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Prophylactic effect of intravenous lidocaine against cognitive deficit after cardiac surgery

A PRISMA-compliant meta-analysis and trial sequential analysis

Kuo-Chuan Hung, MD[a], Chun-Ning Ho, MD[a], Wei-Cheng Liu, MD[a], Ming Yew, MD[a], Ying-Jen Chang, MD[a], Yao-Tsung Lin, MD[a], I-Yin Hung, MD[a], Jen-Yin Chen, MD, PhD[a], Ping-Wen Huang, MD[b], Cheuk-Kwan Sun, MD, PhD [c,d,*]

Abstract

Background: This study aimed at providing an updated evidence of the association between intraoperative lidocaine and risk of postcardiac surgery cognitive deficit.

Methods: Randomized clinical trials (RCTs) investigating effects of intravenous lidocaine against cognitive deficit in adults undergoing cardiac surgeries were retrieved from the EMBASE, MEDLINE, Google scholar, and Cochrane controlled trials register databases from inception till May 2021. Risk of cognitive deficit was the primary endpoint, while secondary endpoints were length of stay (LOS) in intensive care unit/hospital. Impact of individual studies and cumulative evidence reliability were evaluated with sensitivity analyses and trial sequential analysis, respectively.

Results: Six RCTs involving 963 patients published from 1999 to 2019 were included. In early postoperative period (i.e., 2 weeks), the use of intravenous lidocaine (overall incidence = 14.8%) was associated with a lower risk of cognitive deficit compared to that with placebo (overall incidence = 33.1%) (relative risk = 0.49, 95% confidence interval: 0.32–0.75). However, sensitivity analysis and trial sequential analysis signified insufficient evidence to arrive at a firm conclusion. In the late postoperative period (i.e., 6–10 weeks), perioperative intravenous lidocaine (overall incidence = 37.9%) did not reduce the risk of cognitive deficit (relative risk = 0.99, 95% confidence interval: 0.84) compared to the placebo (overall incidence = 38.6%). Intravenous lidocaine was associated with a shortened LOS in intensive care unit/hospital with weak evidence.

Conclusion: Our results indicated a prophylactic effect of intravenous lidocaine against cognitive deficit only at the early postoperative period despite insufficient evidence. Further large-scale studies are warranted to assess its use for the prevention of cognitive deficit and enhancement of recovery (e.g., LOS).

Abbreviations: CI = confidence interval, ICU = intensive care unit, LOS = length of stay, MD = mean difference, MMSE = mini mental state examination, RCTs = randomized clinical trials, RIS = required information size, RR = relative risk, TSA = trial sequential analysis.

Keywords: cardiac surgery, cardiopulmonary bypass, lidocaine, neurocognitive assessment, sodium channel blocker

1. Introduction

Neurocognitive decline after cardiac surgeries remains a major clinical issue that affects >50% of patients at hospital discharge[1] and persists for months to even years in up to 25% to 40% of adult patients.[2] Previous studies have shown that factors other than surgery itself could contribute to late cognitive deficit after cardiac operations.[1,3] Despite the identification of possible etiologies including hemodilution, cerebral hypoperfusion, microembolism from air or particles, ischemia–reperfusion injury, inflammatory reactions, and genetic predisposition,[2,4,5] the therapeutic benefits of different pharmacological[6,7] and immunological[8] approaches as well as technical refinement of cardiopulmonary bypass[9] remain inconclusive.

There has been a renewed interest in lidocaine, a class IIB sodium channel blocking antiarrhythmic being included in

K-CH and C-NH contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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[a] Department of Anesthesiology, Chi Mei Medical Center, Tainan city, Taiwan, [b] Department of Emergency Medicine, Show Chwan Memorial Hospital, Changhua city, Taiwan, [c] Department of Emergency Medicine, E-Da Hospital, Kaohsiung city, Taiwan, [d] College of Medicine, I-Shou University, Kaohsiung city, Taiwan.

**Correspondence: Cheuk-Kwan Sun, Department of Emergency Medicine, E-Da Hospital, Kaohsiung, Taiwan, No.1, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 82445, Taiwan (e-mail: researchgate000@gmail.com).*

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the latest American Heart Association guidelines for treating ventricular arrhythmias unresponsive to defibrillation,[10] regarding its cardioprotective property[11] and potential effectiveness against cognitive deficit after noncardiac surgery.[12] It is also proposed to be neuroprotective because it can cross the blood–brain barrier and may alleviate inflammation and preserve cerebral blood flow.[13] Nevertheless, although a previous in vivo study has demonstrated its neuroprotective effect against ischemia,[14] the effectiveness during cardiopulmonary bypass remains controversial. There have been several randomized clinical trials (RCTs) focusing on its prophylactic impact on cognitive deficit after cardiac surgeries.[15–20] Two previous meta-analyses involving 688 patients reported a reduction in the risk of postoperative cognitive deficit through intravenous lidocaine,[21,22] whereas a recent study recruiting 478 patients did not support this finding.[16] In addition, there is also no pooled evidence endorsing the neuroprotective benefits of lidocaine in patients receiving noncardiac surgery.[12]

To address this issue, this updated meta-analysis aimed at investigating the prophylactic effect of intravenous lidocaine against cognitive deficit as well as its impacts on the length of hospital and intensive care unit (ICU) stay after cardiac surgery.

2. Methods

2.1. Study guidelines and registration

We conducted a meta-analysis of RCTs in accordance with a registered protocol (International Prospective Register of Systematic Reviews registration no. CRD42021257602). The presented meta-analysis was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The proposed study utilizes published data; therefore, ethical approval is not required for the current study.

