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The effect of dexmedetomidine on myocardial ischemia/reperfusion injury in patients undergoing cardiac surgery with cardiopulmonary bypass: a meta-analysis

G.-R. ZHANG[1], C.-M. PENG[2], Z.-Z. LIU[1], Y.-F. LENG[1,3]

[1]Department of First Clinical Medical College, Lanzhou University, Lanzhou, China
[2]Department of Basic Medicine, Qinghai Institute of Health Sciences, Xining, China
[3]Department of Anesthesiology, the First Hospital of Lanzhou University, Lanzhou, China

Guangru Zhang and Chenmei Peng are co-first authors

Abstract. – OBJECTIVE: The purpose of this study was to evaluate the effect of dexmedetomidine administration on myocardial ischemia/reperfusion (I/R) injury in patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).

MATERIALS AND METHODS: Online databases including PubMed, the Cochrane Library, Web of Science, Medline, and EMBASE were searched for clinical trials that investigated the application of dexmedetomidine in CPB patients prior to May 2021. A total of 17 studies involving 866 patients were included in this study.

RESULTS: The result of the meta-analysis showed that there was a significant difference in serum creatinine-kinase-MB (CK-MB) between the dexmedetomidine group and the control group at the end of the operation and 24 h after the operation. Compared to the control group, cardiac troponin I (cTn-I) concentration in the dexmedetomidine group was significantly decreased at the end of the operation, 24 h after the operation, and 48 h after the operation. There was also a significant difference between the dexmedetomidine group and the control group in the length of a patient's ICU stay.

CONCLUSIONS: Dexmedetomidine can reduce CK-MB and cTn-I concentrations and shorten the length of ICU stays for patients undergoing cardiac surgery with CPB. It can also provide myocardial protection from I/R injury.

Key Words:
Dexmedetomidine, Ischemia/reperfusion injury, Myocardial ischemia, Cardiopulmonary bypass, Meta-analysis.

Introduction

Myocardial ischemia, one of the most common complications in cardiopulmonary bypass (CPB) can lead to high patient morbidity and mortality[1]. It is therefore imperative to restore blood flow and oxygen to the ischemic myocardium in a timely manner to achieve successful clinical outcomes[2]. However, blood reperfusion may also cause myocardial ischemia/reperfusion (I/R) injury[3], resulting in cardiac dysfunction, which can include myocardial stunning, myocyte death, reperfusion arrhythmia, and microvascular dysfunction. Therefore, I/R injury may lead to more severe outcomes than those caused by the original ischaemic insult[4].

CPB, a technique used during cardiac surgery, provides oxygen and blood to the body's tissues and organs with myocardial injury and inflammation related to I/R[5]. Although CPB allows patients to undergo open-heart surgery, the technique routes the circulation away from the heart and lungs, which can lead to myocardial tissue injury[6]. It is therefore important to reduce I/R injury in order to prevent postoperative cardiac dysfunction. This can be achieved by reducing myocardial oxygen demand, including non-beating heart and lower body temperature[7]. Additionally, some pharmaceutical drugs, including dexmedetomidine, can also provide myocardial tissue protection during CPB[8]. Dexmedetomidine, a highly selective α2-adrenergic receptor agonist, can reduce the release of cytokines, inhibit the inflammatory response, and alleviate I/R injury. Thus, it exerts organ-protective effects[9]. However, the clinical effects of dexmedetomidine as protection for myocardial injury in patients undergoing cardiac surgery with CPB have not yet been examined. Therefore, we conducted a meta-analysis to evaluate the effect of dexmedetomidine on myocardial I/R injury in patients undergoing cardiac surgery with CPB.

Corresponding Author: Yufang Leng, Ph.D; e-mail: lengyf@lzu.edu.cn

Materials and Methods

Search Strategies

A comprehensive database search was performed by the two authors (Guangru Zhang and Chenmei Peng). Online databases, including PubMed, the Cochrane Library, Web of Science, Medline, and EMBASE, were searched for clinical trials that investigated the application of dexmedetomidine in CPB patients prior to May 2021. The studies were examined without language limitations imposed by an updating search. Articles were identified by using the following keywords: "dexmedetomidine", "myocardial ischemia", "reperfusion injury", "cardiac surgery", and "cardiopulmonary bypass" separately and in combination. The references of all publications and reviews were manually searched in order to identify any missing publications that were relevant to the meta-analysis.

