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Review Article

Does methylprednisolone show benefits in patients undergoing cardiopulmonary bypass? A meta-analysis

Weidong Zhang[1], Zhongchun Ge[1], Yulong Tian[1], Yuliang Xing[1], Yan Sun[1], Jie Ying[2]

Departments of [1]Cardiology, [2]Infectious Diseases, People's Hospital of Xuyi, Xuyi 211700, Jiangsu, P. R. China

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Abstract: Many trials reported methylprednisolone in patients undergoing cardiopulmonary bypass. The use of methylprednisolone in cardiopulmonary bypass is controversial. The aim is to solve controversial problem and summarize clinical benefit of methylprednisolone in patients undergoing cardiopulmonary bypass. The randomized controlled trials were searched from PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and Web of Science without date or language restrictions (last search was updated on March, 2016). We used the method which was recommended by the Cochrane Collaboration to perform a meta-analysis of randomized controlled trials. The results of meta-analyses showed that there were no statistical differences in mortality [OR, 0.86, 95% CI (0.69-1.04), I^2 = 0%, *P* = 0. 68] and infection [OR, 0.93, 95% CI (0.82-1.07), I^2 = 0%, *P* = 0.88] and between methylprednisolone group and placebo group. In conclusion, the present restricted evidence indicates that methylprednisolone show no beneficial impact of patients undergoing cardiopulmonary bypass. Well-design multicenter randomized controlled trials are required to prove this conclusion.

Keywords: Methylprednisolone, cardiopulmonary bypass, meta-analysis, randomized controlled trials

Introduction

Cardiopulmonary bypass (CPB), exposing outer surfaces of the body as well as non physiologic blood flow, is apply to most procedures. A systemic inflammatory response syndrome is initiated by CPB, which is related to adverse clinical outcomes [1-3]. Inflammatory responses contain the activation of platelets, neutrophils, monocytes, macrophages, and a cascade of activation (coagulation, fibrinolytic, and the release of the peptide), leading to the increased permeability of endothelial cells as well as blood vessels and parenchyma damage [1, 4-9]. This kind of inflammation may cause postoperative complications which includes heart failure as well as multiple organ function failure.

A review showed that steroids treatment in patients undergoing CPB are safe and show benefits in postoperative hemodynamics, ventilation, and atrial arrhythmias [10]. In addition, a meta-analysis showed that perioperative steroid therapy may reduce postoperative bleeding as well as curtail the duration of ICU and hospital stay [11]. Another meta-analysis suggests that low-dose corticosteroid and high-dose corticosteroid are contributed equally to decrease the risk of atrial fibrillation but they have fewer potential fewer adverse effects in adult cardiac surgery [12]. However, there is no any current systematic review or meta-analysis which only summarizes clinical benefit of methylprednisolone use in patients undergoing CPB. Clinical benefit of methylprednisolone use during CPB is still unclear and surgeons are afraid of some potential adverse effects associated with methylprednisolone use. Does methylprednisolone show benefits in patients undergoing cardiopulmonary bypass? It is still a controversial problem.

In order to provide surgeons or patients with systematic, comprehensive, synthesised and disseminated information, we did a meta-analysis to summarize clinical benefit of methylprednisolone use during CPB.

Material and methods

Publication search

Our systematic review followed the PRISMA guidelines [13]. The authors searched the

