Review Article
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The efficacy of methylprednisolone treatment in inflammatory response during cardiopulmonary bypass: a systematic review

Abstract

Background: Due to the conflicting results about beneficial effects of methylprednisolone administration on inflammatory response following cardiopulmonary bypass (CPB), this research is aim at evaluate the efficacy of methylprednisolone treatment in inflammatory response during CPB.

Methods: Databases, including PubMed, EMBASE, Cochrane Central and Web of Science, were searched for relevant studies up to April 1, 2016 without language restriction. Randomized controlled trials about the efficacy of methylprednisolone treatment in inflammatory response during CPB were included in this systematic review.

Results: The descriptive analysis showed that methylprednisolone can reduce TNF-α, IL-6, and IL-8 release.

Conclusion: Methylprednisolone is beneficial to reduce the inflammatory response during the CPB. Randomized controlled trials which have high methodological quality are needed to confirm this conclusion.

Keywords: methylprednisolone, inflammatory response, cardiopulmonary bypass, systematic review, randomized controlled trials

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Hong Yan Sun, Lian Liu, Fan Li, Siping Yu, Qiu Xia Liu, Xiao Ling Yang
Nursing School, Southwest Medical University, China

Correspondence: Hong Yan Sun, Nursing School, Southwest Medical University, Luzhou, Si chuan, No. 3, 319 section of Zhong Shan Road, Jiangyang District, Luzhou 646000, China, Email sunhongyan234@163.com

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Introduction

Cardiopulmonary bypass (CPB) a complicated pathophysiology environment, exposures to nonphysiologic surfaces in the pump circuit, hemolysis, and ischemia-reperfusion injury combine to originate a complicated cascade which includes proinflammatory cytokines, anti-inflammatory cytokines, and products of neutrophil activation.[1] The systemic inflammatory response to CPB is launched by touching blood with the extracorporeal circuit, ischemia-reperfusion injury, surgical trauma, and release of endotoxin.[2] The cytokines, including interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-α (TNF-α), are involved in the induction of the inflammatory response in patients undergoing cardiac surgery.[3] Corticosteroids are generally used in patients undergoing CPB attenuate systemic inflammatory response. However, a large retrospective observational analysis showed that corticosteroids may aggrandize morbidity; particularly in lower-risk pediatric cardiac surgery patients.[4] Beneficial effects of methylprednisolone administration on inflammatory response following CPB always have produced conflicting results. Minority of evidence hitherto could state clearly the inflammatory response to methylprednisolone treatment in patients undergoing CPB. Therefore, we did a systematic review to evaluate efficacy of methylprednisolone treatment in inflammatory response during CPB.

Methods

Search strategy and selection criteria

Four electronic databases were searched for articles published up to April 1, 2016 without language restriction, containing Pub Med, EMBASE, Cochrane Central and Web of Science. The search terms used are presented as follows: [‘heart-lung bypass’ OR ‘bypass, heart-lung’ OR ‘bypasses, heart-lung’ OR ‘heart lung bypass’ OR ‘heart-lung bypasses’ OR ‘bypass, cardiopulmonary’ OR ‘bypasses, cardiopulmonary’ OR ‘cardiopulmonary bypasses’] AND [‘metipred’ OR ‘6-methylprednisolone’ OR ‘6 methylprednisolone’ OR ‘urbason’ OR ‘medrol’] AND [‘random’ OR ‘randomized controlled trial’]. The reference lists of relevant reviews were also hand searched to identify additional studies. We included studies according to the following inclusion criteria:

A. Participants undergoing cardiopulmonary bypass;

B. Patients were randomized grouped into the methylprednisolone group (without other drug) and the placebo group (with or without placebo);

C. Not less than one outcome ((tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10));

D. Randomized controlled trials. The articles which were retrospective studies, observational studies, case series, reviews, comments, duplicate published articles, and studies without original data were also eliminated.

Data extraction

Two authors independently collected on the following data: the first author, publication year, sample size, study design, patient characteristics, the methylprednisolone group (dosage, duration), the placebo group (dosage, duration), and measured outcome (tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10)).We made a detailed discussion when disagreements of this process occurred.

Quality assessment

The risk of bias was assessed by two authors independently using the Cochrane risk of bias tools, containing six items: selection bias, performance bias, detection bias, attrition bias, reporting bias, other bias[5] In addition, we adopted the Jadad scale to assess quality of included studies. The Jadad scale which is constantly used to assess the quality of randomized controlled trials is a 5-point scale, including three items: the generation of random grouping method, double blind, and reasons for withdrawals and dropouts. Five points is the maximum score; the studies with 0-2 points belong to low quality, and the studies with 3-5 points belong to high quality.