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: (1) the original study focused on human subjects, (2) the target population comprised patients undergoing cardiovascular surgery with CPB, (3) the study reported an OR or HR with a 95% confidence interval (CI), or sufficient data were presented so that statistics could be calculated, and (4) the full text of the article was available.

The exclusion criteria were as follows: (1) the study lacked key information or usable data, (2) the articles were review articles, letters, single case reports, or conference abstracts. In cases of multiple articles from the same group that reported overlapping data, only the most comprehensive articles were included.

Quality Assessment and Data Extraction

Two authors independently reviewed the potentially eligible articles. The quality of each study was assessed using the Newcastle-Ottawa Scale (NOS)[10]. The following information was extracted from each included study: (1) basic information: first author's name, publication year, country of origin, sample size, patients' mean age, type of surgery, and gender and dose of dexmedetomidine, and (2) clinical outcomes: creatinine kinase-MB (CK-MB) concentration (recorded at the end of the operation, 24 h after the operation, and 48 h after the operation), cTn-I concentration (time on the end of operation, 24 h after operation, 48 h after operation), and the length of a patient's ICU stay.

Statistical Analysis

The statistical heterogeneity within studies was tested with the Q-test, and absence of heterogeneity across studies was identified if I^2>50%. In the absence of heterogeneity, the fixed-effects model was used. If significant heterogeneity was found (I^2<50%), it was calculated using the random-effects model. Publication bias was assessed by Egger regression and the Begg funnel plot, whereas p<0.1 indicates a statistically significant value. The sources of heterogeneity were quantitatively assessed using a meta-regression analysis. Statistical analyses were performed using STATA Version 12.0, and all p-values were two-sided.

Results

Characteristics of the Included Studies

A total of 847 articles were found through database mining and manual searches. After excluding duplicates, the data of 212 articles remained. Based on the title and abstract, 114 full-text articles were excluded; finally, 17 articles[11-27], which involved 843 patients, were included in this meta-analysis. The selection procedure is illustrated in Figure 1. The characteristics of the 16 publications, involving 843 participants, are summarised in Table I. All the included studies were retrospective studies that were published from 2013 to 2020 in English and Chinese journals, and 12 of these[11-16,18-21,25,26] were conducted in China. The NOS scores for the included studies ranged from 7-8, which indicates their high quality.

CK-MB Concentration at the End of the Operation

A total of 9 studies[11,12,15,17,19-21,23,27] reported CK-MB serum concentrations measured at the end of the operation. Between-study heterogeneity was noted (I^2=88.3%, p=0.000), and the meta-analysis was performed using a random-effects model. The result of the meta-analysis showed that there was a significant difference in the CK-MB concentration at the end of the operation (SMD=-0.72, 95% CI: -1.27, -0.17, p=0.011)