2.2. Identification of relevant trials

Four databases (i.e., EMBASE, MEDLINE, Google scholar, The Cochrane Central Register of Controlled Trials [CENTRAL]) were systematically searched to identify relevant trials published as journal articles from inception till May 29, 2021. We also reviewed the reference lists of the retrieved articles for additional trials. Detailed search strategies are shown in Table 1, Supplemental Digital Content1, http://links.lww.com/MD/H232.

2.3. Eligibility criteria

Only RCTs recruiting patients undergoing cardiac surgeries were included. Inclusion criteria in accordance with the "population, intervention, comparator, outcome, study design" (PICOS) criteria were as follows: Population: adult patients (age ≥ 18 years) undergoing cardiac surgeries with or without the use of cardiopulmonary bypass; Intervention: patients receiving intraoperative intravenous lidocaine; Comparator: placebo or no treatment; Outcome: the risk of postoperative cognitive deficit was the primary endpoint, while secondary endpoints were in-hospital mortality (according to the definition of the original article), and length of stay (LOS) in hospital or ICU. Study design: RCTs were included when the predefined PICOS criteria were reported. Exclusion criteria were studies in which intravenous lidocaine was mainly used to reduce pain stimulus caused by propofol administration, tracheal intubation or surgery, studies in which cognitive dysfunction was not assessed with a validated neurocognitive test, information regarding primary outcome (i.e., postoperative cognitive deficit) was unavailable, and non-English publications as well as RCTs published as letters or abstracts only.

2.4. Trial selection and data extraction

The trials for this meta-analysis were screened by examining their titles and abstracts to identify potentially relevant articles. The full text of relevant articles was then read by 2 independent authors to select studies for inclusion. The reasons for exclusion of the ineligible studies were also documented. Two reviewers independently recorded data based on the PICOS criteria. If necessary, the corresponding authors of the included studies were contacted twice to request the missing information. For multiple studies reporting data from the same trial, only the study with the largest sample size was chosen. Two reviewers independently extracted data that included primary author, year of publication, sample size, gender distribution, type of surgery, dosage of lidocaine, patient characteristics, perioperative circulating lidocaine concentration. In the situation of disagreements, a third author was involved until a consensus was reached.

2.5. Primary outcome, secondary outcomes, and definition

The risk of postoperative cognitive deficit was the primary outcome, while the secondary outcomes included the risk of in-hospital mortality, length of hospital stay, and length of ICU stay. Postoperative cognitive deficit was defined according to the criteria of each trial. When this outcome was available at different time points, the pooled results were reported based on similar time points.

2.6. Risk of bias assessment

Two reviewers independently assessed the risk of bias for the included studies based on the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions.[23] The risk of bias in each study was reported as "low," "unclear," or "high" in the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. We categorized the risk of "selective outcome reporting" bias as "unclear" if the registered protocols of the included trials were not published or registered previously. Moreover, the sources of funding were evaluated for the potential existence of other biases. Disagreements were solved by discussion. The overall risk of bias of all the included studies and the risk of bias of individual studies were analyzed.

2.7. Data synthesis

The pooled risk ratios (ORs) and 95% confidence intervals (CIs) of binary outcomes (e.g., risk of cognitive deficit) were calculated. For ICU and hospital LOS, the mean difference (MD) and 95% CI were reported. Statistical heterogeneity was assessed by the I^2 statistic with substantial heterogeneity predefined as I^2 >50%. In view of the expected heterogeneity among the studies, we decided a priori to adopt a random-effects model for outcome evaluation, independent of the finding of statistical heterogeneity. The potential publication bias was examined visually using a funnel plot when we identified 10 or more trials reporting on a particular outcome. The potential influence of the data from a single trial on the overall results was assessed with sensitivity analyses that involved one-at–a-time omission of the trials from the meta-analysis.

The strength and reliability of the cumulative evidence were examined by trial sequential analysis (TSA) that aimed at reducing false-negative or false-positive findings from multiple testing and sparse data.[24,25] TSA viewer version 0.9.5.10 Beta (www.ctu.dk/tsa) was used for the analysis. For the primary outcome, we calculated the required information size (RIS) as well as the trial sequential monitoring boundaries. The variance was obtained from the data of the included studies. The level of

evidence for the anticipated intervention effect is deemed sufficient without the need for further studies when the cumulative Z-curve crosses the TSA boundary, whereas failing of the Z-curve to cross the TSA boundary or reach the RIS signifies insufficient evidence for a robust conclusion. For dichotomous outcomes, 2-sided tests with a type I error of 5% and a power of 80% as well as a relative risk reduction of 20%[26] were adopted for RIS computation.

