) Test for subgroup differences: Not applicable	Peng-4 2016	2	40	3	40	0.5%	0.67 [0.12, 3.78]	
Peng-6 2016 11 40 8 40 1.3% 1.38 [0.62, 3.06] Peng-7 2016 9 40 8 40 1.3% 1.13 [0.62, 3.06] Peng-8 2016 4 40 5 40 0.8% 0.80 [0.23, 2.76] Subtotal (95% CI) 704 706 35.3% 1.00 [0.87, 1.16] Total events 220 220 Heterogeneity: Chi ^P = 5.93, df = 11 ($P = 0.88$); $P = 0\%$ Test for overall effect: $Z = 0.04$ ($P = 0.96$) 4.1.3 long-term Klinger 2019 89 185 108 192 17.2% 0.85 [0.70, 1.03] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Michell 2009 19 54 20 53 3.2% 0.93 [0.57, 1.54] Mitchell 1999 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng-2016 3 40 3 40 0.5% 1.00 [0.11, 3.19] Peng-2 2016 2 40 2 40 0.3% 1.00 [0.11, 3.19] Peng-4 2016 2 40 4 40 0.6% 0.50 [0.10, 2.58] Subtotal (95% CI) 477 4 519 29.9% 0.83 [0.71, 0.97] Total events 147 201 Heterogeneity: Chi ^P = 1.74, df = 7 ($P = 0.97$); $P = 0\%$ Test for overall effect: $Z = 3.87$ ($P = 0.001$) Total events 512 641 Heterogeneity: Chi ^P = 36.35, df = 34 ($P = 0.36$); $P = 6\%$ Test for overall effect: $Z = 3.87$ ($P = 0.001$) Total events 612 641 Heterogeneity: Chi ^P = 36.35, df = 34 ($P = 0.36$); $P = 6\%$ Test for overall effect: $Z = 3.87$ ($P = 0.0001$) Total events 612 641 Heterogeneity: Chi ^P = 36.35, df = 34 ($P = 0.36$); $P = 6\%$ Test for overall effect: $Z = 3.87$ ($P = 0.0001$) Total events 512 641 Heterogeneity: Chi ^P = 6.37; $P = 0.0001$)	Peng-5 2016	15	40	14	40	2.2%	1.07 [0.60, 1.92]	
Peng-7 2016 9 40 8 40 1.3% 1.13 [0.48, 2.62] Peng-8 2016 4 40 5 40 0.8% 0.80 [0.23, 2.76] Subtotal (95% CI) 704 706 35.3% 1.00 [0.87, 1.16] Total events 220 220 Heterogeneity: Chi ² = 5.93, df = 11 (P = 0.88); l ² = 0% Test for overall effect: $Z = 0.04$ (P = 0.96) 4.1.3 long-term Klinger 2019 89 185 109 192 17.2% 0.85 [0.70, 1.03] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Michell 2009 19 54 20 53 3.2% 0.93 [0.57, 1.54] Mitchell 1999 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng 2016 3 40 3 40 0.5% 1.00 [0.21, 4.66] Peng-2 2016 2 40 2 40 0.3% 1.00 [0.15, 6.76] Peng-3 2016 5 40 5 40 0.8% 0.50 [0.10, 2.58] Subtotal (95% CI) 4774 519 29.9% 0.83 [0.71, 0.97] Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); l ² = 0% Test for overall effect: $Z = 3.37$ (P = 0.02) Total events 512 641 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); l ² = 6% Test for overall effect: $Z = 3.87$ (P = 0.001) Test for subgroup differences: Not applicable	Peng-6 2016	11	40	8	40	1.3%	1.38 [0.62, 3.06]	
Peng-8 2016 4 40 5 40 0.8% 0.80 [0.23, 2.76] Subtotal (95% CI) 704 706 35.3% 1.00 [0.87, 1.16] Total events 220 220 Heterogeneity: Chi ² = 5.93, df = 11 (P = 0.88); l ² = 0% Test for overall effect: $Z = 0.04$ (P = 0.96) 4.1.3 long-term Klinger 2019 89 185 109 192 17.2% 0.85 [0.70, 1.03] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Michell 2009 19 54 20 53 3.2% 0.93 [0.57, 1.54] Mitchell 1999 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng 2016 3 40 3 40 0.5% 1.00 [0.15, 6.76] Peng-2 2016 2 40 2 40 0.3% 1.00 [0.15, 6.76] Peng-3 2016 5 40 5 40 0.8% 1.00 [0.13, 3.19] Peng-4 2016 2 40 4 40 0.6% 0.50 (0.10, 2.58] Subtotal (95% CI) 477 9 = 0.02) Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); l ² = 0% Test for overall effect: $Z = 2.32$ (P = 0.02) Total events 512 641 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); l ² = 6% Test for subgroup differences: Not applicable	Peng-7 2016	9	40	8	40	1.3%	1.13 [0.48, 2.62]	