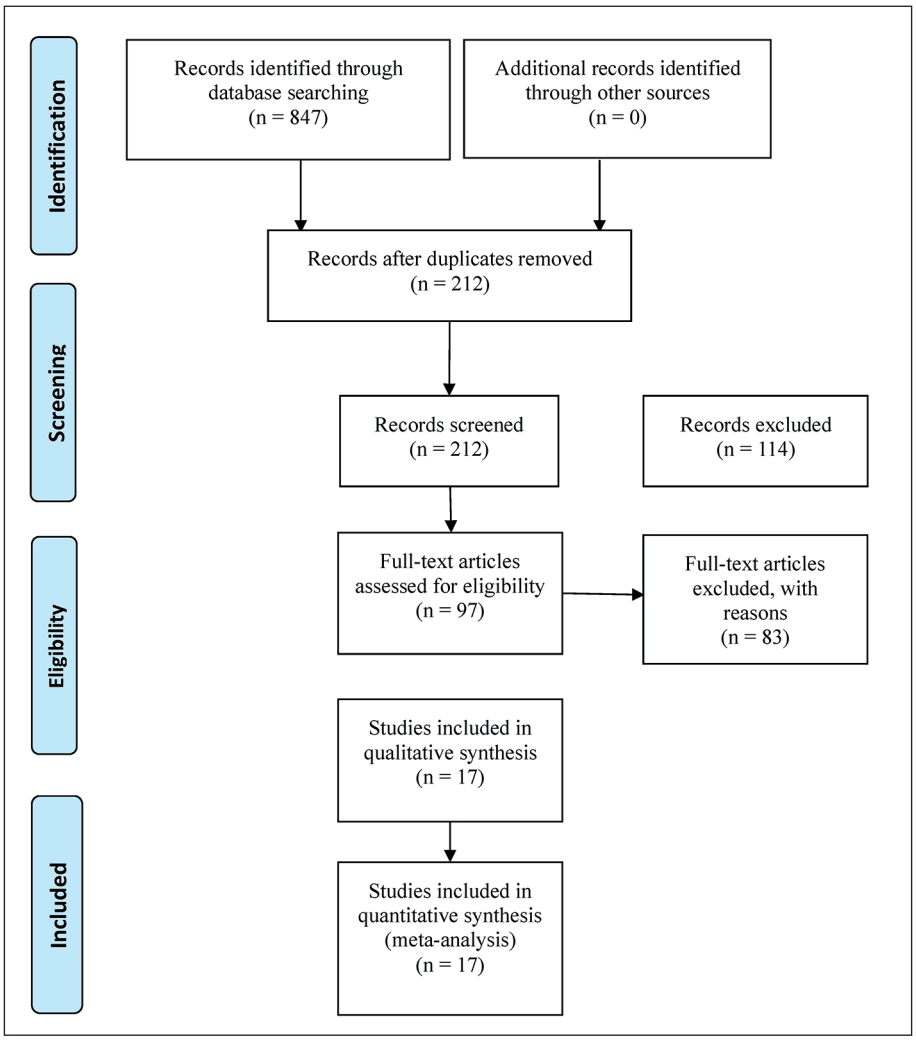

Figure 1. The flowchart of study selection process.

between the dexmedetomidine group and the control group (Figure 2).

CK-MB Concentration 24 h After the Operation

Among the included studies, 11 reported[11,12,14,15,17-21,23,27] CK-MB serum concentrations taken 24 h after the operation. Between-study heterogeneity was noted (I^2=92.8%, p=0.000), and a random-effects model was used to perform the meta-analysis. The result of the meta-analysis showed that there was a significant difference in the CK-MB concentration 24 h after the operation (SMD=-1.72, 95% CI: -2.49, -1.01, p=0.000) between the dexmedetomidine group and the control group (Figure 3).

CK-MB Concentration 48 h After the Operation

Five of the included studies[14,17,18,21,23] reported CK-MB concentrations 48 h after the operation. Between-study heterogeneity was noted (I^2=92.9%, p=0.000), and a random-effects model was used to perform the meta-analysis. The result of the meta-analysis showed that there was no significant difference in the CK-MB concentrations 48 h after the operation (SMD=-1.03, 95% CI: -2.05, -0.00, p=0.050) between the dexmedetomidine group and the control group (Figure 4).

cTn-I Concentration

Compared to the control group, the cTn-I concentration in the dexmedetomidine group was

Table I. Characteristics of included studies.