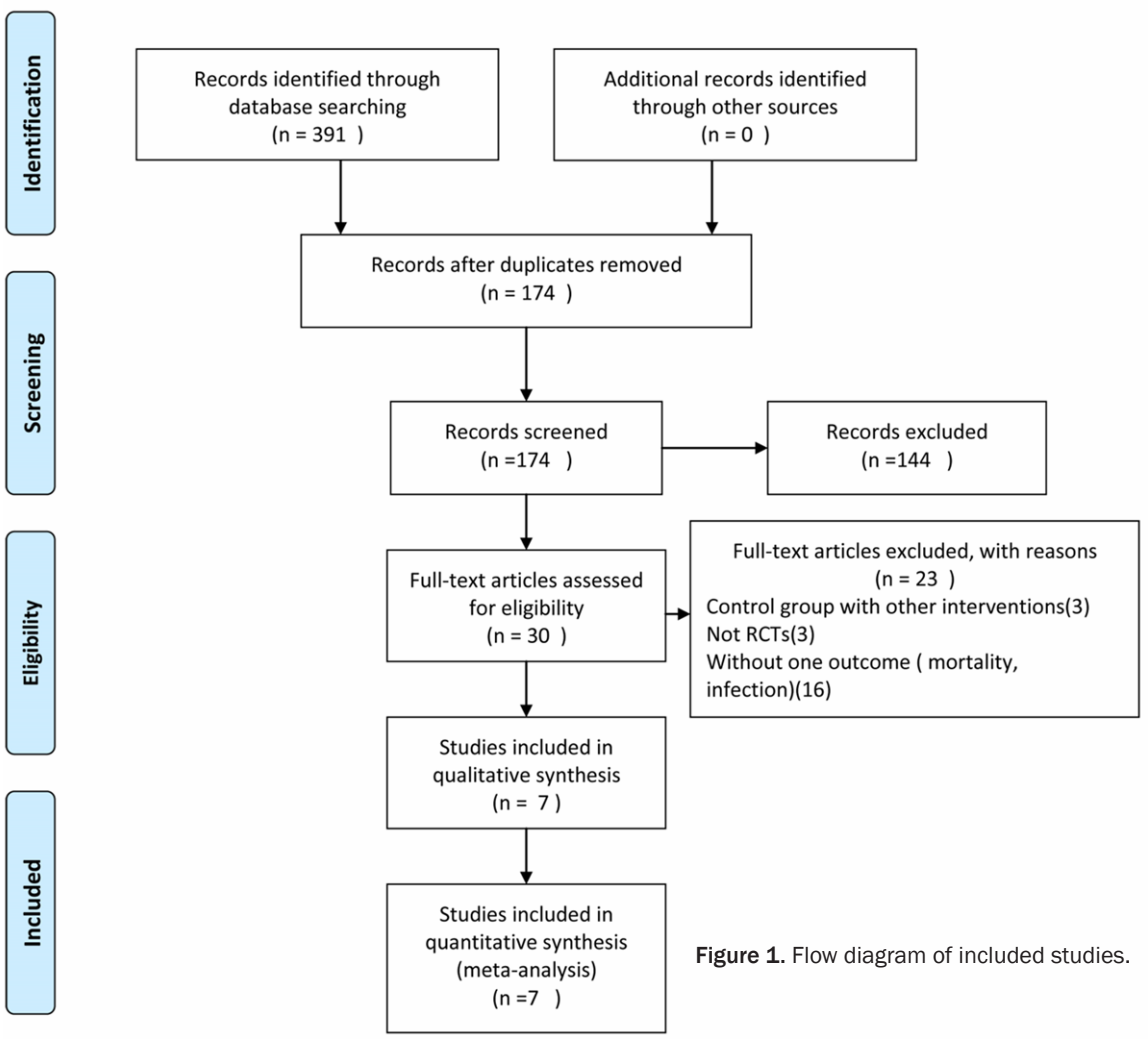

Figure 1. Flow diagram of included studies.

