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Review Article

Effect of perioperative dexmedetomidine on inflammatory mediators and oxidative stress response after surgery: a meta-analysis

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Abstract: This meta-analysis aimed to evaluate effect of perioperative dexmedetomidine on inflammatory response and oxidative stress after surgery. A literature search on databases such as PubMed, Embase, Springer, Science direct and Google Scholar was conducted up to September 2017. The pooled standard mean difference (SMD) and the corresponding 95% confidence intervals (CIs) were calculated using the Revman 5.3. Total 13 studies were included in this meta-analysis. The patients undergoing general anesthesia with dexmedetomidine had lower levels of IL-6 than patients undergoing placebo/normal saline at the end of surgery, but showed similar levels of IL-6 with patients in control groups at 6 h after surgery. Dexmedetomidine anesthesia was associated with the significantly decreased levels of TNF-α at end of surgery and 24 h post-operation and CRP (C-reactive protein) at 24 h post-operation, but not WBC (white blood cell) at 24 h and 72 h post-operation. Meanwhile, the levels of superoxide dismutase (SOD) and malondialdehyde (MDA) at 30 min post-One-lung Ventilation (OLV) were similar between patients undergoing dexmedetomidine anesthesia and normal saline/placebo. The perioperative dexmedetomidine significantly improved the inflammatory response after surgery. However, more studies should be performed to further investigate the effect of perioperative dexmedetomidine on oxidative stress after surgery.

Keywords: Dexmedetomidine, anesthesia, inflammation, oxidative stress, meta-analysis

Introduction

Generally, a systemic inflammatory response to surgery may lead to many postoperative complications including postoperative pains [1, 2], recurrence and metastasis of tumor [3, 4], and increased mortality [5, 6]. Hence, it is essential to inhibit the perioperative inflammatory responses for improving the prognosis of patients after surgery.

Dexmedetomidine, which is a selective α 2 adrenoreceptor agonist with the anti-inflammatory effect, has been popularly used as a safe adjunct in many clinical applications, such as sedation in the ICU (adult and pediatric), neurosurgery, awake fiber-optic intubation and general anesthesia during surgeries [7-9]. Many animal and human studies have proved the effect of dexmedetomidine on post-operative inflammatory factors, such as interleukins (IL) and tumor necrosis factor (TNF)-α [10-14]. An previous meta-analysis showed that dexmedetomidine could significantly improve the inflammatory response after surgery based on the factors such as IL-6, IL-8 and TNF-α [15]. Huang *et al*. performed a meta-analysis for the effect of dexmedetomidine on improve arterial oxygenation and intrapulmonary shunt during One-lung Ventilation (OLV) after thoracic surgery, and also showed the significantly decreased levels of IL-6, and TNF-α after surgery compared with placebo [16]. Meanwhile, Huang *et al*. also investigated the effect of dexmedetomidine on improve oxidative stress based on indexes superoxide dismutase (SOD) and malondialdehyde (MDA), and showed a negative result [16]. However, some animal studies have proved the improvement of SOD and MDA levels by dexmedetomidine in ischemia-reperfu-