3. Results

3.1. Studies identification

The systemic search initially yielded 102 publications (Fig. 1). Of the 14 potentially eligible trials, 1 was a review article, 4 did not meet the PICO criteria, 1 was a non-English article, primary outcome was unavailable in 1 study, and full text was unavailable in another; therefore, all were excluded. Finally, 6 publications were included for the current meta-analysis.[15–20]

3.2. Characteristics of studies

The characteristics of the 6 eligible RCTs[15–20] involving 963 patients (lidocaine group, n = 480; placebo group, n = 483) published from 1999 to 2019 are detailed in Table 1. The sample size of the included studies ranged from 49 to 420. There was a male predominance in the lidocaine group, ranging from 60.7%[19] to 97.7%.[20] The dosage of lidocaine varied among the included studies (Table 1). Five studies used an intravenous lidocaine bolus of 1 to 1.5 mg/kg followed by continuous infusion,[16–20] while 1 study only administered intravenous lidocaine at a dose of 2 mg/kg.[15] Information regarding plasma lidocaine concentration was available in all trials.[15–20] In 5 RCTs, the mean plasma lidocaine concentration ranged from 1.6 to 3.9 μg/mL,[15–19] while the mean concentration was 4.78 to 7.1 μg/mL in 1 trial.[20] All studies used the neurocognitive test to assess cognitive deficit at different time points (i.e., from postoperative 9 days to 1 year) (Table 1); 1 trial used Mini Mental State Examination (MMSE),[15] while the other 5 studies used cognitive test battery.[16–20] The criteria for the diagnosis of postoperative cognitive deficit were described in Table 2, Supplemental Digital Content 2, http://links.lww.com/MD/H233.

3.3. Risk of bias assessment

The results of the risk of bias assessment are shown in Figure 2. All studies had at least 1 domain carrying an unclear or a high risk of bias. Of the four studies that did not specify the information about sequence generation for randomization and concealment of group allocation,[15,16,19,20] 1 recruited lidocaine group participants who had a significantly higher proportion of Caucasians, a lower ejection fraction, and a lower level of education compared to those in individuals of the placebo group.[16] The risk for the sequence generation for randomization was considered high for this study.[16] All studies adopted a placebo solution to blind the participants and outcome assessors; therefore, the risks of bias for performance and detection bias were deemed low.[15–20] On the other hand, the risk of attrition bias was unclear in 2 studies[18,20] because >15% of their patients were lost to follow-up or did not receive neurocognitive examination. In addition, the reporting bias was unclear in five trials that did not specify the information regarding trial registration.[15,17–20] Information on bias assessment of the included RCTs is provided in Table 3, Supplemental Digital Content 3, http://links.lww.com/MD/H234.

3.4. Synthesis of results

3.4.1. Risk of cognitive deficit within postoperative 2 weeks. Three included trials[15,19,20] reported cognitive deficit within postoperative 2 weeks (Fig. 3A) with the overall incidences being 14.8% and 33.1% in lidocaine and placebo groups, respectively. Based on synthesis of data from 243 patients, the forest plot demonstrated a lower risk of cognitive deficit among patients receiving intravenous lidocaine within postoperative 2 weeks compared with that in the placebo group (RR = 0.49, 95% CI: 0.32–0.75, $P = .001$; $I2 = 0\%$). Sensitivity analysis showed a significant influence on the pooled outcome from the study by Wang et al,[20] indicating a blemished robustness of the conclusion. The study by Wang et al,[20] demonstrated a higher perioperative plasma lidocaine concentration (i.e., 4.78–7.1 μg/mL) compared with that in other studies (i.e., 1.6–3.9 μg/mL). Besides, TSA demonstrated a failure of the cumulative Z-curve to reach the RIS or cross the trial sequential monitoring boundary, signifying insufficient evidence to arrive at a firm conclusion (Fig. 3B).

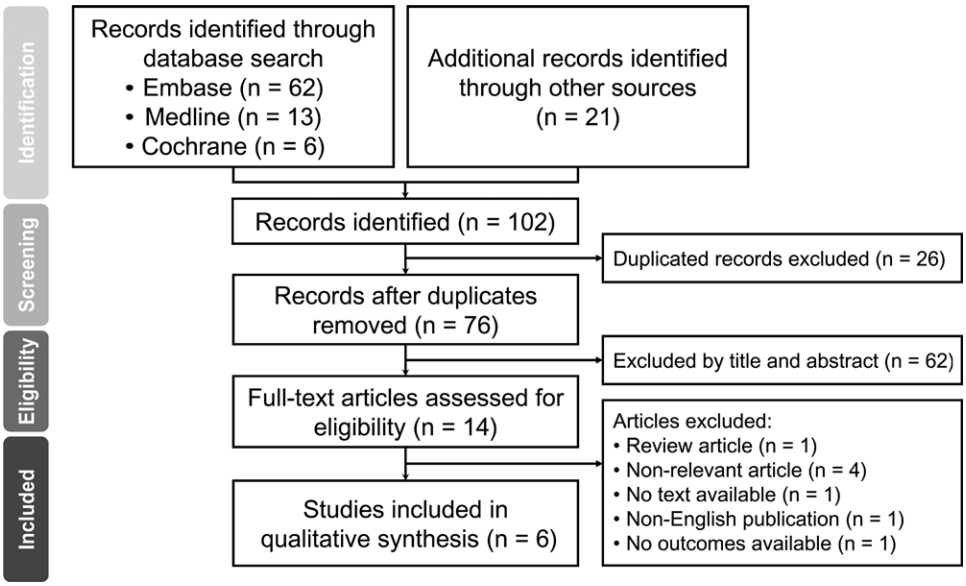

Figure 1. PRISMA flow diagram of study selection for the current meta-analysis.

Table 1

Characteristics of included studies (n = 6).