PubMed, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and Web of Science databases for relevant articles without date or language restrictions (last search was updated on March, 2016). Search terms were as follows: "Heart-Lung Bypass", "Bypass, Heart-Lung", "Bypasses, Heart-Lung", "Heart Lung Bypass", "Heart-Lung Bypasses", "Bypass, Cardiopulmonary", "Bypasses, Cardiopulmonary", "Cardiopulmonary Bypasses", "Metipred", "6-Methylprednisolone", "6 Methylprednisolone", "Urbason" and "Medrol". The searches were confined to human subjects and randomized controlled trials. Besides, we searched other potential eligible trials by checking the reference lists of identified studies and relevant reviews. We did this process until no additional trials could be identified. The inclusion criteria of this meta-analysis is as follows: (1) participants undergoing cardiopulmonary bypass; (2) patients were randomized grouped into methylprednisolone group (without other drugs) and placebo group (with or without placebo); (3) not less than one outcome (mortality, infection); (4) randomized controlled trials. The following studies were also excluded: (1) studies were retrospective studies, observational studies, case series, reviews and comments; (2) studies' control group with other interventions.

Data extraction

Two authors independently extracted the following data, including of characteristics of publication year, duration, setting and design, sample size, patient characteristics, methylprednisolone group (dose or follow up time), placebo group (dose or follow up time), measured out-

Table 1. Characteristic of included studies

Study (year)	N (M/P)	Age	Sex (female/male)	Intervention	Follow up
Rao 1997	150 (75/75)	NR	NR	M: methylprednisolone (1 g) P: not receive methylprednisolone	NR
Coetzer 1996	295 (165/130)	18-45 years	NR	M: methylprednisolone (30 mg/kg) P: not receive methylprednisolone	NR
Schurr 2001	50 (24/26)	M: 64 (mean year) P: 60.8 (mean year)	M: 3/21, P: 4/22	M: methylprednisolone (10 mg/kg) P: not receive Methylprednisolone	NR
Demir 2009	30 (15/15)	M: 61.66 (mean year) P: 61.66 (mean year)	M: 7/8, P: 3/12	M: methylprednisolone (1 g) P: not receive methylprednisolone	NR
Keski-Nisula 2013	40 (20/20)	Age ≤ 28 days	NR	M: methylprednisolone (30 mg/kg) P: saline (30 mg/kg)	NR
Lomivorotov 2013	44 (22/22)	M: 57.8 (mean year) P: 57.3 (mean year)	M: 6/16, P: 1/21 M: 1498/2257, P: 1472/2280	M: methylprednisolone (20 mg/kg) P: 20 mL of 0.9% Nacl	NR
Whitlock 2015	7505 (3755/3752)	M: 67.5 P: 67.3		M: methylprednisolone (500 mg) P: placebo (500 mg)	NR

Notes: M: methylprednisolone therapy group, P: placebo therapy group; NR: not report.

comes (mortality, infection). The investigators made contact with the corresponding authors to acquire and verify the data when studies had insufficient information. We would solve any disagreements by discussion.

Quality assessment

The authors assessed the risk of bias using the Cochrane risk of bias tool, including seven items: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias) and other bias [14]. All disagreements of this process were solved by discussion.

Statistical analysis

The statistical analysis was performed by Review Manager 5.3 (The Nordic Cochrane Centre) and Stata13.0. The weighted mean difference (WMD) was used to compare continuous variables; odds ratio (OR) was used to compare dichotomous variables. The results of meta-analysis were reported with 95% confidence intervals (CIs). The impact of study heterogeneity on the results of the meta-analysis was assessed by I-square (I^2) test. The random effect models were used when significant heterogeneity was present at I^2>50%; otherwise, the fixed effect models were selected [14]. The sensitivity analyses were performed by deleting each study individually to assess the quality and consistency of the results. Both Egger's test and Begg's test were used to examine publication bias.

Results

There were a total of 391 studies were identified by the initial database search. One hundred and seventy-four duplicate studies were excluded, and 144 studies were excluded on the basis of the titles and abstracts. There were 30 of full-text articles assessed for eligibility. Finally, a total of 7 randomized controlled trials [15-21] were included in quantitative synthesis (meta-analysis). The selection process of this meta-analysis is shown in **Figure 1**. The characteristics of the extracted data from each study are summarized in **Table 1**. The risk of bias of 7 studies is shown in **Figure 2**. The risk of bias summary is shown in **Figure 3**. There are two high quality trials. The quality of 5 trails is moderate.