Data synthesis

We did not do a meta-analysis because of greater heterogeneity and without suitable data. Hence, we adopted a descriptive analysis instead of meta-analysis.

Results

The initial search identified 406 records, but this systematic review only included 6 trials[6–11] by the inclusion criteria and exclusion criteria as shown in Figure 1. Patient characteristics and Jadad scale were summarized in Table 1 the risk of bias as noted in Table 2. The quality of the studies was various; the majority was poor quality studies, and there were only 2 high quality trials.[10,11] Two trials 7, 8 reported levels of TNF-α. Ayda et al.[7] showed that levels of TNF-α ($p<0.05$) at 24 hours after CPB were significantly greater in the placebo group than in the methylprednisolone group. In addition, Jale Bengi et al.[8] showed that levels of TNF-α ($p<0.05$) at 24 hours after CPB were significantly greater in the placebo group than in the methylprednisolone group. Only one trial 7 reported levels of IL-1β at 24 hours after CPB, but there was no statistically significant difference between the methylprednisolone group and the placebo group. Six studies[6–11] reported levels of IL-6. Four trials[6–9] indicated that levels of IL-6 at 24 hours after CPB were significantly greater in the placebo group than in the methylprednisolone group. However, Keski Nisula et al.,[11] showed that no significant differences were found in the IL-6. Three trials 6-8 reported levels of IL-8. Yilmaz et al.,[6] showed that levels of IL-8 at 24 hours after CPB were no statistically significant difference between the methylprednisolone group and the placebo group. Ayda et al.,[7] showed levels of IL-8 ($p<0.05$) at 24 hours after CPB were significantly greater in the placebo group than in the methylprednisolone group. Jale Bengi et al.,[8] showed that levels of IL-8 ($p<0.05$) at 24 hours after CPB were significantly greater in the placebo group than in the methylprednisolone group. Four trials 8-11 reported levels of IL-10. Jale Bengi et al.[8] ($p<0.05$) and Vladimir et al.,[10] ($p<0.05$) showed that levels of IL-10 were significantly greater in the methylprednisolone group than in the placebo group, but Demir et al.,[9] and Keski-Nisula et al.,[11] showed that there was no statistically significant difference between the methylprednisolone group and the placebo group. According to the overall analysis, methylprednisolone can reduce TNF-α, IL-6, and IL-8 release. However, we did not know whether methylprednisolone can reduce IL-1β release or increase IL-10 release.