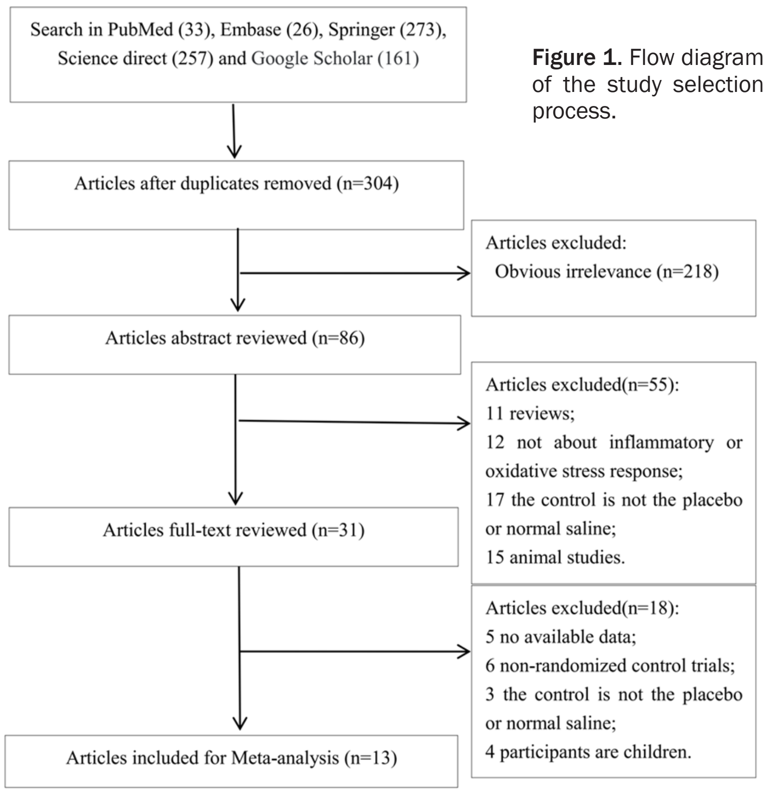

Figure 1. Flow diagram of the study selection process.

sion injury [17, 18] which is a common clinical problem in many surgeries. Currently, many randomized control studies have been performed to further prove the effect of perioperative dexmedetomidine on inflammatory response and oxidative stress after surgery. Moreover, the controversies still exist among studies. So we performed this meta-analysis to further evaluate those effects of dexmedetomidine.

Materials and methods

The methods used for this meta-analysis and generation of inclusion criteria were based on PRISMA recommendations.

Literature search strategy

Databases such as PubMed, Embase, Springer, Science direct and Google Scholar were used for the literature search up to September 2017, using the following keywords: "dexmedetomidine" AND "randomized" AND (inflammatory OR proinflammatory OR oxidative stress OR TNF-α OR IL-6 OR MDA OR SOD). In addition, the references of relevant reviews were searched for additional studies. Only the studies in English were searched and included in this study.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the study type was randomized control trial; (2) subjects were adults aged > 18 years; (3) subjects underwent general anesthesia with dexmedetomidine in DEX group or normal saline/placebo in control group; and (4) some inflammatory factors or oxidative stress indexes after surgery were investigated (such as IL-6, TNF-α, MDA and SOD).

The exclusion criteria were (1) duplicated publications, (2) reviews, letters, or comments, (3) animal studies, or (4) no available data. Only articles with full-text access were included.

Data extraction and quality assessment

The following data were recorded in a predesigned form: first author name, country, publication year, sample size, age, sex, surgery, and outcome. Data extraction was independently performed by two investigators. Differences were resolved by discussion to ensure consistent evaluation.

The modified Jadad scale [19] with total scores of 7 was used to assess the quality of included studies. Parameters judging the quality included randomization, allocation concealment, double blind and withdrawals and dropouts. High quality study was regarded as the study with scores of 4-7. Otherwise, low quality was defined.

Statistical analysis

The Revman 5.3 software was used for this meta-analysis. The I^2 and Cochran Q tests were used to assess heterogeneity among the included studies, with P values of < 0.1 or I^2 values of > 50% being considered as significant. An appropriate statistical model (fixed- or random-effects model) was used to pool the standard mean difference (SMD) and corresponding 95% confidence intervals (CIs) based on the