	Number of patients* (L vs P)	Mean age (y/r) (L vs P)*	Male % (L vs P)*	Procedure	Bypass time (min) (L vs P)	Intervention group	Placebo group	Lidocaine concentration (μg/mL)	Postoperative examination
Ghafari 2012	54 vs 52	58.7 vs 58.3	61.1 vs 63.5	CABG	80.8 vs 83.1	Cardioplegia solution containing lidocaine 2 mg/kg	Procaine hydrochloride 5 mg/kg	2.14–2.61†	10 d; 2 mo
Klinger 2019	211 vs 209	67 vs 67	71.6 vs 76.6	CABG, valve surgery, or CABG plus valve surgery	157 vs 166	Lidocaine 1 mg/kg bolus followed by a continuous infusion‡	Normal saline	1.82–2.86§	6 wks; 1 y
Mathew 2009	88 vs 94*	61.7 vs 61.4‖	72.8 vs 66.9‖	CABG, valve surgery, or CABG plus valve surgery	168 vs 161	Lidocaine as a 1 mg/kg bolus followed by a continuous infusion¶	Normal saline	2.3–2.6#	6 wks; 1 y
Mitchell1999	25 vs 24	56.9 vs 54.4‖	60.7 vs 51.9‖	Heart valve procedures	129.3 vs 109.5	1 mg/kg bolus followed by continuous infusion**	Dextrose 5%	1.8–3.9††	10 d; 10 wk; and 6 mo
Mitchell 2009	59 vs 59	61.5 vs 58.1‖	74.1 vs 81.8‖	CABG, valve surgery, or combined procedures	NA	1 mg/kg bolus followed by a continuous infusion‡‡	Normal saline	1.6–2.1§§	10 and 25 wk
Wang 2002	43 vs 45	57.8 vs 59.3	97.7 vs 97.8	CABG with CPB	149.4 vs 132.2	1.5 mg/kg bolus followed by a continuous infusion‖‖	Normal saline	4.78–7.1¶¶	9 d

CABG = coronary artery bypass graft, CPB = cardiopulmonary bypass, L = lidocaine group, P = placebo group.

*Data from patients receiving neurocognitive test.

†Injection of cardioplegia to declamping of the aorta.

‡48 μg/kg/min for the first hour, 24 μg/kg/min for the second hour, and 10 μg/kg/min for the next 46 h.

§End-bypass to 48 h postbypass.

‖Data from patients allocated to initial treatment.

¶4 mg/min for the first hour, 2 mg/min for the second hour, and 1 mg/min for the next 46 h.

#End-bypass to 24 h postbypass.

**240 mg over the first hour and 120 mg over the second hour, and then 60 mg/h thereafter.

††Aortic cannulation to 24 h postoperatively.

‡‡2 mg/min for 2 h, and 1 mg/min thereafter for a total of 12 h.

§§2 and 10 h postoperatively.

‖‖4 mg/min infusion during operation and 4 mg/kg in the priming solution of cardiopulmonary bypass.

¶¶Before cardiopulmonary bypass to 60 min postbypass.

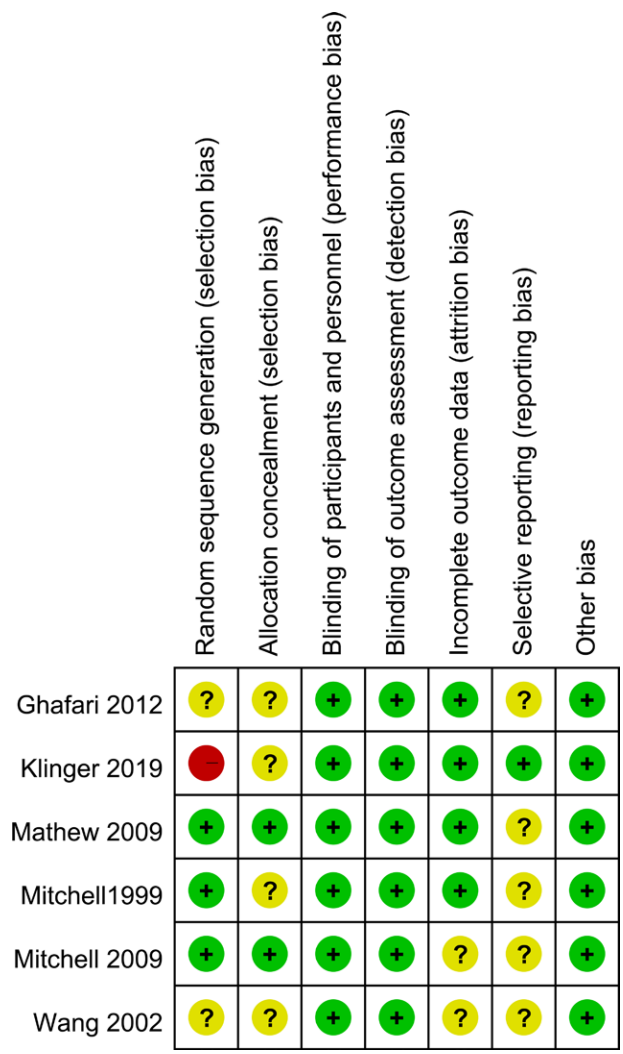

Figure 2. Risks of bias of the included studies.

3.4.2. Risk of cognitive deficit at postoperative 6–10 weeks. Pooled results for five RCTs (lidocaine group, n = 438 vs placebo group, n = 438) were reported.[15–19] The overall incidences of cognitive deficit at postoperative 6 to 10 weeks were 37.9% and 38.6% in lidocaine and placebo groups, respectively. Perioperative intravenous lidocaine was not associated with a reduction in the risk of cognitive deficit within postoperative 6–10 weeks (RR: 0.99, 95% CI: 0.84–1.16, *P* = .87; I2 = 17%) (Fig. 4A). Sensitivity analysis showed no significant impact on outcome by omitting certain trials, suggesting robustness of the evidence. Crossing of the cumulative Z-curve through the futility boundaries indicated sufficient evidence for a firm conclusion (Fig. 4B).