Five trials [15, 16, 19-21] reported the mortality of patients. The result of meta-analysis showed that there were no statistical differences in mortality [OR, 0.86, 95% CI (0.69-1.04), I^2 = 0%, P = 0. 68] (**Figure 4**) between methylprednisolone group and placebo group. Moreover, only three trials [17, 18, 21] reported numbers of infection. The result of meta-analysis showed that there were no statistical differ-

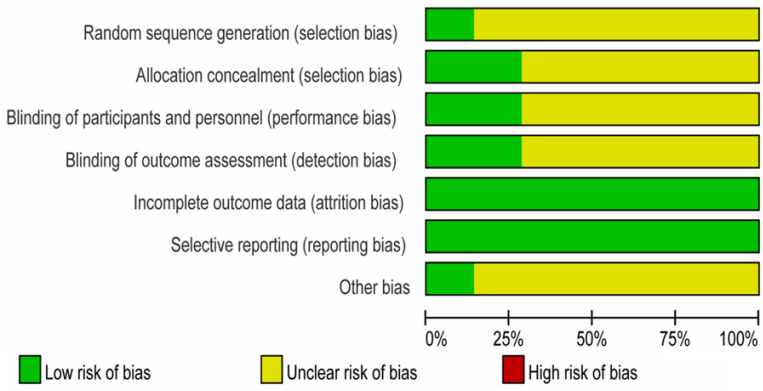

Figure 2. Risk of bias graph.