Subtotal (95% Cl) 704 706 35.3% 1.00 [0.87, 1.16] Total events 220 220 Heterogeneity: Chi ² = 5.93, df = 11 (P = 0.88); I ² = 0% Test for overall effect: $Z = 0.04$ (P = 0.96) 4.1.3 long-term Klinger 2019 89 185 109 192 17.2% 0.85 [0.70, 1.03] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Mitchell 2009 19 54 20 53 3.2% 0.93 [0.57, 1.54] Mitchell 1999 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng 2016 3 40 3 40 0.5% 1.00 [0.31, 3.19] Peng-4 2016 2 40 4 0.6% 0.50 [0.10, 2.58] Subtotal (95% Cl) 4774 519 29.9% 0.83 [0.71, 0.97] Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); I ² = 0% 1.00 0.01 0.1 1 10 100 Total (95% Cl) 1700 1761 100.0% 0.84 [0.76, 0.92] <td>Peng-8 2016</td> <td>4</td> <td>40</td> <td>5</td> <td>40</td> <td>0.8%</td> <td>0.80 [0.23, 2.76]</td> <td></td>	Peng-8 2016	4	40	5	40	0.8%	0.80 [0.23, 2.76]	
Total events 220 220 Heterogeneity: Chi ^P = 5.93, df = 11 (P = 0.88); I ^P = 0% Test for overall effect: $Z = 0.04$ (P = 0.96) 4.1.3 long-term Klinger 2019 89 185 109 192 17.2% 0.85 [0.70, 1.03] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Mitchell 2009 19 54 20 53 3.2% 0.93 [0.57, 1.54] Mitchell 1999 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng 2016 3 40 3 40 0.5% 1.00 [0.21, 4.66] Peng-2 2016 2 40 2.40 0.3% 1.00 [0.31, 3.19] Peng-3 2016 5 40 519 29.9% 0.83 [0.71, 0.97] Total events 147 201 201 404 40 0.6% Test for overall effect: $Z = 2.32$ (P = 0.02) 7 7 9 9 0.84 [0.76, 0.92] 10.1 10 100 Total events 512 641 642 643 10.1 10	Subtotal (95% CI)		704		706	35.3%	1.00 [0.87, 1.16]	Ţ
Heterogeneity: Chi ² = 5.93, di = 11 (P = 0.88), P = 0% Test for overall effect: $Z = 0.04$ (P = 0.96) 4.1.3 long-term Klinger 2019 89 185 109 192 17.2% 0.85 [0.70, 1.03] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Michell 2009 19 54 20 53 3.2% 0.93 [0.57, 1.54] Mitchell 1989 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng 2016 3 40 3.40 0.5% 1.00 [0.21, 4.66] Peng-2 2016 2 40 2.40 0.3% 1.00 [0.31, 3.19] Peng-3 2016 5 40 5.40 0.6% 0.50 [0.10, 2.58] Subtotal (95% CI) 474 519 29.9% 0.83 [0.71, 0.97] Total events 147 201 144 519 29.9% 0.84 [0.76, 0.92] Total events 512 641 641 641 641 641 641 Heterogeneity: Chi ² = 3.87 (P = 0.001) 100 10 10 100 Favours	l otal events	220	44.00	220	0.00			
4.1.3 long-term Klinger 2019 89 185 109 192 17.2% 0.85 0.70 1.03 Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Michell 2009 19 54 20 53 3.2% 0.93 [0.57, 1.54] Mitchell 1999 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng 2016 3 40 3 40 0.5% 1.00 [0.21, 4.66] Peng-2 2016 2 40 2 40 0.3% 1.00 [0.31, 3.19] Peng-3 2016 5 40 5 40 0.6% 0.50 [0.10, 2.58] Subtotal (95% Cl) 474 519 29.9% 0.83 [0.71, 0.97] 10.01 Total events 147 201 1474 519 29.9% 0.83 [0.76, 0.92] 10.01 10.01 10.01 10.01 10.01 10.01 10.01 10.01 10.01 10.01 10.01 10.01 10.01 10.01 10.	Test for overall effect:	: 5.93, ut = : 7 = 0.04 i	: 11 (P : /P = 0.0	= 0.88); I [_] IGN	= 0%			
4.1.3 long-term Klinger 2019 89 185 109 192 17.2% 0.85 [0.70, 1.03] Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Michell 2009 19 54 20 53 3.2% 0.93 [0.57, 1.54] Mitchell 1999 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng 2016 3 40 3 40 0.5% 1.00 [0.21, 4.66] Peng-2 2016 2 40 2.40 0.3% 1.00 [0.31, 3.19] Peng-3 2016 5 40 5 40 0.6% 0.50 [0.10, 2.58] Subtotal (95% CI) 474 519 29.9% 0.83 [0.71, 0.97] 4.44 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); I ² = 0% 7.25 4.41 4.40 0.6% 0.50 [0.10, 2.58] Subtotal (95% CI) 1700 1761 100.0% 0.84 [0.76, 0.92] 4.41 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); I ² = 6% 6.41 4.41 4.41 4.41 4.41 4.41 4.41 4.41 4.41	Testion overall effect.	. 2 - 0.041	(F – 0.8)))				
Klinger 2019 89 185 109 192 17.2% 0.85 0.70, 1.03 Mathew 2009 20 50 47 91 5.4% 0.77 [0.52, 1.15] Michell 2009 19 54 20 53 3.2% 0.93 [0.57, 1.54] Mitchell 1999 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng 2016 3 40 3 40 0.5% 1.00 [0.21, 4.66] Peng-2 2016 2 40 2 40 0.3% 1.00 [0.15, 6.76] Peng-3 2016 5 40 5 40 0.6% 0.50 [0.10, 2.58] Subtotal (95% CI) 474 519 29.9% 0.83 [0.71, 0.97] 1 Total events 147 201 1 1 1 1 1 0 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); l ² = 0% 0.84 [0.76, 0.92] 1 1 0.01 0.1 1 0 0.01 0.1 1 0.01 0.1 1 0.01	4.1.3 long-term							