Table 1. Characteristics of included studies

Author	Year	Country	Surgery	Group	Anesthetic drugs	Sample size	Age	Sex (M/F)	Inflammatory indexes	Jadad Score
M. Ueki	2014	Japan	Cardiac surgery with cardiopulmonary bypass	DEX	Dexmedetomidine	18	70.5 ± 9.5	8/10	WBC, CRP	5
				Control	Normal saline	19	69.0 ± 11.7	8/11		
Shenqiang Gao	2015	China	One-lung ventilation	DEX	Dexmedetomidine	25	40-65	NA	TNF-α, MDA, SOD	3
				Control	Normal saline	25				
Alex Bekker	2013	USA	Multilevel spinal fusion	DEX	Dexmedetomidine	26	55.3 ± 12.3	21/5	CRP, TNF-α, IL-1, IL-6, IL-8, IL-10, IL-2, IL-12	5
				Control	Placebo-saline	28	57.0 ± 11.1	15/13		
Rui Xia	2015	China	One-Lung Ventilation	DEX	Dexmedetomidine	25	55 ± 12	17/8	MDA, SOD, NO	5
				Control	Normal saline	24	56 ± 11	16/8		
W. DONG	2017	China	Radical resection of gastric cancer	DEX	Dexmedetomidine	37	36.3 ± 7.4	23/14	IL-6, IL-1α, IL-1β, TNF-α, CRP	3
				Control	Normal saline	37	38.7 ± 7.6	20/17		
Yulan Wang	2014	China	Radical gastrectomy	DEX	Dexmedetomidine	20	56.7 ± 9.0	17/3	TNF-α, IL-6, IL-1β	4
				Control	Normal saline	20	57.2 ± 8.3	14/6		
Hongmei Zhou	2017	China	Multilevel spinal fusion	DEX	Dexmedetomidine	20	51.6 ± 9.0	9/11	WBC, CRP	4
				Control	Normal saline	20	51.1 ± 12.9	10/10		
Ahmed G. Yacout	2012	Egypt	Elective major abdominal surgery	DEX	Dexmedetomidine	15	49.60 ± 6.56	8/7	IL-6	5
				Control	Placebo	15	47.07 ± 6.52	9/6		
Xiahong Luo	2016	China	Craniotomy resection	DEX	Dexmedetomidine	30	47.2 ± 10.9	14/16	TNF-α, IL-6, SOD, MAD	3
				Control	Normal saline	30	46.8 ± 11.4	17/13		
Yun Li	2016	China	Elective open gastrectomy	DEX	Dexmedetomidine	30	56.5 ± 5.2	22/8	TNF-α, IL-6, IL-10	4
				Control	Normal saline	30	54.0 ± 6.9	21/9		
Lili Xu	2014	China	Non-cardiac surgery	DEX	Dexmedetomidine	40	60.1 ± 5.1	19/21	TNF-α, IL-6	5
				Control	Normal saline	40	58.6 ± 6.2	18/22		
So Hui Yun	2015	Korea	NA	DEX	Dexmedetomidine	15	72.5 ± 6.4	NA	IL-6	3
				Control	Normal saline	15	73.9 ± 3.8			
X.-H. YANG	2017	China	Radical mastectomy	DEX	Dexmedetomidine	62	50.32 ± 12.24	0/62	IL-6, IL-2, IL-4, IL-10, TNF-γ	4
				Control	Normal saline	62	49.62 ± 11.41	0/62		