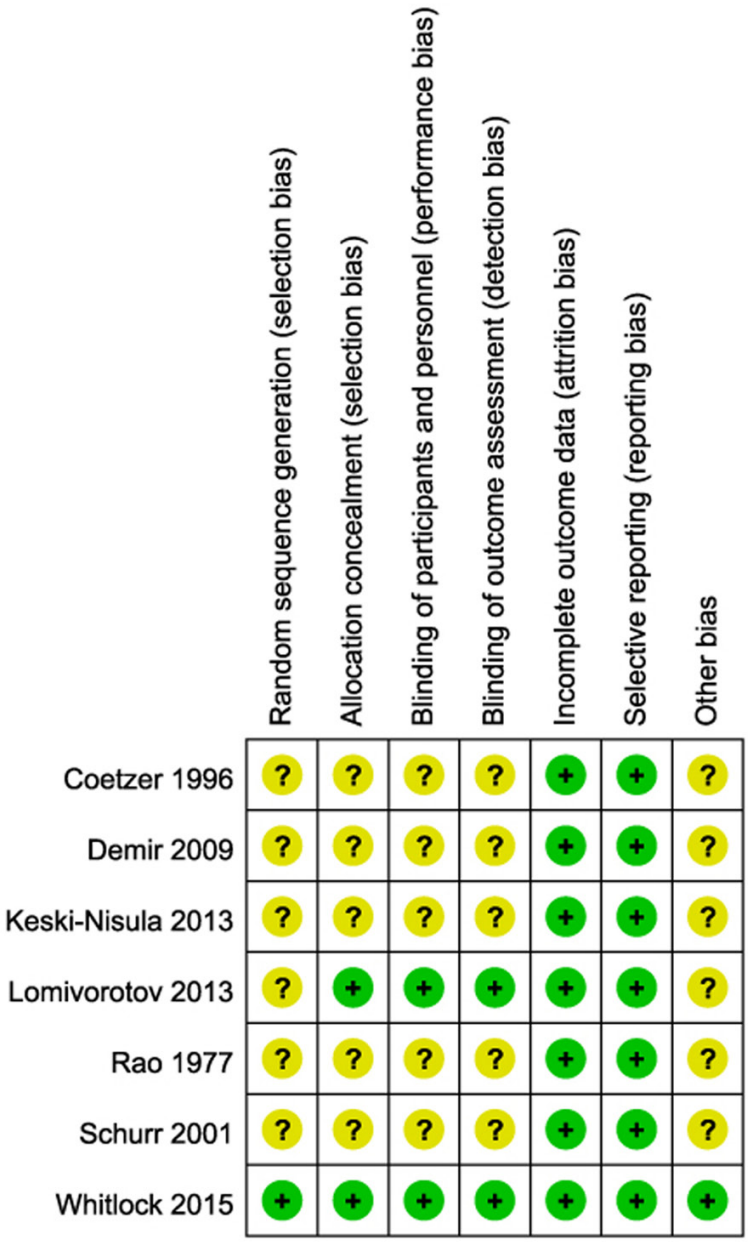

Figure 3. Risk of bias summary.

ences in infection [OR, 0.93, 95% CI (0.82-1.07), I^2 = 0%, *P* = 0.88] (**Figure 5**). The random effect models were chosen because of I^2 = 0%, which showed homogeneity among studies. Sensitivity analysis indicated that there was no an individual study affected the aggregate result. This meta-analysis only included seven studies, and Egger's test and Begg's test were difficult to exam publication bias in such a small number studies. Thus, we did not exam publication bias.

Discussion

This is the first meta-analysis of randomized controlled trials to efficacy and safety of methylprednisolonein patients undergoing cardiopulmonary bypass. The main finding is that methylprednisolone did not significantly decrease the incidence of death and infection.

Whitlock et al. [21] showed that methylprednisolone did not show marked influence on mortality or major morbidity in patients undergoing cardiopulmonary bypass and should be as the routine use for patients undergoing cardiopulmonary bypass. Although this is a well-design multicenter randomized controlled trial, single study is lack of reliability in patients undergoingcardiopulmonarybypass.Nevertheless, we considered that to combine data would provide a more clinically useful result than a single study. A meta-analysis suggests that perioperative steroid treatment may decrease postoperative bleeding and shorten the duration

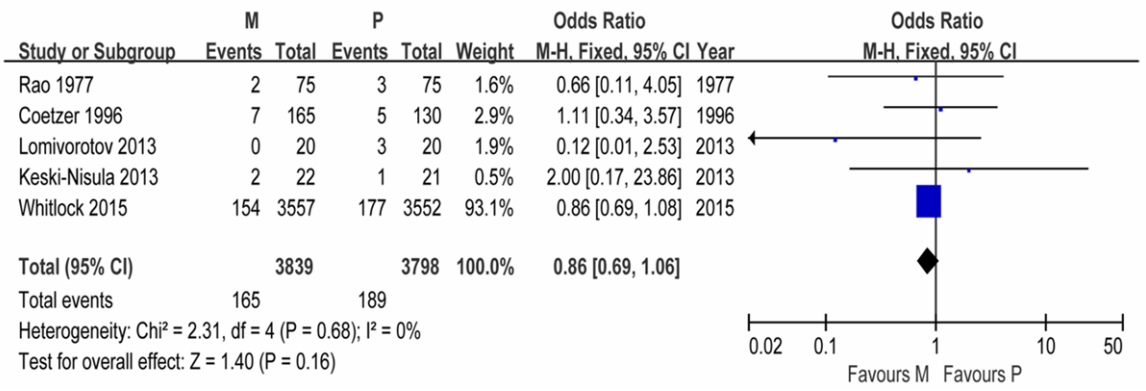

Figure 4. Odds ratio (OR) 95% CI (confidence interval) in mortality between methylprednisolone group and placebo group. Notes: M: methylprednisolone group, P: placebo group.