Mathew 2009 20 50 47 91 5.4% 0.77 0.52 1.15 Michell 2009 19 54 20 53 3.2% 0.93 0.57 1.54 Mitchell 1999 7 25 11 23 1.8% 0.59 0.27 1.25 Peng 2016 3 40 3 40 0.5% 1.00 0.21 4.66 Peng-2 2016 2 40 2 40 0.3% 1.00 0.15 6.76 Peng-3 2016 5 40 5 40 0.8% 1.00 0.31 3.19 Peng-4 2016 2 40 4 40 0.6% 0.50 0.10 2.58 Subtotal (95% Cl) 474 519 29.9% 0.83 0.77 0.97 7 Total events 147 201 20 11 100.0% 0.84 0.76 0.92 10 Total events 512 641 641 10 10 10 10 100 100 Favours lidocaine <td< td=""><td>Klinger 2019</td><td>89</td><td>185</td><td>109</td><td>192</td><td>17.2%</td><td>0.85 [0.70, 1.03]</td><td>-</td></td<>	Klinger 2019	89	185	109	192	17.2%	0.85 [0.70, 1.03]	-
Michell 2009 19 54 20 53 3.2% $0.93 [0.57, 1.54]$ Mitchell 1999 7 25 11 23 1.8% $0.59 [0.27, 1.25]$ Peng 2016 3 40 3 40 0.5% $1.00 [0.21, 4.66]$ Peng-2 2016 2 40 2 40 0.3% $1.00 [0.31, 3.19]$ Peng-3 2016 5 40 5 40 0.6% $0.50 [0.10, 2.58]$ Subtotal (95% CI) 474 519 29.9% $0.83 [0.71, 0.97]$ Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); l ² = 0% $0.84 [0.76, 0.92]$ Total events 512 641 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); l ² = 6% $0.01 \ 0.1 \ 1 \ 100$ Test for overall effect: Z = 3.87 (P = 0.0001) Test for subgroup differences: Not applicable $0.01 \ 0.1 \ 1 \ 100$	Mathew 2009	20	50	47	91	5.4%	0.77 [0.52, 1.15]	
Mitchell 1999 7 25 11 23 1.8% 0.59 [0.27, 1.25] Peng 2016 3 40 3 40 0.5% 1.00 [0.21, 4.66] Peng-2 2016 2 40 2 40 0.3% 1.00 [0.31, 3.19] Peng-3 2016 5 40 5 40 0.6% 0.50 [0.10, 2.58] Peng-4 2016 2 40 440 0.6% 0.50 [0.10, 2.58] Subtotal (95% CI) 474 519 29.9% 0.83 [0.71, 0.97] Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); I ² = 0% 760 0.84 [0.76, 0.92] Total events 512 641 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); I ² = 6% 0.01 0.1 1 10 100 Test for overall effect: Z = 3.87 (P = 0.0001) Test for subgroup differences: Not applicable 0.01 0.1 1 10 100	Michell 2009	19	54	20	53	3.2%	0.93 [0.57, 1.54]	
Peng 2016 3 40 3 40 0.5% $1.00 [0.21, 4.66]$ Peng-2 2016 2 40 2 40 0.3% $1.00 [0.15, 6.76]$ Peng-3 2016 5 40 5 40 0.8% $1.00 [0.31, 3.19]$ Peng-4 2016 2 40 440 0.6% $0.50 [0.10, 2.58]$ Subtotal (95% Cl) 474 519 29.9% $0.83 [0.71, 0.97]$ Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); l ² = 0% 0.83 [0.71, 0.97] Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); l ² = 0% 0.84 [0.76, 0.92] Total events 512 641 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); l ² = 6% 0.84 [0.76, 0.92] Tost for overall effect: Z = 3.87 (P = 0.0001) 76 = 0.0001) 70 = 0.0001 Test for subgroup differences: Not applicable 70 = 0.0001 70 = 0.0001	Mitchell 1999	7	25	11	23	1.8%	0.59 [0.27, 1.25]	
Peng-2 2016 2 40 2 40 0.3% 1.00 [0.15, 6.76] Peng-3 2016 5 40 5 40 0.8% 1.00 [0.31, 3.19] Peng-4 2016 2 40 4 40 0.6% 0.50 [0.10, 2.58] Subtotal (95% Cl) 474 519 29.9% 0.83 [0.71, 0.97] Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); l ² = 0% 0.83 [0.76, 0.92] 0.84 [0.76, 0.92] Total (95% Cl) 1700 1761 100.0% 0.84 [0.76, 0.92] Total events 512 641 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); l ² = 6% 0.01 0.1 1 10 100 Test for overall effect: Z = 3.87 (P = 0.0001) Test for subgroup differences: Not applicable Favours control Favours control	Peng 2016	3	40	3	40	0.5%	1.00 [0.21, 4.66]	
Peng-3 2016 5 40 5 40 0.8% 1.00 [0.31, 3.19] Peng-4 2016 2 40 4 40 0.6% 0.50 [0.10, 2.58] Subtotal (95% Cl) 474 519 29.9% 0.83 [0.71, 0.97] Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); l ² = 0% 0.83 [0.71, 0.97] Total (95% Cl) 1700 1761 100.0% 0.84 [0.76, 0.92] Total events 512 641 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); l ² = 6% 0.01 0.1 1 10 100 Test for overall effect: Z = 3.87 (P = 0.0001) Test for subgroup differences: Not applicable 500011 100 Favours lidocaine Favours control	Peng-2 2016	2	40	2	40	0.3%	1.00 [0.15, 6.76]	