3.4.3. Length of ICU and hospital stay. Meta-analysis of the three available trials[18–20] revealed a shorter ICU stay in the lidocaine group compared with that in the placebo group (MD: −50.29 hours, 95% CI: −99 to −1.58, *P* = .04; I2 = 97%; n = 300) (Fig. 5A). Sensitivity analysis showed an inconsistent finding when the studies by Mitchell et al[19] and Wang et al[20] were excluded, implicating weakness of evidence for this outcome. TSA showed that the cumulative Z-curve failed to cross the RIS or the trial sequential monitoring boundary, indicating insufficient evidence to support a robust conclusion (Figure 1, Supplemental Digital Content 4, http://links.lww.com/MD/H235).

In respect of hospital stay, forest plot on 4 available trials[16,18–20] (n = 804) demonstrated a shorter LOS in the lidocaine group compared with that in the placebo group (MD: −0.37 days, 95% CI: −0.71 to −0.03, *P* = .03; I2 = 0%) (Fig. 5B). Sensitivity analysis indicated an inconsistent finding when some studies were excluded 1 at each time,[16,17,19] implicating weakness of evidence for this outcome. Failure of the cumulative Z-curve to cross the trial sequential monitoring and the RIS boundaries on TSA also suggested insufficient evidence to reach a sound conclusion (Figure 2, Supplemental Digital Content 5, http://links.lww.com/MD/H236).

3.4.4. Risk of in-hospital mortality. Four studies with a total of 937 patients (lidocaine group, n = 463 vs placebo group, n = 474) were available for analysis.[16–18,20] Pooled analysis showed no significant difference in risk of in-hospital mortality between the 2 groups (RR = 1.54, 95% CI: 0.45–5.34, *P* = .49; I2 = 29%) (Figure 3, Supplemental Digital Content 6, http://links.lww.com/MD/H237). Sensitivity analysis demonstrated that this outcome was not significantly impacted by omitting certain trials. TSA was not conducted due to a lack of available information (data not shown).

4. Discussion

The clinical impact of cognitive deficit after cardiac surgery cannot be overemphasized considering its high prevalence after cardiopulmonary bypass and long-lasting nature.[2] Through a systematic review of updated evidence, our results suggested a prophylactic effect of intravenous lidocaine on cognitive deficit 2 weeks after cardiac surgeries. However, this potential benefit of intravenous lidocaine did not persist through the late postoperative period (i.e., 6–10 weeks). Interestingly, a correlation between the intraoperative use of lidocaine and a reduction in length of ICU and hospital stay, which has not been previously addressed in the current literature, was also noted.

Two previous meta-analyses[21,22] focused on 5 RCTs had suggested a correlation between the use of intravenous lidocaine and a reduced risk of cognitive deficit at about postoperative 2 weeks, but not at 8 to 10 weeks. Nevertheless, a lack of validation regarding the strength of evidence because TSA was not performed as well as the small number of patients in those meta-analyses remain important concerns.[21,22] Our findings from TSA showed that the prophylactic effect of intravenous lidocaine on cognitive dysfunction remained inconclusive at an early postoperative period. Furthermore, the association became nonsignificant when 1 study reporting a circulating lidocaine concentration up to 4.78 to 7.1 μg/mL[20] was removed. The negative correlation between circulating lidocaine concentration and the risk of postoperative cognitive deficit has also been confirmed by a previous meta-analysis.[22] More studies are required to investigate whether a dose-dependent neuroprotective effect exists between intravenous lidocaine and risk of cognitive deficit. Because the therapeutic plasma concentration of lidocaine is between 1.5 and 6 μg/mL (6.4 to 25.6 μmol/L) with possible toxicity at a circulating level of >5 μg/mL,[27] an appropriate strategy to strike a balance between the potential risk and benefit may be needed.

The possible mechanisms underpinning the neuroprotective effect of lidocaine against postoperative cognitive deficit have been proposed to include the preservation of cerebral blood flow,[28] modulation of inflammatory mediators,[13,19] deceleration of ischemic ion fluxes[29,30] that involves the blockade of Na^+ channels and termination of synaptic electrical activity under normothermic conditions[31] as well as reduction in cerebral metabolism[32] through the inhibition of ion leaks (K^+ efflux and Na^+ influx) under hypothermic conditions.[31] Regarding the anti-inflammatory property of lidocaine,[13,19] previous studies have reported an important role of intraoperative brain hypoperfusion and microemboli in the development