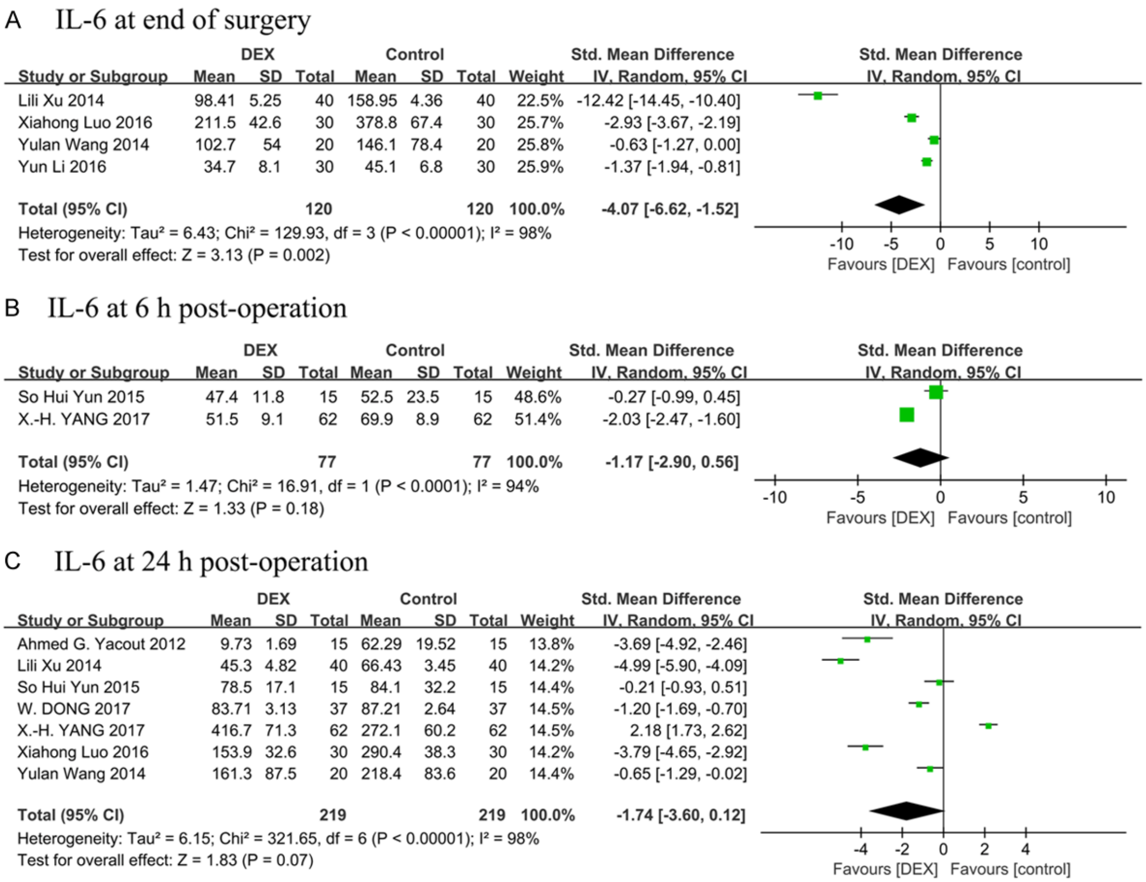

Figure 2. Forest plots for the pooled estimate of IL-6 at end of surgery (A), 6 h post-operation (B) and 24 h post-operation (C).

results of the heterogeneity test. For all of these analyses, *P* values of < 0.05 indicated statistical significance. Sensitivity analyses were performed by omitting one study at a time. Publication bias was assessed by Begg's test using Stata 11.0 software.

Results

Characteristics of the included studies

The initial literature search was performed on PubMed, Embase, Springer, Science direct and Google Scholar databases. After excluding duplicates and irrelevant studies, 86 potentially relevant articles remained. Of these, 55 articles were excluded by scanning the abstracts, whereas 18 articles were excluded by reading the complete text based on the inclusion and exclusion criteria. Finally, 13 studies [20-32] were included in this meta-analysis (**Figure 1**).

Total 13 studies involving 345 patients undergoing general anesthesia with dexmedetomidine and 345 undergoing normal saline/placebo were reanalyzed in this meta-analysis. The publication year ranged from 2012 to 2017. The surgery was different among these included studies. Nine studies were conducted in China and the rest four studies were conducted in Japan, USA, Egypt and Korea, respectively. There were nine high quality studies and four low quality studies (**Table 1**).