Peng-4 2016 2 40 4 40 0.6% 0.50 [0.10 , 2.58] Subtotal (95% CI) 474 519 29.9% 0.83 [0.71 , 0.97] Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); I ² = 0% 0.83 [0.71 , 0.97] Test for overall effect: Z = 2.32 (P = 0.02) 0.84 [0.76 , 0.92] Total (95% CI) 1700 1761 100.0% 0.84 [0.76 , 0.92] Total events 512 641 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); I ² = 6% 0.01 0.1 1 10 100 Test for overall effect: Z = 3.87 (P = 0.0001) Test for subgroup differences: Not applicable Favours control	Peng-3 2016	5	40	5	40	0.8%	1.00 [0.31, 3.19]	
Subtotal (95% Cl) 474 519 29.9% 0.83 [0.71, 0.97] Total events 147 201 Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); I ² = 0% 700 1761 100.0% 0.84 [0.76, 0.92] Total (95% Cl) 1700 1761 100.0% 0.84 [0.76, 0.92] 1000 Total events 512 641 641 1000 100 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); I ² = 6% 0.01 0.1 1 10 100 Test for overall effect: Z = 3.87 (P = 0.0001) Test for subgroup differences: Not applicable Favours lidocaine Favours control	Peng-4 2016	2	40	4	40	0.6%	0.50 [0.10, 2.58]	
Total events 147 201 Heterogeneity: $Chi^2 = 1.74$, $df = 7$ (P = 0.97); $I^2 = 0\%$ Test for overall effect: $Z = 2.32$ (P = 0.02) Total (95% Cl) 1700 1761 100.0% 0.84 [0.76, 0.92] Total events 512 641 Heterogeneity: $Chi^2 = 36.35$, $df = 34$ (P = 0.36); $I^2 = 6\%$ 0.01 0.1 1 10 100 Test for overall effect: $Z = 3.87$ (P = 0.0001) Test for subgroup differences: Not applicable Favours lidocaine Favours control	Subtotal (95% CI)		474		519	29.9%	0.83 [0.71, 0.97]	•
Heterogeneity: Chi ² = 1.74, df = 7 (P = 0.97); l ² = 0% Test for overall effect: Z = 2.32 (P = 0.02) Total (95% CI) 1700 1761 100.0% 0.84 [0.76, 0.92] Total (95% CI) 1700 1761 100.0% 0.84 [0.76, 0.92] Total events 512 641 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); l ² = 6% 0.01 0.1 1 10 100 Test for overall effect: Z = 3.87 (P = 0.0001) Test for subgroup differences: Not applicable Favours lidocaine Favours control	Total events	147		201				
Test for overall effect: Z = 2.32 (P = 0.02) Total (95% CI) 1700 1761 100.0% 0.84 [0.76, 0.92] Total events 512 641 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); l ² = 6% 0.01 0.1 1 10 100 Test for overall effect: Z = 3.87 (P = 0.0001) Favours lidocaine Favours control	Heterogeneity: Chi² =	:1.74, df=	7 (P =	0.97); l² =	:0%			
Total (95% Cl) 1700 1761 100.0% 0.84 [0.76, 0.92] Total events 512 641 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); l ² = 6% 0.01 0.1 1 10 100 Test for overall effect: Z = 3.87 (P = 0.0001) Favours lidocaine Favours control Favours control	Test for overall effect:	Z = 2.32	(P = 0.0	12)				
Total events 512 641 Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); P = 6% 0.01 0.1 1 10 100 Test for overall effect: Z = 3.87 (P = 0.0001) Favours lidocaine Favours lidocaine Favours control	Total (95% CI)		1700		1761	100.0%	0.84 [0.76, 0.02]	•
Heterogeneity: Chi ² = 36.35, df = 34 (P = 0.36); l ² = 6% I	Total (95% CI)	610	1700	G / 4	1/01	100.0%	0.04 [0.70, 0.92]	'
Test for overall effect: Z = 3.87 (P = 0.0001) Test for subgroup differences: Not applicable Test for subgroup differences: Not applicable	Hotorogonoity: Chiž –	710 Ph 36.36	- 34 /0	140 -/ac.n.=	≊ – a0.			
Test for subgroup differences: Not applicable Favours lidocaine Favours control	Test for overall effect:	· 30.33, ul	- 34 (F (P = 0 f	= 0.00); 1001)	0.%			0.01 0.1 i 10 100
	Test for subaroun dif	ferences:	Not an	plicable				Favours lidocaine Favours control