First author	Year of publication	Country	Sample size (n) Dex/Control	Age (years) Dex/Control	Type of surgery	Gender (n) F/M	Dose of dexmedetomidine
Qin et al[11]	2013	China	30/30	17-66/17-66	valve replacement surgery	36/24	0.5 μg/(kg·h)
Zhang et al[12]	2013	China	20/20	51±8/55±10	valve replacement surgery	16/24	0.5 μg/(kg·h)
Jin et al[13]	2014	China	25/23	46.7±11.3/46.2±9.6	valve replacement surgery	28/20	0.5 μg/(kg·h)
Zhang et al[14]	2014	China	20/20	51±5/52±7	valve replacement surgery	23/17	0.2 μg/(kg·h)
Zhang et al[15]	2014	China	15/15	51.6±8.5/52.1±9.7	valve replacement surgery	17/14	0.5 μg/(kg·h)
Zhao et al[16]	2014	China	30/30	50-75/50-75	CABG surgery	NA	0.5 μg/(kg·h)
Ueki et al[17]	2014	Japan	18/19	70.5±9.5/69±11.7	CABG and valve replacement surgery	21/16	0.5 μg/(kg·h)
Fu et al[18]	2015	China	20/20	48±7/45±8	valve replacement surgery	10/10	0.6 μg/(kg·h)
He et al[19]	2015	China	25/25	48.4±10.2/47.3±10.8	valve replacement surgery	13/37	0.5 μg/(kg·h)
Yuan et al[20]	2015	China	40/40	63.5±5.4/64.1±5.3	CABG surgery	67/13	0.7 μg/(kg·h)
Song et al[21]	2015	China	50/50	59±9/56±9	CABG surgery	59/41	0.5 μg/(kg·h)
Bulow et al[22]	2016	Brasil	12/11	60±6/65±8	CABG surgery	8/15	0.5 μg/(kg·h)
Ammar et al[23]	2016	Egypt	25/25	55.4±7.1/59.1±6.2	CABG and valve replacement surgery	12/38	0.5 μg/(kg·h)
Türktan et al[24]	2017	Turkey	30/30	59.83 ± 14.22/53.90 ± 15.43	CABG surgery	22/38	0.5 μg/(kg·h)
Zhou et al[25]	2019	China	14/14	57.4±9.3/58.6±8.9	valve replacement surgery	16/12	0.5 μg/(kg·h)
Wang et al[26]	2020	China	30/30	42.77±5.91/44.25±5.82	CABG and valve replacement surgery	24/36	0.5 μg/(kg·h)
Elgebaly et al[27]	2020	Egypt	30/30	58.5±7.9/57.8±8.3	CABG surgery	27/33	0.4 μg/(kg·h)

Dex dexmedetomidine, *CABG* coronary artery bypass grafting,

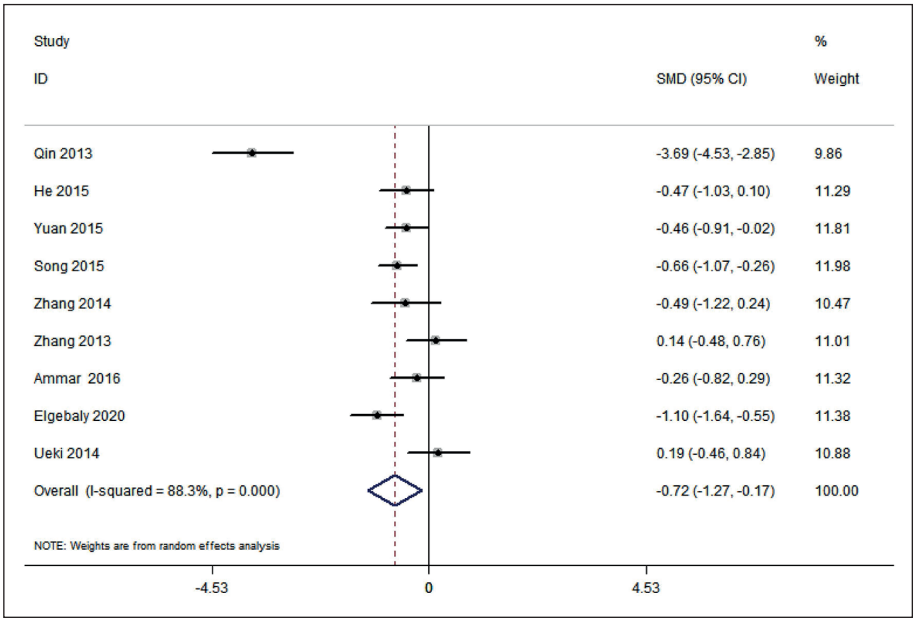

Figure 2. Meta-analysis of CK-MB concentration in the end of operation.

significantly decreased at the end of the operation (SMD=-2.12, 95% CI: -2.82, -1.43, p=0.000), 24 h after the operation (SMD=-2.12, 95% CI: -2.95, -1.30, p=0.000), and 48 h after the operation (SMD=-0.96, 95% CI: -1.18, -0.11, p=0.027). The subgroup and sensitivity analyses failed to eliminate the between-study heterogeneity, and a random-effects analysis was used for further investigation (Figure 5).

Meta-Analysis of the Length of Patient ICU Stays (in hours)

Among the studies included, eight reported[14,18,21-25,27] the length of the patient ICU stays. Between-study heterogeneity between studies was noted (I^2=87.7%, p=0.000), and a random-effects model was used to perform the meta-analysis. The result of the meta-analysis showed that there was a significant difference in the length of ICU stay (SMD=-0.84, 95% CI: -1.46, -0.21, p=0.000) between the dexmedetomidine group and the control group (Figure 6).