Meta-analysis regarding inflammatory factors

A total of seven included studies [21, 24, 26, 28-31] reported the IL-6 levels at 24 h after surgery. Among the studies, significant heterogeneity ($I^2 = 98\%$; $P < 0.00001$) was observed; thus, the random-effects model was used for pooling data. Meanwhile, there were also no less than two studies showing the IL-6 levels at the end of surgery ($I^2 = 98\%$; $P < 0.00001$) and 6 h after surgery ($I^2 = 94\%$; $P < 0.00001$). Similarly, significant heterogeneity existed among included studies and random-effects model

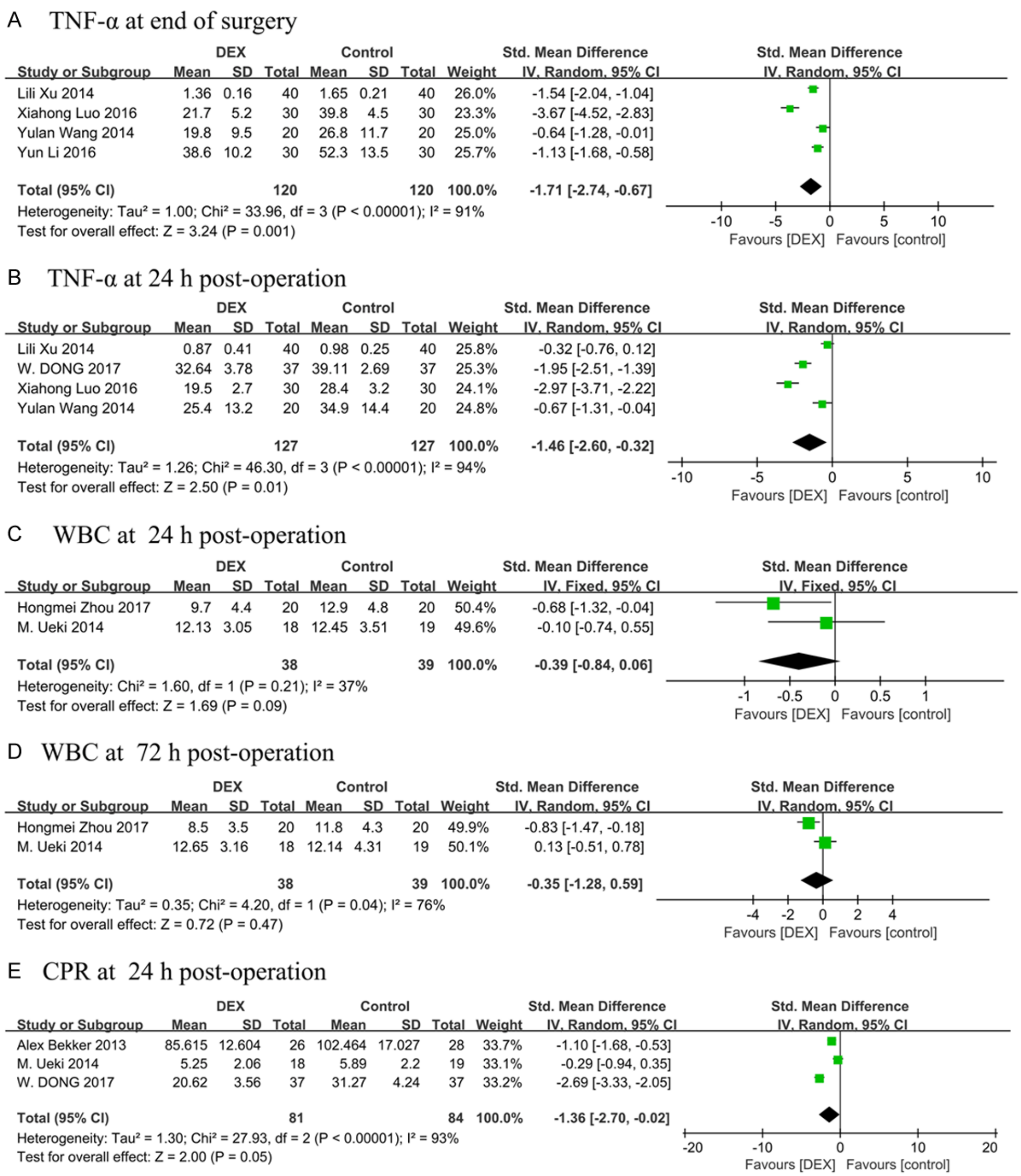

Figure 3. Forest plots for the pooled estimate of TNF-α at end of surgery (A) and 24 h post-operation (B), WBC at 24 h post-operation (C), WBC at 72 post-operation (D) and CRP at 24 h post-operation (E).