Fig. 2 Forest plot of the incidence of POCD.



Fig. 3 Funnel plot of the studies on the incidence of POCD.

bias by using funnel plots for fewer studies. Egger's test was applied to analyze publication bias, and the results revealed no differences (P>0.05).

A sensitivity analysis was conducted by omitting one study. We removed the study conducted by Wang et al. [20] because of its higher standard error in subgroups of digit symbol, accumulation, trail making A, pegboard favored hand, and pegboard unfavored hand (10.96,19.72, 52.14, 14.63, 13.56 and 11.53, 17, 68, 15.91, 23.92, in the lidocaine and placebo groups, respectively). The overall effect of lidocaine remained with the Standardized mean difference changing from -2.4 (95% CI: -3.31 to -1.49) to -2.58 (95% CI: -3.52 to -1.64).

The GRADEpro assessed the overall quality of the eligible studies in the NP test and deduced the quality grade as moderate.

The risk of bias in the included studies is demonstrated in Fig. 7, and the summary risk of bias is demonstrated in Fig. 8.

Discussion

The effectiveness of lidocaine in POCD is still unclear, and to the best of our knowledge, no previous metaanalysis studies have assessed the effect of intravenous lidocaine on the incidence and severity of POCD. We demonstrated that lidocaine treatment significantly reduced the occurrence of POCD, especially in the short and long term. A meta-analysis conducted by Baradari et al. [28] revealed that lidocaine consistently reduced the incidence of cognitive deficits significantly after cardiac surgery, particularly during the first postoperative month. Although there were no differences between lidocaine and placebo in the overall severity of POCD, lidocaine attenuated the severity of POCD in a short term subgroup meta-analysis.

Variability in the follow-up time of cognitive assessment is an important factor that complicates the interpretation of the literature. The follow-up period was covered from the discharge of the post-anesthesia care unit through one year after the surgery in the eligible studies. POCD frequently occurred in the short term [29, 30], and a previous study suggested a pattern of improvement in the short term postoperative cognitive function, which predicted a later decline [29]. We found that lidocaine decreased the incidence and attenuated the severity of POCD in the short and long term. Thus, lidocaine may be a useful agent for treating POCD.

It had been identified in the literature that risk factors for POCD include advanced age and shorter education [31]. Although the eligible studies were randomized

	Lidocaine			C	ontrol			Std. Mean Difference	Std. Mean Difference	
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl	
3.1.1 short-term										
Chen 2015	0.81	1.73	40	1.97	1.34	40	3.3%	-0.74 [-1.20, -0.29]		
Peng 2016	1.3	0.84	40	2	1.69	30	3.1%	-0.54 [-1.03, -0.06]		
Peng-6 2016	0.3	0.84	40	1	1.69	40	3.3%	-0.52 [-0.97, -0.07]		
Peng-3 2016	0	2.12	40	0.65	1.42	40	3.4%	-0.36 [-0.80, 0.09]		
Hashemi-2 2013	1.7	4.93	35	2.6	4.76	35	3.2%	-0.18 [-0.65, 0.29]		
Hashemi-3 2013	0	4.71	35	0.5	4.02	35	3.2%	-0.11 [-0.58, 0.36]		
Hashemi 2013	3.5	4.88	35	3.6	4.57	35	3.2%	-0.02 [-0.49, 0.45]		
Peng-2 2016	1.35	3.02	40	1.36	2.2	40	3.4%	-0.00 [-0.44, 0.43]	-	
Peng-5 2016	0.65	1.41	40	0.65	1.41	40	3.4%	0.00 [-0.44, 0.44]		
Peng-7 2016	0.71	3.57	40	0.71	2.84	40	3.4%	0.00 [-0.44, 0.44]		
Peng-8 2016	1.65	2.2	40	1.35	3.04	40	3.4%	0.11 [-0.33, 0.55]	+-	
Peng-4 2016	0.35	2.2	40	0	1.69	40	3.4%	0.18 [-0.26, 0.62]		
Subtotal (95% CI)			465			455	39.5%	-0.18 [-0.34, -0.01]	•	
Heterogeneity: Tau ² =	0.03; C	hi² = 13	7.59, dt	f= 11 (P	= 0.09	9); l ² = 3	37%			
Test for overall effect:	Z = 2.12	(P = 0	0.03)							
3.1.2 median-term										
Peng-7 2016	0	2.53	40	1.65	2.2	40	3.3%	-0.69 [-1.14, -0.24]		
Peng-8 2016	2	2.12	40	2.35	1.42	40	3.4%	-0.19 [-0.63, 0.25]		
Peng-6 2016	0.29	2.53	40	0.64	2.2	40	3.4%	-0.15 [-0.59, 0.29]		
Peng-4 2016	0.7	2.12	40	1	2.12	40	3.4%	-0.14 [-0.58, 0.30]		
Peng-2 2016	0.29	2.53	40	0.35	2.21	40	3.4%	-0.03 [-0.46, 0.41]		
Mathew 2009	0.1	0.3	88	0.1	0.3	94	4.6%	0.00 [-0.29, 0.29]	+	
Peng 2016	0.35	0.77	40	0.35	1.42	40	3.4%	0.00 [-0.44, 0.44]		
Klinger 2019	0.074	0.32	211	0.072	0.37	209	5.5%	0.01 [-0.19, 0.20]	+	
Peng-5 2016	0.7	0.84	40	0.35	1.42	40	3.4%	0.30 [-0.14, 0.74]	+	
Peng-3 2016	1.65	3.02	40	0	2.84	40	3.3%	0.56 [0.11, 1.00]		
Subtotal (95% CI)			619			623	37.1%	-0.03 [-0.20, 0.14]	•	
Heterogeneity: Tau ² = 0.04; Chi ² = 18.12, df = 9 (P = 0.03); I ² = 50%										
Test for overall effect: $Z = 0.32$ (P = 0.75)										
3.1.3 long-term										
Peng-3 2016	1.35	3.02	40	3.65	2.2	40	3.2%	-0.86 [-1.32, -0.40]		
Peng-2 2016	0.29	2.53	40	0.64	2.2	40	3.4%	-0.15 [-0.59, 0.29]		
Klinger 2019	0.09	0.34	185	0.07	0.34	192	5.5%	0.06 [-0.14, 0.26]	+	
Peng 2016	0.7	0.84	40	0.35	1.42	40	3.4%	0.30 [-0.14, 0.74]	+	
Peng-4 2016	3.35	1.42	40	2.64	2.86	40	3.4%	0.31 [-0.13, 0.75]	+	
Mathew 2009	0.19	0.25	88	0.09	0.3	94	4.6%	0.36 [0.07, 0.65]		
Subtotal (95% CI)			433			446	23.4%	0.02 [-0.29, 0.33]	•	
Heterogeneity: Tau ² =	0.11; C	hi² = 23	2.69, di	r= 5 (P =	= 0.000	04); l² =	78%			
Test for overall effect:	Z = 0.13	(P = 0)	1.89)							
Total (95% CI)			1517			1524	100.0%	-0.07 [-0.19, 0.04]	•	
Heterogeneity: Tau ² =	0.05; C	hi² = 69	5.28, di	7= 27 (P	< 0.00	001); I ^z	= 59%			
Test for overall effect:	Z = 1.25	i (P = 0	1.21)						Eavours lidocaine Eavours control	
									avoura nuocame ravoura control	