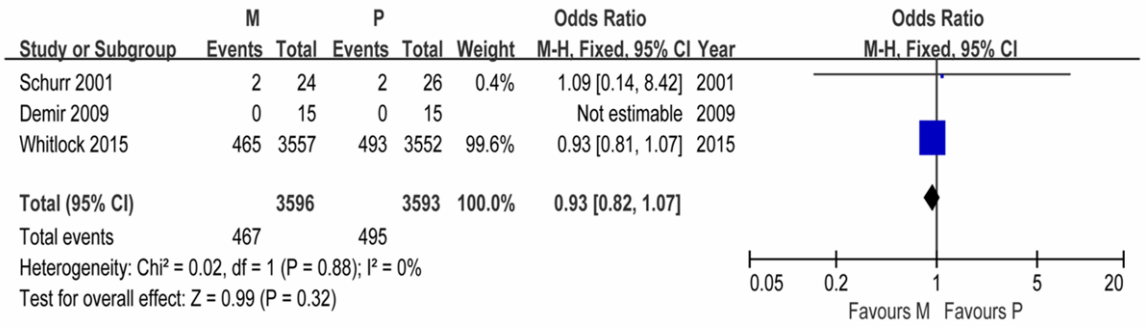

Figure 5. Odds ratio (OR) 95% CI (confidence interval) in infection between methylprednisolone group and placebo-group. Notes: M: methylprednisolone grou

of ICU and hospital stay as well as have a trend towards reduced risk of death in patients [11]. However, this meta-analysis only summarized clinical benefits of steroid in patients undergoing cardiopulmonary bypass and did not summarize clinical benefits of methylprednisolone in patients undergoing cardiopulmonary bypass. We believe that this study is the most comprehensive meta-analysis so far for use of methylprednisolone in patients undergoing cardiopulmonary bypass, including 7691 patients.

However, our meta-analysis has some limitations. Firstly, this meta-analysis was on the basis of 7 published randomized controlled trials. Many unpublished studies were not searched; there a relatively small number of available trials which result in a potential restriction for any meta-analysis. The lack of gray literature resulted in another restriction. There is only one trial [21] which has large sample size, but other six trials [15-20] are small sample size. Hence, this meta-analysis still cannot define the long-range efficacy and safety of methylprednisolone in patients undergoing cardiopulmonary bypass. If the blinding method of the 7 included trials had not been well performed, it might lead to a higher performance bias.

In conclusion, the present restricted evidence indicates that methylprednisolone shows no beneficial impact of patients undergoing cardiopulmonary bypass, so methylprednisolone should not be recommended for clinical application. Randomized controlled trials which are well-design multicenter are required to prove the main finding.

Disclosure of conflict of interest

None.

Address correspondence to: Jie Ying, Department of Infectious Diseases, People's Hospital of Xuyi, No. 28 Hongwu Avenue, Xuyi 211700, Jiangsu Prov-

ince, P. R. China. Tel: +86-0517-80811552; Fax: +86-0517-80811552; E-mail: jying8611@yeah.net

References

[1] Chaney MA. Corticosteroids and cardiopulmonary bypass: a review of clinical investigations. Chest 2002; 121: 921-931.

[2] Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, Das SR, de Ferranti S, Despres JP, Fullerton HJ, Howard VJ, Huffman MD, Isasi CR, Jimenez MC, Judd SE, Kissela BM, Lichtman JH, Lisabeth LD, Liu S, Mackey RH, Magid DJ, McGuire DK, Mohler ER 3rd, Moy CS, Muntner P, Mussolino ME, Nasir K, Neumar RW, Nichol G, Palaniappan L, Pandey DK, Reeves MJ, Rodriguez CJ, Rosamond W, Sorlie PD, Stein J, Towfighi A, Turan TN, Virani SS, Woo D, Yeh RW and Turner MB. Heart Disease and Stroke Statistics-2016 Update: A Report From the American Heart Association. Circulation 2016; 133: e38-60.

[3] Paparella D, Yau TM and Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. Eur J Cardiothorac Surg 2002; 21: 232-244.

[4] Asimakopoulos G, Smith PL, Ratnatunga CP and Taylor KM. Lung injury and acute respiratory distress syndrome after cardiopulmonary bypass. Ann Thorac Surg 1999; 68: 1107-1115.