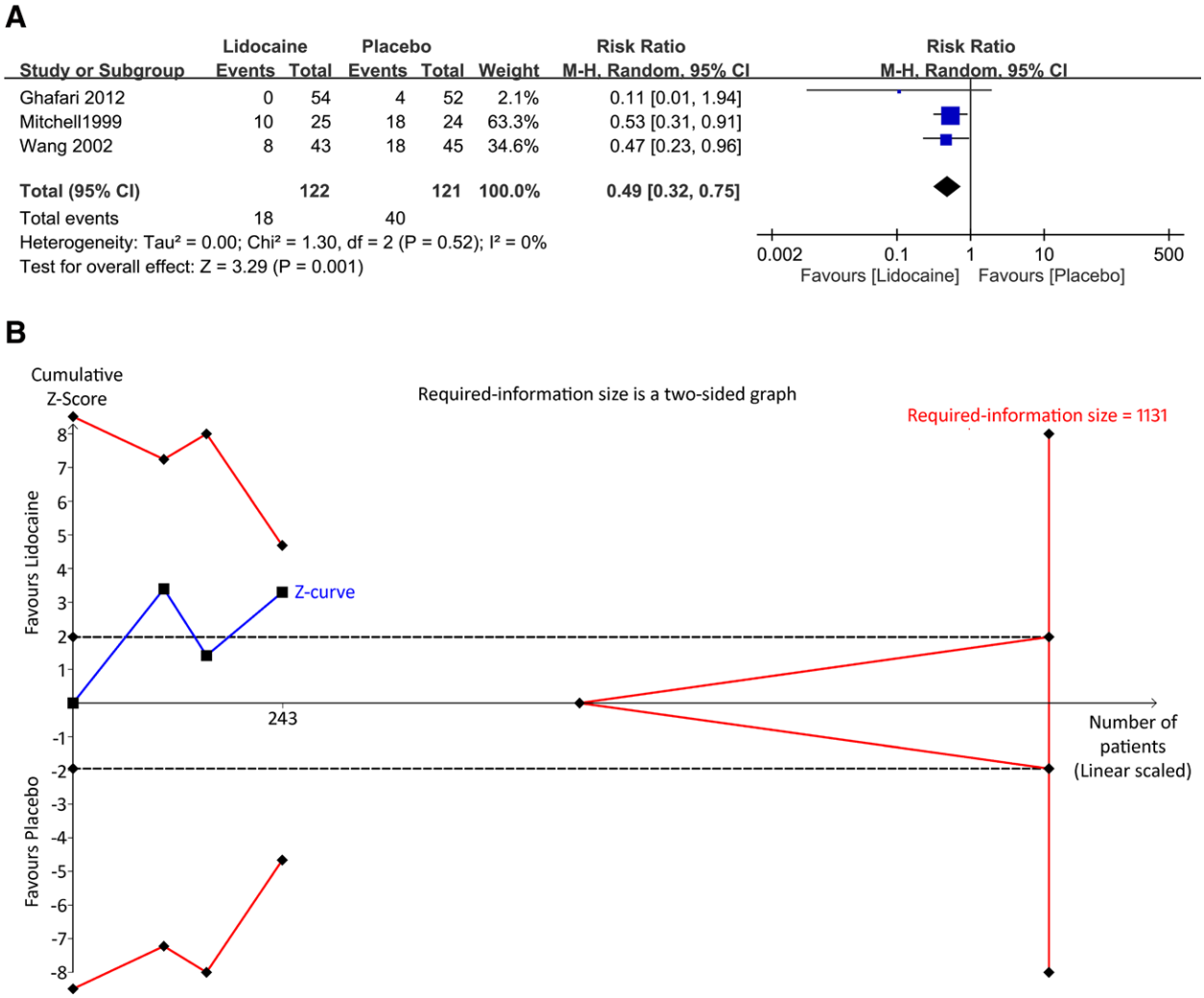

Figure 3. (A) Forest plot comparing the risk of postoperative cognitive deficit within postoperative 2 weeks between lidocaine and placebo groups. (B) Trial sequential analysis on risk of cognitive deficit within postoperative 2 weeks. Variance computed from data acquired from included trials with risk of type I error and relative risk reduction set at 5% and 20%, respectively, with a power of 80%. CI = confidence interval, M-H = Mantel-Haenszel, RR = risk ratio.

of postoperative cognitive deficit,[33,34] highlighting the impact of ischemia. Together with the results of previous experimental studies that demonstrated a significant reduction in ischemia/reperfusion-induced inflammatory response associated with the use of lidocaine,[35,36] our finding appeared to support its anti-inflammatory role in this setting. On the other hand, a previous study demonstrated no significant difference in inflammatory reaction between patients undergoing cardiac procedures with systemic lidocaine administration and those without.[37] Although that study did not investigate the cognitive functions of the recruited patients,[37] the same research team failed to show improvement in neurological outcomes among those with the same intravenous dosage of lidocaine.[37] Whether a relatively low plasma concentration of lidocaine contributed to its lack of significant impact on cognitive function in that study[16] remains unclear.

Based on sensitivity analysis and TSA involving 876 patients, the present study did not find a prophylactic effect of intravenous lidocaine against cognitive deficit during the late postoperative period (i.e., 6–10 weeks). This is supported by the finding of previous studies demonstrating a decline in the incidence of cognitive deficit after cardiac surgeries over time, with the highest rate being 30% to 70% at hospital discharge, followed by 20% to 30% 6 months after surgery and 15% to 25% at 12-month follow-up.[38,39] In addition, because old age[40,41] and diabetes[42] are also known provoking factors of cognitive deficit after cardiac surgery, the inclusion of such patients may also partially account for a blemish prophylactic effect during the late postoperative period.