Fig. 4 Forest plot of the severity of POCD.

trials, the intervention and control groups were rigorously compared under the same circumstances. We compared the age and education between the lidocaine and placebo groups and did not find any differences. This means that the biases of the two risk factors were balanced. Whether the surgical procedure is an independent risk factor for POCD remains controversial. The high rate of POCD occurrence after CABG in multiple studies [3, 29], suggests that the CABG procedure puts patients at risk of cognitive decline. However, most outcomes of CABG studies are limited by a lack of appropriate control groups. Most importantly, although cognitive changes are well documented, assessment of whether they are specifically related to the procedure itself or whether other surgical procedures would produce similar postoperative cognitive changes has been difficult. In other words, some of the short term cognitive changes after CABG may not be specific to the procedure but may



Fig. 5 Funnel plot of the studies on the severity of POCD.

also accompany other surgical procedures. POCD may be suggested as a multifactorial etiology of prolonged cardiopulmonary bypass time [32] and cerebrovascular pathology [3]. Regarding study variability, it may be said that there were no significant variables, except for lidocaine treatment. Based on the above literature, we did not set the inclusion criteria for the surgical procedure in this study.

Given that dropout can result in worse outcomes [33] and even 26% dropout after randomization, there were no differences between lidocaine and placebo overall. Thus, it can be concluded that missing follow-up data may not significantly affect the outcome.

It had been shown that neuroinflammation is correlated with the occurrence of POCD [34]. It is believed that the BBB is formed by brain endothelial cells that line the cerebral microvasculature. The BBB is a vital mechanism that protects the brain from changes in the composition of plasma and circulating compounds capable of disrupting neuronal function [35]. The immune response and surgical trauma may trigger cellular damage; these cells begin to release endogenous molecules, exacerbating the inflammatory response [36]. The immune response can trigger vascular endothelial cell damage and interrupt tight junction proteins. The BBB breaks down, allowing and facilitating the entry of peripheral immune cells into the brain, which triggers or exacerbates the activation of glial cells and neuroinflammation [37].