was applied. The pooled estimates showed that the patients undergoing general anesthesia with dexmedetomidine had lower levels of IL-6 than patients undergoing placebo/normal saline at the end of surgery (SMD = -4.07, 95% CI = -6.62 to -1.52, P = 0.002, **Figure 2A**), but showed similar levels of IL-6 with patients in control groups at 6 h (SMD = -1.17, 95% = -2.90 to 0.56, P = 0.18, **Figure 2B**) or 24 h (SMD = -1.74, 95% CI = -3.60 to 0.12, P = 0.07, **Figure 2C**) after surgery.

Except IL-6, the inflammatory factors including TNF-α, WBC (white blood cell) and CRP (C-reactive protein) were also analyzed in this meta-analysis. Among the included studies, no sig-

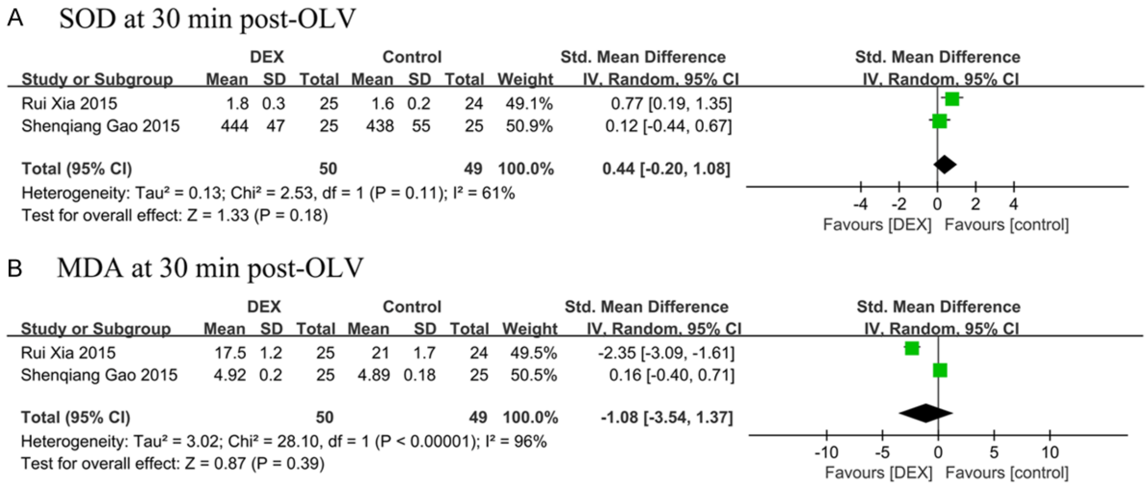

Figure 4. Forest plots for the pooled estimate of SOD at 30 min post-OLV (A) and MDA at 30 min post-OLV (B).