Despite the lack of robustness of evidence after sensitivity and TSA, another novel finding of the current study that was not addressed in previous meta-analytical studies[21,22] was the association between the use of intravenous lidocaine and reduction in the length of hospital and ICU stay. Although the underlying mechanism remains unknown, this finding may be attributed to its cardioprotective properties. Previous clinical studies have demonstrated a lidocaine-associated reduction in myocardial injury among patients undergoing off-pump coronary artery bypass graft surgery.[43] Moreover, the addition of lidocaine to cardioplegic solution was found to be related to an improved intraoperative hemodynamic status as well as reduced circulating troponin-I concentrations in children undergoing cardiac surgery.[44] Consistently, animal experiments also showed that lidocaine could alleviate myocardial dysfunction during resuscitation from ventricular fibrillation[45] and reduce the size of myocardial infarct from ischemia–reperfusion injury.[46] In addition, previous studies have attributed its cardioprotective effects to its abilities to suppress ventricular arrhythmia by blocking the sodium fast channels[47,48] as well as inhibit the late component of the cardiac sodium channel current involved in the

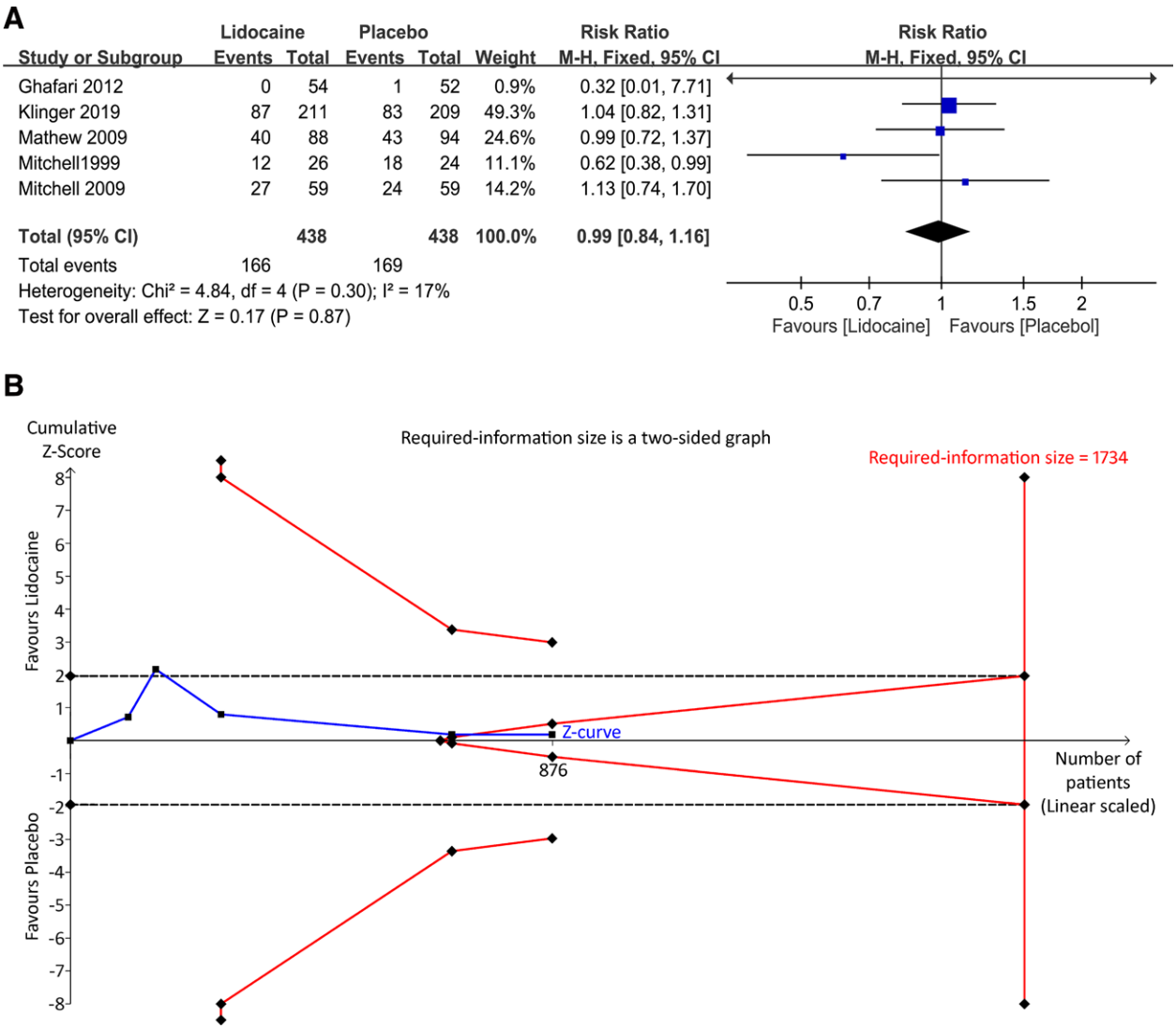

Figure 4. (A) Forest plot comparing the risk of postoperative cognitive deficit at postoperative 6–10 weeks between lidocaine and placebo groups. (B) Trial sequential analysis on risk of cognitive deficit at postoperative 6–10 weeks. Variance calculated from data of included trials after setting risk of type I error and relative risk reduction at 5% and 20%, respectively, with a power of 80%. CI = confidence interval, M-H = Mantel-Haenszel, RR = risk ratio.