In addition to the neuroinflammation mechanism, danger-associated molecular patterns released following surgical trauma may be another factor resulting in POCD. Danger-associated molecular patterns interact with pattern recognition receptors that are present within the BBB endothelium and further activate proinflammation [38]. The anti-inflammatory and immune protective effects of lidocaine have been reported in the literature [39, 40], which reduces the permeability of cell membranes to Na⁺, avoiding membrane depolarization [41]. Thus, it can be thought that lidocaine can inhibit the release of inflammatory cytokines and vascular permeability. Additionally, lidocaine inhibits neutrophil adhesion, migration and accumulation [42], macrophage activity, and enzyme release [43]. In other words, it can be inferred that lidocaine attenuated the incidence and severity of POCD by stabilizing the BBB membrane

	Li	docaine		C	ontrol			Mean Difference	Mean Difference		
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl		
1.1.1 Digit symbol							6.000	0.00/1.07.1.77	1		
Wang 2002 Wang 2004	2.4	4.8	43	2.4	4.0	45	5.0%	0.00[-1.97, 1.97]			
7hu 2015	0.81	0.80	30	4 91	1 79	30	6 4 %	-4 10 [-4 79 -3 41]	-		
Subtotal (95% CI)	0.01	0.00	116	1.01	1.10	120	13.8%	-1.67 [-5.07, 1.74]	•		
Heterogeneity: Tau ² =	7.29; C	hi² = 17.	17, df=	= 2 (P =	0.0002)	; I² = 88	3%				
Test for overall effect:	Z = 0.98	i (P = 0.3	34)								
1.1.2 ACCUMUIATION	2.2	11.6	42	0.0	15	45	1.0%	100.0 00.01030			
Wang 2002 Wang 2004	4	19.72	43	0.0	17	45	1.5%	4 00 1-3 71 11 71			
Zhu 2015	2.43	0.79	30	17.13	1.03	30	6.5%	-14.70 [-15.1614.24]			
Subtotal (95% CI)			116			120	9.5%	-3.04 [-17.32, 11.23]			
Heterogeneity: Tau ² =	151.45;	Chi ² = t	58.39, 0	df = 2 (P	< 0.000	001); P	= 97%				
Test for overall effect:	Z = 0.42	P = 0.6	68)								
1 1 3 The digit span f	oward										
Wang 2002	∩ 4	1	43	0.4	1	45	6.5%	0.00 [-0.42 0.42]	-		
Wang 2004	0.4	1.53	43	0.4	1.72	45	6.4%	0.00 [-0.68, 0.68]	+		
Zhu 2015	0.21	0.16	30	0.19	0.07	30	6.6%	0.02 [-0.04, 0.08]	1		
Subtotal (95% CI)			116			120	19.5%	0.02 [-0.04, 0.08]			
Heterogeneity: Tau ² =	0.00; C	hi ² = 0.0	1, df =	2 (P = 0	.99); I ^z =	:0%					
Test for overall effect:	Z = 0.62	P = 0.9	(4)								
1.1.4 The digit span b	ackwar	d									
Wang 2002	0.07	0.7	43	0.3	0.9	45	6.5%	-0.23 [-0.57, 0.11]			
Wang 2004	0	1.04	43	0.3	1.53	45	6.4%	-0.30 [-0.84, 0.24]	-		
Zhu 2015	0.11	0.08	30	0.12	0.04	30	6.6%	-0.01 [-0.04, 0.02]	1		
Subtotal (95% CI)			116			120	19.6%	-0.07 [-0.22, 0.09]			
Heterogeneity: Tau ² =	0.01; C	$hi^2 = 2.7$	0, df = 1	2 (P = 0	.26); l²=	: 26%					
Test for overall effect.	2 = 0.86	(P = 0)	99)								
1.1.5 Trail making A											
Wang 2002	4.6	30.6	43	9.1	35.6	45	0.4%	-4.50 [-18.35, 9.35]			
Wang 2004	5	52.14	43	9	68	45	0.1%	-4.00 [-29.25, 21.25]			
Zhu 2015	2.13	1.41	30	17.71	1.43	30	6.3%	-15.58 [-16.30, -14.86]			
Subtotal (95% CI)			116			120	6.9%	-12.07 [-20.07, -4.06]	-		
Heterogeneity: Tau* =	24.16; 0	Chi*= 3.	25, df =	= 2 (P =	0.20); P	= 39%					
restion overall ellect.	2 = 2.90) (F = 0.0	103)								
1.1.6 pegboard favor	ed hand	í.									
Wang 2002	5.7	10.4	43	5.2	9.1	45	2.8%	0.50 [-3.59, 4.59]			
Wang 2004	6	14.63	43	5	15.91	45	1.6%	1.00 [-5.38, 7.38]	<u> </u>		
Subtotal (95% CI)			86			90	4.4%	0.65 [-2.80, 4.09]	+		
Heterogeneity: Tau ² =	0.00; C	hi² = 0.0	2, df =	1 (P = 0	.90); l²=	:0%					
restior overall ellect.	2 = 0.37	(P = 0.)	1)								
1.1.7 pegboard unfav	ored ha	nd									
Wang 2002	5.3	9.5	43	9.6	13	45	2.4%	-4.30 [-9.04, 0.44]			
Wang 2004	6	13.56	43	10	23.92	45	1.1%	-4.00 [-12.08, 4.08]			
Subtotal (95% CI)			86			90	3.4%	-4.22 [-8.31, -0.13]	•		
Heterogeneity: Tau ² =	0.00; C	hi ² = 0.0	0, df =	1 (P = 0	.95); I * =	:0%					
rest for overall effect:	Z = 2.02	: (P = U.(14)								
1.1.8 visual retention											
Wang 2002	0.05	2.6	43	0.4	2.7	45	6.0%	-0.35 [-1.46, 0.76]	+		
Wang 2004	0	3.29	43	1	3.29	45	5.7%	-1.00 [-2.38, 0.38]	-		
Subtotal (95% CI)	the series over		86	N VEV IN		90	11.7%	-0.61 [-1.47, 0.26]	1		
Heterogeneity: Tau ² =	0.00; C	hi ² = 0.5	2, df =	1 (P = 0	.47); 2=	:0%					
Test for overall effect: Z = 1.38 (P = 0.17)											
1.1.9 paired associat	ed verb	al learni	ing								
Wang 2002	0.9	3.9	43	1.7	2.6	45	5.7%	-0.80 [-2.19, 0.59]	-		
Wang 2004	1	3.92	43	1	3.29	45	5.6%	0.00 [-1.52, 1.52]	+		
Subtotal (95% CI)			86			90	11.3%	-0.43 [-1.46, 0.59]	•		
Heterogeneity: Tau ² =	0.00; C	hi ² = 0.5	8, df =	1 (P = 0	.45); I²=	:0%					
rest for overall effect:	Z = 0.83	(P = 0.4	11)								
Total (95% CI)			924			960	100.0%	-2,40 [-3.31, -1.49]	•		
Heterogeneity: Tau ² =	3.26; C	hi² = 576	63.04. 0	df = 22 (P < 0.00	0001):1	= 100%				
Test for overall effect:	Z= 5.18	(P < 0.0	00001)						-20 -10 0 10 20 Favours lidocaine Favours control		
									ravours nuovanie ravours control		