Table 2. Results of sensitivity analyses

Indexes	Excluded studies	SMD [95% CI], *P*-value	I^2, *P*-value
CRP at 24 h post-operation	Low quality study (W. DONG 2017)	-0.71 [-1.50, 0.08], P = 0.08	70%, P = 0.07
	Alex Bekker 2013	-1.49 [-3.84, 0.86], P = 0.21	96%, P < 0.00001
IL-6 at 6 h post-operation	Low quality study (So Hui Yun 2015)	-2.03 [-2.47, -1.60], P < 0.00001	NA
IL-6 at 24 h post-operation	X.-H. YANG 2017	-2.38 [-3.84, -0.93], P = 0.001	96%, P < 0.00001
TNF-α at 24 h post-operation	Low quality study (W. DONG 2017)	-1.30 [-2.78, 0.18], P = 0.09	95%, P < 0.00001
	Low quality study (Xiahong Luo 2016)	-0.98 [-1.98, 0.03], P = 0.06	90%, P < 0.00001
MDA at 30 min post-OLV	Low quality study (Shenqiang Gao 2015)	-2.35 [-3.09, -1.61], P < 0.00001	NA
SOD at 30 min post-OLV	Low quality study (Shenqiang Gao 2015)	0.77 [0.19, 1.35], P = 0.01	NA
WBC at 24 h post-operation	M. Ueki 2014	-0.68 [-1.32, -0.04], P = 0.04	NA
WBC at 72 h post-operation	M. Ueki 2014	-0.83 [-1.47, -0.18], P = 0.01	NA

Notes: only the inconsistent results with overall analyses were shown in this table.

nificant heterogeneity (I^2 = 37%; P = 0.21) was observed for WBC levels at 24 h after surgery; hence, the fixed-effects model was used. However, randomized effects model should be used due to significant heterogeneity (I^2 > 50%; P < 0.1) among studies for TNF-α at end of surgery, TNF-α at 24 h post-operation, WBC at 72 h post-operation and CRP at 24 h post-operation. Results showed that dexmedetomidine anesthesia was associated with the significantly decreased levels of TNF-α at end of surgery (SMD = -1.71, 95% CI = -2.74 to -0.67, P = 0.001, **Figure 3A**) and 24 h (SMD = -1.46, 95% CI = -2.60 to -0.32, P = 0.01, **Figure 3B**) post-operation and CRP at 24 h post-operation (SMD = -1.36, 95% CI = -2.70 to -0.02, P = 0.05, **Figure 3E**). However, the levels of WBC at 24 h (SMD = -0.39, 95% CI = -0.84 to 0.06, P = 0.09, **Figure 3C**) and 72 h (SMD = -0.35, 95% CI = -1.28 to 0.59, P = 0.47, **Figure 3D**) post-operation were similar in DEX and control groups.

Meta-analysis regarding oxidative stress indexes

Figure 4 shows the results for oxidative stress indexes. Only two studies [22, 27] reported the SOD and MDA levels after OLV (One-Lung Ventilation). Among the studies, significant heterogeneity (I^2 > 50%; P < 0.1) was observed in the analysis of SOD at 30 min post-OLV and MDA at 30 min post OLV; thus, the random-effects model should be used. Pooled data showed that the dexmedetomidine anesthesia was not associated with the SOD (SMD = 0.44, 95% CI = -0.20 to 1.08, P = 0.18, **Figure 4A**) and MDA (SMD = 0.44, 95% CI = -0.20 to 1.08, P = 0.18, **Figure 4B**) levels variety among patients at 30 min after OLV.

Sensitivity analyses and publication bias

As shown in **Table 2**, some results of sensitivity analyses were inconsistent with the overall analysis. Besides the low-quality studies including W. DONG 2017, So Hui Yun 2015, Xiahong Luo 2016 and Shenqiang Gao 2015 [21, 22, 24, 31], the exclusion of studies of X.-H. YANG 2017, M. Ueki 2014 and Alex Bekker 2013 [20, 25, 30] also can change the results of overall analyses (**Table 2**).

In addition, Begg's test showed there was no significant publication bias in this meta-analysis ($P > 0.05$).