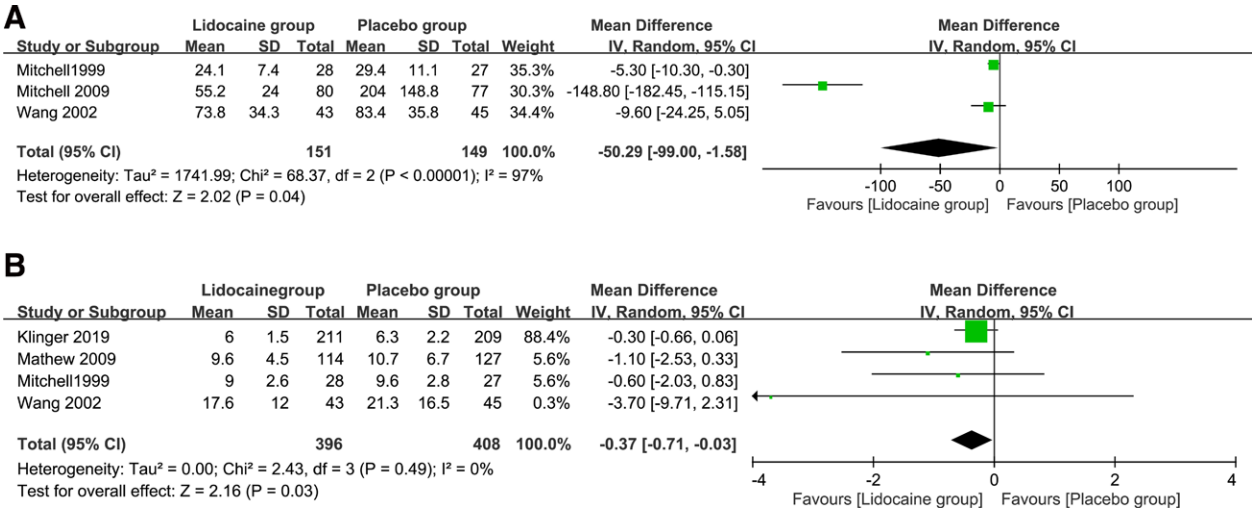

Figure 5. Forest plot comparing (A) length of intensive care unit stay, (B) length of hospital stay between lidocaine and placebo groups. CI = confidence interval, IV = inverse variance.

development of heart failure.[49] Such a sodium channel blockade also helps preserve myocardial adenosine triphosphate during ischemia and reperfusion due to the suppression of Na^+/K^+-ATPase activity and mitochondrial calcium loading.[45,50] Furthermore, lidocaine has been reported to reduce myocardial free radical generation[51] and apoptosis.[46] Those mechanisms may partly explain the association between intravenous lidocaine and a reduction in the length of hospital and ICU stay in the current meta-analysis. Further studies are needed to elucidate the therapeutic benefits of lidocaine in this clinical setting.

With regard to the potential confounders of the current study, a meta-analysis of 14 studies enrolling a total of 13,286 participants has identified aging, diabetes, mild cognitive impairment, preoperative depression, carotid artery stenosis, time of mechanical ventilation, NYHA functional class III or IV, and LOS at the ICU as the risk factors for postoperative cognitive deficit after cardiac surgery.[52] Therefore, although patients with diabetes have been reported to have an increased risk of postoperative cognitive dysfunction,[17] its impacts as well as those of other underlying diseases and perioperative factors on our study outcome remain to be elucidated.

Despite our finding of a positive impact of intravenous lidocaine on cognitive dysfunction within postoperative 2 weeks, TSA showed a weak level of evidence. Therefore, our results may suggest a need for a multimodal approach to the prevention of cognitive deficit after cardiac surgery. Taking into account the reported association between the perioperative use of dexmedetomidine or dexamethasone and a lower incidence of impaired neurological outcomes (i.e., delirium) following cardiac surgery[53] as well as the multifactorial etiology of postoperative cognitive deficit, combination of intravenous lidocaine with other pharmacological agents may be a feasible prophylactic strategy against postoperative cognitive dysfunction.

5. Limitations

The present meta-analysis had its limitations. First, the sample size of our study was relatively small because of the sparsity of RCTs on this topic. Second, a previous study has shown that a younger age, male gender, a longer cardiopulmonary bypass and a higher plasma concentration of lidocaine may be associated with a desirable therapeutic effect of lidocaine against postoperative cognitive deficit.[22] Therefore, the wide variation in gender prevalence (Table 1) and the relatively low plasma concentration of lidocaine in the majority of the included studies may bias our results. Besides, the effects of underlying diseases and other perioperative factors on postoperative cognitive deficit after cardiac surgery[17,52] on our study outcome were not investigated. Third, the risk of publication bias could not be assessed because of the small number of included studies. Fourth, variations in the definition of postoperative cognitive deficit and the lack of a standard diagnostic approach were also potential confounders. Fifth, since a previous study has demonstrated an association between cardiac valvular surgeries and postoperative cognitive dysfunction,[54,55] the inclusion of patients with and without valvular operations in the current study may bias our findings. Finally, apart from those observable parameters, the patient's physiological status and other factors including the use of different anesthetics, intraoperative hemodynamic changes, the mechanism of cerebral autoregulation, the use of neuroprotective agents, temperature, and concentrations of serum biomarkers related to cognitive function after cardiac surgery may all have a part to play in the cognitive outcome.[56] Further investigations are warranted to specifically address these issues.

6. Conclusion

The present meta-analysis demonstrated a weak association between intraoperative administration of intravenous lidocaine and a reduced risk of cognitive deficit after cardiac surgeries at early postoperative period. Intravenous lidocaine was also weakly correlated with a reduction in the length of hospital and ICU stay but had no influence on in-hospital mortality. Further studies are warranted to support our findings.

Author contributions

Conceptualization and literature search: K.-C.H and C.-N.H; Methodology: W.-C.L.; Trial selection: Y.-J.C. and Y.-T.L; Data analysis: I.-Y.H. and P.-W.H.; Data extraction: J.-Y.C. and M.Y.; Writing – original draft preparation: K.-C.H., P.-W.H. and C.-K.S; Writing – review and editing: K.-C.H, M.Y. and C.-K.S. All authors have read and agreed to the published version of the manuscript.

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