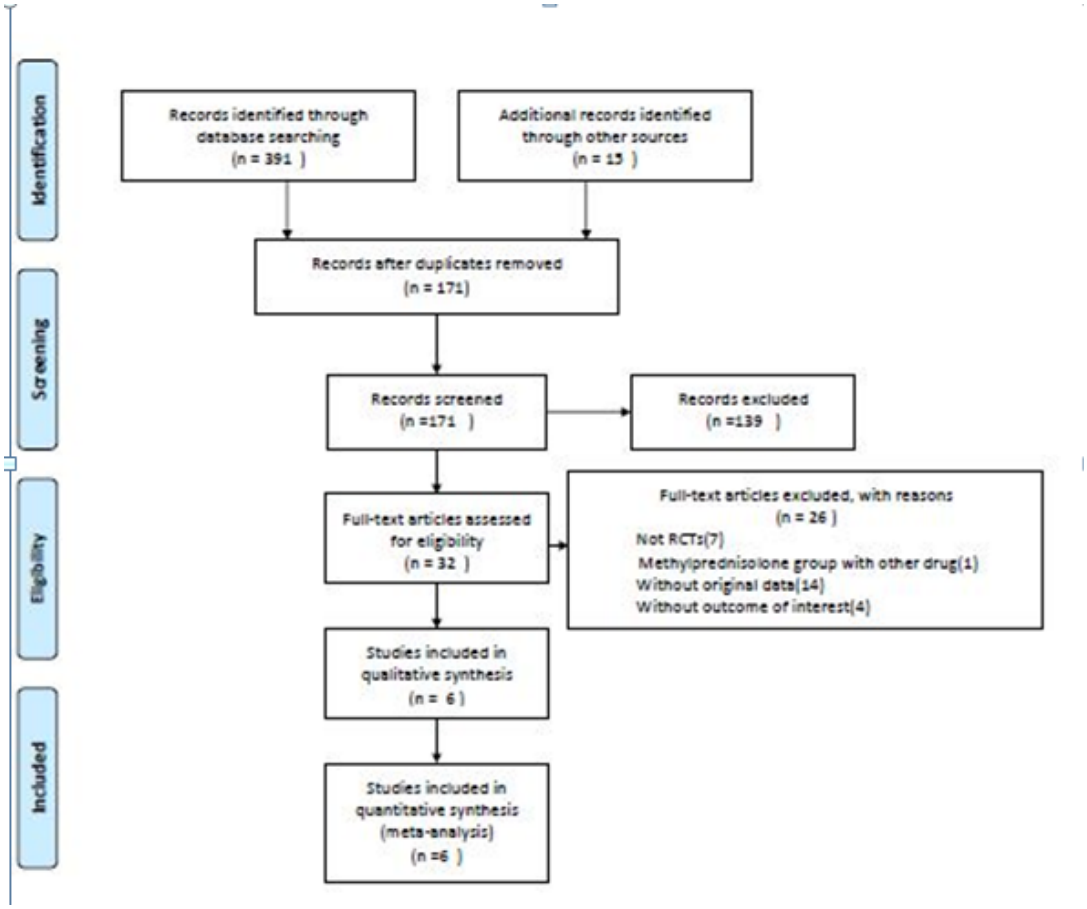

Figure 1 Flow diagram of included studies.

Table 1 Patient characteristics and Jadad score

Study (Year)	N(M/P)	Age	Sex (Male/ Female)	Intervention	Follow up time	Jadad score
Yilmaz 1999	20(10/10)	M:49.6* P:55.1*	M:8/2 P:8/2	M: methylprednisolone(1mg/kg) P: placebo(1mg/kg)	NR	2
Ayda 2001	20(10/10)	M:58.3* P:63.8*	M:8/2 P:9/1	M: methylprednisolone(30mg/kg) P: without any additional medication	NR	2
JaleBengi 2004	60(30/30)	M:60* P:62*	NR	M: methylprednisolone(30mg/kg) P: normal saline(30mg/kg)	NR	2
Demir 2009	30(15/15)	M:61.66* P:61.66*	M:8/7 P:12/3	M:methylprednisolone(1mg) P: without any additional medication	NR	1
Lomivorotov 2013	44(22/22)	M:57.8* P:57.3*	M:16/6 P:21/1	M: methylprednisolone(20mg/kg) P: 20mL of 0.9%Nacl	NR	3
Keski-Nisula 2015	45(30/15)	NR	NR	M:methylprednisolone (30mg/kg) P: placebo(30mg/kg)	NR	3

Notes: M: methylprednisolone group; P: placebo group; NR: Not report*: mean year.

Table 2 The risk of bias of included studies

Study(Year)	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias
Yilmaz 1999	High	Unclear	Unclear	Low	Unclear	Unclear
Ayda 2001	Unclear	Unclear	Unclear	Low	Unclear	Unclear
JaleBengi 2004	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Demir 2009	Unclear	Unclear	Unclear	Low	Unclear	Unclear
Lomivorotov 2013	Unclear	Unclear	Unclear	Low	Low	Low
Keski-Nisula 2015	Low	Low	Unclear	Low	Low	Low

Notes: High: high risk of bias; Low: low risk of bias; Unclear: unclear risk of bias.

Discussion

This systematic review showed that methylprednisolone can restrain TNF-α, IL-6, and IL-8 release. Methylprednisolone therapy may reduce the inflammatory response during the CPB. A larger RCT showed that administration of perioperative methylprednisolone in patients, who were at high risk of morbidity and mortality undergoing cardiac surgery with the use of cardiopulmonary bypass, did not reduce the risk of death, or the composite risk of death, myocardial injury, stroke, renal failure, and respiratory failure at 30 days. However, perioperative methylprednisolone in the treatment of patients at high risk of morbidity and mortality undergoing cardiac surgery with the use of cardiopulmonary bypass significant increased the risk of myocardial injury.[12] In addition, Later et al.,[13] antifibrinolytics had effects on inflammatory response, so the results of the trial were lack of reliability. There are some limitations in this systematic review, hence the reason why this systematic review could only do descriptive analysis. Most studies which were included this systematic review had poor methodological quality. These small-scale studies are not conclusive because of small sample size. Despite, another limitation was caused by lack of gray literature. This systematic review only did descriptive analysis.

Conclusion

In summary, the current limited evidence shows that methylprednisolone can reduce the inflammatory response during the CPB to a certain degree. Randomized controlled trials which are well-design and large sample size are required to confirm this conclusion.

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None.

Conflict of interest

The author declares no conflict of interest.

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