Discussion

Ischaemic heart disease (IHD) is one of the most serious cardiovascular diseases that can negatively affect the quality of life and survival rate of patients[28]. In developed and developing countries, the incidence rate of ischaemic heart disease is increasing[29]. As we all know, timely recovery of myocardial perfusion is the main treatment for myocardial ischemia[30]. Although reperfusion therapy after ischemia can bring about nutrients and oxygen for myocardial aerobic metabolism, it also causes more serious myocardial damage[31]. Therefore, protecting the myocardium from perfusion injury and choosing appropriate pharmaceutical drugs to avoid and prevent reperfusion injury are the goals of clinical treatment.

Cardiac surgery using CPB has been shown to cause reversible post-ischemic cardiac dysfunction and is associated with reperfusion injury and myocardial cell death[32]. Therefore, it is very important to have a series of measures in place to reduce oxygen consumption and provide myocardial protection. Dexmedetomidine has been extensively studied because it can inhibit the inflammatory response, reduce the release of cytokines, and reduce I/R injury[33]. Changes in CK-MB and cTn-I serum concentrations may provide a more precise diagnostic evaluation as to the extent of a patient's myocardial injury[34]. The results of this meta-analysis showed that the addition of dexmedetomidine can significantly reduce the levels of CK-MB and cTn-I after CPB as shown by serum measurements taken at the end of the operation, 24 h after the operation, and 48 h after the operation. It also suggested that dexmedeto-

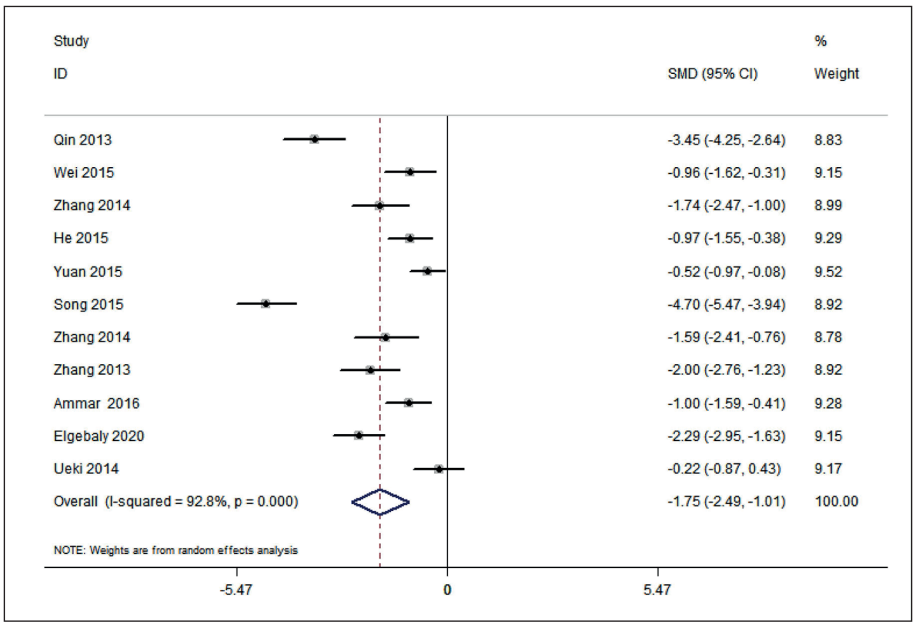

Figure 3. Meta-analysis of CK-MB concentration in 24h after operation.

midine may provide myocardial tissue protection postoperatively.

Other clinical studies[35-37] have discussed the effects of myocardial protection under CPB. Additionally, most of these studies reported that dexmedetomidine can inhibit the inflammatory response thereby providing myocardial tissue protection[36,37]. A meta-analysis conducted by Chen et al[38] reported that no significant difference was found between the two groups at the time points of CPB at the end of operation and 48 h after surgery. Alternatively, we found that cTn-I concentration in the dexmedetomidine group was significantly decreased at the end of the operation