through ion exchange and inhibiting the inflammatory response.

The study conducted by Ghafari et al. [44], which focused on the effect of lidocaine on cognitive deficits after coronary artery bypass graft surgery, was not

included in this meta-analysis. It included 110 patients scheduled for CABG with CPB. This demonstrated that lidocaine could improve postoperative cognitive outcomes compared with procaine. Although we did not set the inclusion criteria for the surgical procedure, we Adequate sequence generation?

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exercised when interpreting the outcomes. Although some have argued that the Jadad score is a simplistic measure that does not characterize all elements of trial quality, it is still perhaps the most common measure of trial quality for assessing the methodological quality of a trial [17].Blinding, randomization, and description of dropouts are the three basic minimum assessment tools before inclusion of trials in meta-analysis. It is known to have good validity and reliability. Its brevity and ease of use makes it one of the most widely used scales, and it offers the prospect of objectivity, which is much more efficient than some other subjective methods. The use of the modified Jadad score thus helped to avoid misinterpreting the quality of studies.

aimed to evaluate the effect of intravenous lidocaine.

while the intervention agent was used in a cardioplegia

solution in this study. Another study by Zhu et al. [25]

compared a mixture of lidocaine and ketamine with nor-

mal saline. The mixture was used as a bolus, and lido-

caine was continued. Although ketamine is a short-acting reagent, the anesthesia time in the study was approxi-

mately 3 h (236.2±41.7 min and 233.7±38.2 min in

lidocaine and placebo, respectively). Most importantly, a meta-analysis revealed that ketamine did not change

the incidence of POCD [45]. Therefore, we included this

study in the meta-analysis. However, caution should be

This meta-analysis had several limitations. First, some discrepancies are attributable to the use of different tests and the assessment of diverse populations. To balance the bias of the different tests, we used the difference in values compared with the baseline. Second, we performed a meta-analysis of the data from the study conducted by Peng et al.[24], which used several tests to assess POCD at different follow-up times. Although the study quality was high (Jadad score of 5), it may have deteriorated weight bias. Third, the surgical procedure was not an independent risk factor for POCD, and we included 4 (out of 10) trials that underwent cardiac surgery. Prolonged hospitalization and increased resource use may be associated with neurobehavioral declines [46, 47]. Finally, the total dose of lidocaine was not set the same as different regimens were used in studies. Different dose of lidocaine may aggravate the bias in different studies.

Taken together, multiple studies have demonstrated that POCD occurring in the short term is predictive of late cognitive decline [29, 48, 49]. In this systematic review and meta-analysis, we found that lidocaine could alleviate the overall incidence of POCD in the short and long term, especially the occurrence and severity in the short term. Thus, lidocaine can be a valuable preventive intervention to significantly reduce the risk of both short term and long term POCD. Most eligible studies did not find any significant differences on long term POCD. It may be because these studies were underpowered to



Zhu 2015

detect an effect on long term POCD as there are more confounders. It warrants further studies on long term POCD.

Supplementary Information

The online version contains supplementary material available at https://doi. org/10.1186/s12871-023-02202-0.

Supplementary Material 1

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Author contributions

BJ H: Data curation, Funding acquisition; C G: Methodology, Data curation; JH J: Resources, Software, Supervision; YH Z: Validation, Roles/Writing - original draft, Writing - review & editing; WQ T: Investigation; MZ P: Visualization; LL S: Formal analysis; PF C: Conceptualization; HY W: Project administration. All authors reviewed the manuscript.

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Data Availability

The datasets used and analysed during the current study available from the corresponding author on reasonable request.

Declarations

Ethical approval and consent to participate

Ethics committee approval and consent to participate were not applicable because only published research data were analyzed.

Consent for publication

Not available.

Competing interests

The authors declare no competing interests. The funders in the study had no roles in design and collection, analysis, and interpretation of the results.

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