Discussion

Consistent with the previous meta-analysis [15], we proved the effect of perioperative dexmedetomidine on inflammatory response based on the IL-6 at end of surgery, TNF-α at end of surgery, TNF-α at 24 h post-operation and CRP at 24 h post-operation, although no significant effect of perioperative dexmedetomidine on IL-6 at 6 h and 24 h post-operation as well as WBC at 24 h and 72 h post-operation. Compared with that meta-analyses, there were some advantages: firstly, we only included the studies published in English; secondly, the other inflammatory factors such as CRP and WBC were investigated; thirdly, more recent studies published in recent 3 years were included and reanalyzed. The effect of perioperative dexmedetomidine on CRP after surgery was firstly investigated and proved by meta-analysis in this study. Previous studies have showed that epinephrine can simulate CRP biosynthesis and release and β-adrenergic antagonists can decrease the circulating CRP levels [33]. Thus, we speculated that the α-2 adrenoreceptor also can reduce CRP levels by inhibiting the stimulation of epinephrine on CRP biosynthesis and release. The mechanism of dexmedetomidine on improving inflammatory response should be further explored in further studies.

In this study, we found the IL-6 levels at 6 h and 24 h post-operation were similar between DEX and control groups. Thus, we speculated that the effect of perioperative dexmedetomidine on IL-6 level after surgery may be transitory. More studies should be performed to verify these results. However, the significantly decreased IL-6 level at 24 h post-operation by perioperative dexmedetomidine application was found after excluding the study of X.-H. YANG 2017 [30] in sensitivity analyses. It was reported sex steroids can regulate IL-6 [34, 35]. Compared with the other 6 studies, only females were investigated in the study of X.-H. YANG 2017 [30], which may be the main reason resulting in the inconsistent results. Similarly, the significant result on TNF-α at 24 h post-operation disappeared after excluding the study of W. DONG 2017 or Xiahong Luo 2016 [21, 24]. Compared with the other two studies [26, 28], the participants was visually younger in the studies of W. DONG 2017 or Xiahong Luo 2016 [21, 24]. As shown in previous studies, age is a factor influencing the TNF-α regulation in many diseases [36, 37]. Thus, the age may be a factor influencing the result of this meta-analysis for TNF-α at 24 h post-operation. More studies should be performed to further investigate the influence of age and sex on the effect of perioperative dexmedetomidine on inflammatory response.

There may be no effect of perioperative dexmedetomidine on oxidative stress based on the results on MDA and SOD levels at 30 min after OLV, which is consistent with the results of a previous meta-analysis [16]. Differently, we included a recent study of Shengqiao Gao 2015 in this meta-analysis. In sensitivity analyses, the results showed that the two included studies indicated different results in MDA and SOD levels at 30 min after OLV. Given only two studies were included and inconsistent results exist between these studies, the conclusion on effect of perioperative dexmedetomidine on oxidative stress could not be determined in this meta-analysis. More studies should be performed to further investigate the effect of perioperative dexmedetomidine on oxidative stress.

There were some limitations in this study. Firstly, significant heterogeneity was found in this study, sex, age, country and surgery may be the sources of heterogeneity. However, subgroup analyses were not performed due to no enough data. Secondly, except IL-6, TNF-α, CRP and WBC, many other inflammatory factors (IL-2, IL-10, TNF-β) should be performed in future studies. In addition, only two studies were used to evaluate the effect of perioperative dexmedetomidine on IL-6 at 6 h post-operation, WBC at 24 h and 72 h post-operation, and MDA and SOD levels at 30 min after OLV. Meanwhile, Sensitivity analyses showed obviously inconsistent results between those two studies. Thus, the results are instability and more study should be performed to verify the results of this meta-analysis.

In conclusion, perioperative dexmedetomidine can significantly improve the inflammatory response via IL-6, TNF-β and CRP. There may be no association between perioperative dexmedetomidine and oxidative stress after surgery and further studies are needed to verify it.

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Disclosure of conflict of interest

None.

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