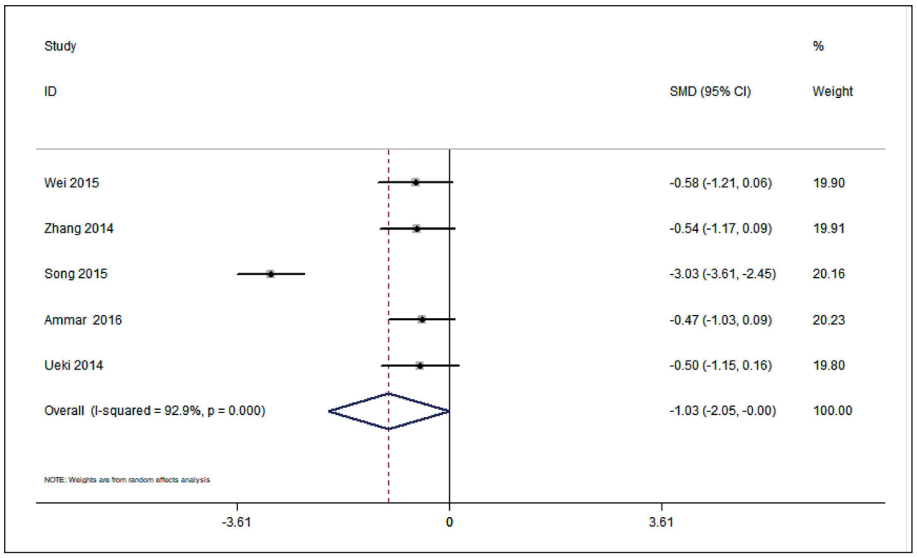

Figure 4. Meta-analysis of CK-MB concentration in 48h after operation.

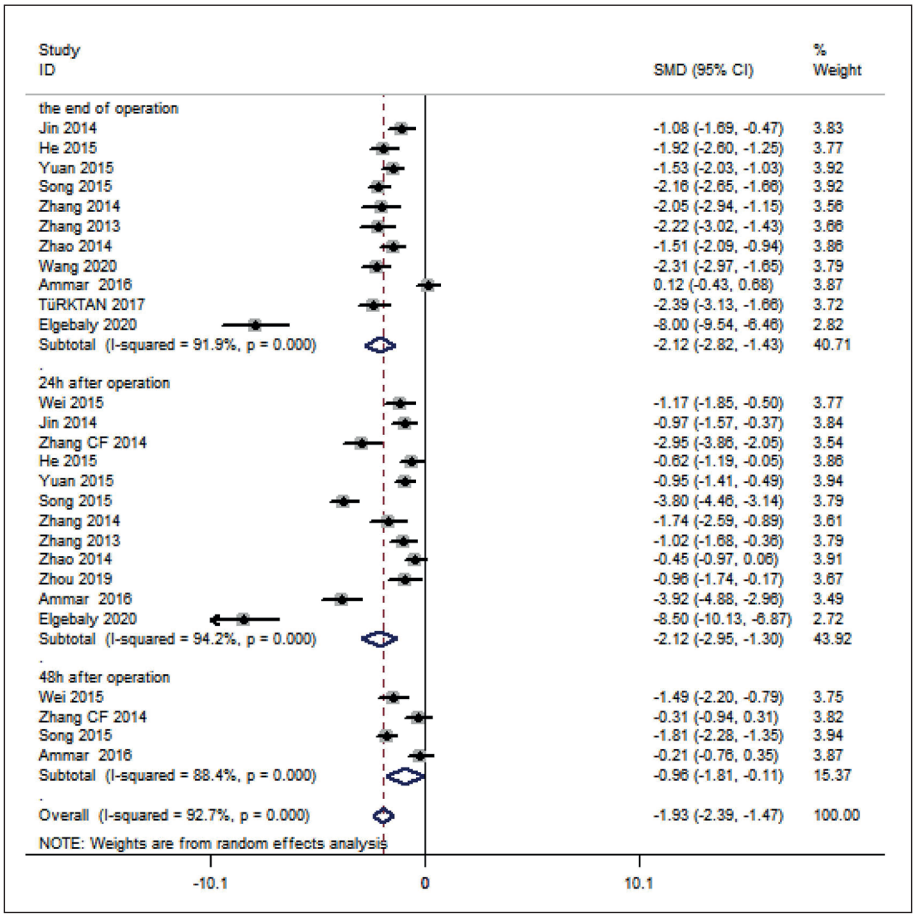

Figure 5. Meta-analysis of cTn-I concentration after CPB operation.

