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ORIGINAL ARTICLE

Preoperative Statin Treatment for the Prevention of Acute Kidney Injury in Patients Undergoing Cardiac Surgery: A Meta-Analysis of Randomised Controlled Trials

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Background The effect of preoperative statin treatment (PST) on the risk of postoperative acute kidney injury (AKI) after cardiac surgery remains controversial. We performed a meta-analysis of randomised controlled trials (RCT) to investigate whether PST could improve the renal outcomes in patients undergoing cardiac surgery.

Methods We conducted a comprehensive search on PubMed, Embase and Cochrane Central Register of Controlled Trials. Randomised controlled trials which reported incidence of AKI and renal replacement treatment (RRT), mean change of serum creatine (SCr) and C-reactive protein (CRP), length of stay in intensive care unit (LOS-ICU) and hospital (LOS-HOS) were included.

Results A total of nine RCTs, covering 3,201 patients were included. Based on the results of our meta-analysis, PST could not reduce the incidence of AKI (risk ratio (RR) 1.12, 95% confidence interval (CI) 0.97 to 1.29, p = 0.37), and RRT (RR 1.13, 95% CI 0.45 to 2.85, p = 0.80). Furthermore, SCr was not likely to be improved by PST (weighted mean difference (WMD) 0.03, 95% CI 0.00 to 0.06, p = 0.055). However, the level of CRP (WMD -5.93, 95% CI 11.71 to 0.15, p = 0.044) in patients treated with PST was significantly lower than that of patients administered with placebo. In addition, no significant difference was observed in LOS-ICU and LOS-HOS between PST and control groups.

Conclusion Our meta-analysis suggests that PST cannot provide any benefit for improving renal complications and clinical outcomes, but may slightly reduce postoperative inflammation in patients undergoing cardiac surgery. In the future, more powerful RCTs will be needed to confirm these findings.

Keywords Statin • Acute kidney injury • Coronary artery bypass grafting • Cardiac surgery • Meta-analysis

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Introduction

In recent years, despite a dramatic decline in mortality from cardiac surgery due to surgical and perioperative care advancements, the incidence of postoperative acute kidney injury (AKI) is still up to 30% and the risk of postoperative dialysis remains high [1–3]. It is reported that AKI is independently associated with greater mortality and may promote the occurrence of postoperative arrhythmias, myocardial infarction and systemic infection [4,5]. Several interventions to prevent the AKI in patients undergoing cardiac surgery have been developed, however, none of them showed promising benefits for protecting renal function [6–8].

The mechanism of cardiac surgery related AKI is multifactorial and endothelial injury as well as systemic inflammation are recognised as critical contributors to the development of AKI [9,10]. Statins have been commonly recommended for the management of hyperlipidaemia and coronary heart disease [11]. Furthermore, in addition to lowering serum lipids, statins also have other pleiotropic effects, such as antioxidant, anti-inflammatory and immunomodulatory effects [12]. Due to these properties, statins may have the potential to attenuate the incidence of AKI in patients after cardiac surgery.

An observational study of 17,000 patients who underwent cardiac surgery, suggested that preoperative statin treatment (PST) achieved a 22% relative risk (RR) reduction in AKI [13]. A recent meta-analysis of observational studies also demonstrated that PST significantly reduced the incidence of AKI [14]. On the contrary, Kuhn et al. [15] and Argalious et al. [16] reported that PST had no impact on AKI in patients undergoing cardiac surgery. Moreover, results from a recent randomised controlled trial (RCT) indicated that AKI was more common with preoperative rosuvastatin [17]. Hence the effect of PST on the prevention of AKI remains controversial. Considering the strength of estimates from meta-analyses of observational studies was relatively weak and several large RCTs were reported recently, we performed an updated meta-analysis of RCTs to investigate whether PST could improve the renal outcomes in patients after cardiac surgery.

Methods

This meta-analysis was performed according to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines [18].

Literature Search

We performed a comprehensive, computerised literature search in PubMed, Embase and Cochrane Central Register of Controlled Trials without any restrictions from inception to June 1, 2016. The search strategy consisted of the following MeSH headings or keywords:'cardiac surgery'; 'coronary artery bypass surgery'; 'valve surgery'; 'acute kidney injury'; 'renal dysfunction'; 'renal insufficiency'; 'hydroxymethylglutaryl-CoA reductase inhibitors'; 'statin' (Supplementary Table 1). In addition; the reference lists of retrieved articles were reviewed to identify potentially relevant studies.

Study Selection

Studies which met the following criteria were included: (1) RCTs; (2) patients were assigned to receiving PST or placebo; (3) studies reported the primary endpoints including incidence of AKI and renal replacement treatment (RRT), or the secondary endpoints including mean change of serum creatine (SCr) and C-reactive protein (CRP), length of stay in intensive care unit (LOS-ICU) and LOS in hospital (LOS-HOS). Studies were excluded if they met any of the following criteria: (1) animal studies, case reports, observational studies, reviews and letters; (2) duplicate publication. Acute kidney injury was formally defined according to the AKIN [19] or RIFLE [20] criteria.

Data Extraction and Quality Assessment

Two authors independently extracted data with divergences resolved by discussion. The following data were retrieved from each included study: baseline characteristics of included studies (authors, journal, publication year, country, sample size, study design), characteristics of patients (number, average age, sex, type of cardiac surgery, medical history), treatments (statin type, dose, duration), outcomes (incidence of AKI and RRT, mean change of SCr and CRP, LOS-ICU, LOS-HOS). If several articles reported the same research, the most complete one was eligible for inclusion.

The risk of bias of included RCTs was assessed independently by two authors using a similar methodology to that of our earlier study [21,22].

Statistical Analysis

We used similar statistical methods of our previous studies with STATA 14.0 (Stata Corp, College Station, Texas) [22,23]. Heterogeneity among studies was examined using chi-square test and I^2 test with $p \leq 0.10$ or $I^2 > 50\%$ indicating significant heterogeneity. Risk ratio (RR) and 95% confidence interval (CI) were calculated for incidence of AKI and RRT with fixed effect model, if there was no significant heterogeneity. Otherwise, we used a random effect model. Weighted mean difference (WMD) and 95% CI were calculated for mean change of SCr and CRP, LOS-ICU, LOS-HOS, when there was no significant heterogeneity. Otherwise, we used a random effect model. In addition, sensitivity analysis, funnel plots and Egger's test were performed to assess the stability of estimates and publication bias respectively. A two-tailed p value < 0.05 was considered significant.

Results

Study Characteristics

The process of literature selection and reasons for exclusion are described in Figure 1. A total of 2,670 articles were obtained through database search. After removal of duplicates and initial screening, 48 articles were included for full

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