[5] Boyle EM Jr, Pohlman TH, Johnson MC and Verrier ED. Endothelial cell injury in cardiovascular surgery: the systemic inflammatory response. Ann Thorac Surg 1997; 63: 277-284.

[6] Mojcik CF and Levy JH. Aprotinin and the systemic inflammatory response after cardiopulmonary bypass. Ann Thorac Surg 2001; 71: 745-754.

[7] Kirklin JK and McGiffin DC. Early complications following cardiac surgery. Cardiovasc Clin 1987; 17: 321-343.

[8] Teoh KH, Bradley CA, Gauldie J and Burrows H. Steroid inhibition of cytokine-mediated vasodilation after warm heart surgery. Circulation 1995; 92: II347-53.

[9] Vincent JL, Wan S and Yim AP. Steroids in cardiopulmonary bypass. Crit Care Med 2000; 28: 3373-3374.

[10] Whitlock RP, Rubens FD, Young E and Teoh KH. Pro: Steroids should be used for cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2005; 19: 250-254.

[11] Whitlock RP, Chan S, Devereaux PJ, Sun J, Rubens FD, Thorlund K and Teoh KH. Clinical benefit of steroid use in patients undergoing cardiopulmonary bypass: a meta-analysis of randomized trials. Eur Heart J 2008; 29: 2592-2600.

[12] Ho KM and Tan JA. Benefits and risks of corticosteroid prophylaxis in adult cardiac surgery: a dose-response meta-analysis. Circulation 2009; 119: 1853-1866.

[13] Moher D, Liberati A, Tetzlaff J and Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336-341.

[14] In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011. Available from www.cochrane-handbook.org.

[15] Rao G, King J, Ford W and King G. The effects of methylprednisolone on the complications of coronary artery surgery. Vasc Surg 1977; 11: 1-7.

[16] Coetzer M, Coetzee A and Rossouw G. The effect of methylprednisolone, given prior to cardiopulmonary bypass, on indices of gas exchange. Cardiovascular Journal of Southern Africa 1996; 86: C188-C192.

[17] Schurr UP, Zünd G, Hoerstrup SP, Grünenfelder J, Maly FE, Vogt PR and Turina MI. Preoperative administration of steroids: Influence on adhesion molecules and cytokines after cardiopulmonary bypass. Ann Thorac Surg 2001; 72: 1316-1320.

[18] Demir T, Demir H, Tansel T, Kalko Y, Tireli E, Dayioglu E, Barlas S and Onursal E. Influence of methylprednisolone on levels of neuron-specific enolase in cardiac surgery: a corticosteroid derivative to decrease possible neuronal damage. J Card Surg 2009; 24: 397-403.

[19] Keski-Nisula J, Pesonen E, Olkkola KT, Peltola K, Neuvonen PJ, Tuominen N, Sairanen H, Andersson S and Suominen PK. Methylprednisolone in neonatal cardiac surgery: reduced inflammation without improved clinical outcome. Ann Thorac Surg 2013; 95: 2126-2132.

[20] Lomivorotov VV, Efremov SM, Kalinichenko AP, Kornilov IA, Knazkova LG, Chernyavskiy AM, Lomivorotov VN and Karaskov AM. Methylprednisolone use is associated with endothelial cell activation following cardiac surgery. Heart Lung Circ 2013; 22: 25-30.

[21] Whitlock RP, Devereaux PJ, Teoh KH, Lamy A, Vincent J, Pogue J, Paparella D, Sessler DI, Karthikeyan G, Villar JC, Zuo Y, Avezum Á, Quantz M, Tagarakis GI, Shah PJ, Abbasi SH, Zheng H, Pettit S, Chrolavicius S and Yusuf S. Methylprednisolone in patients undergoing cardiopulmonary bypass (SIRS): A randomised, double-blind, placebo-controlled trial. Lancet 2015; 386: 1243-1253.