(SMD=-2.12, 95% CI: -2.82, -1.43, p=0.000), and 48 h after the operation (SMD=-0.96, 95% CI: -1.18, -0.11, p=0.027). Many studies[13,16,22,24-26] have been limited to the changes in haemodynamics and do not involve the detection of myocardial injury markers.

This meta-analysis also had some limitations. First, the small sample size and limited amount of literature included decrease the robustness of these results. Therefore, it is necessary to increase the number of enrolled studies and increase the sample size. Although heterogeneity is eliminated for data collected from different origins, data on race, age, and other factors remain the source of heterogeneity.

Conclusions

Dexmedetomidine can reduce CK-MB and cTn-I concentrations and shorten the length of ICU stay for patients undergoing cardiac surgery with CPB. It can also provide myocardial protection from I/R injury. However, further studies are needed to explore the effect of dexmedetomidine on the long-term prognosis of these patients.

Acknowledgements

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Conflicts of Interest

Guangru Zhang, Chenmei Peng, Zhenzhen Liu and Yufang Leng declare that they have no conflict of interest. This manuscript is a review article and does not involve a research protocol requiring approval by the relevant institutional review board or ethics committee.

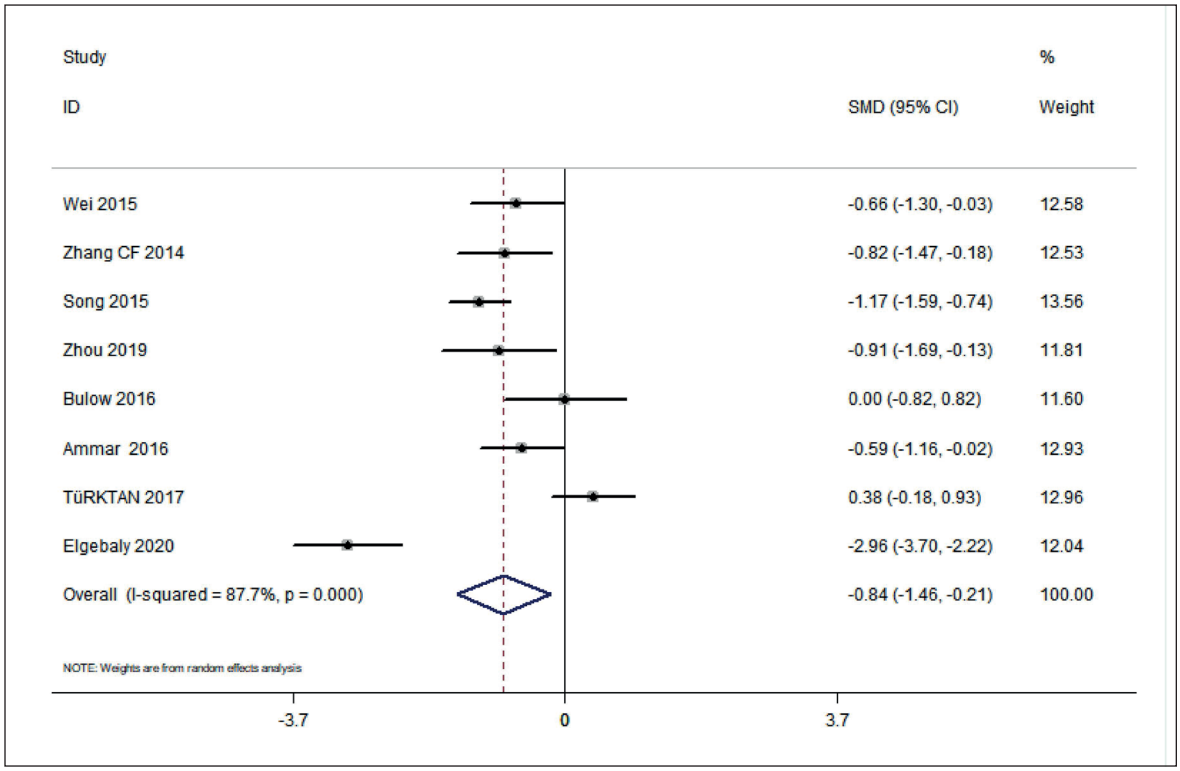

Figure 6. Meta-analysis of length of ICU stays after CPB operation.

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