ORIGINAL ARTICLE

Does Intra-operative Dexmedetomidine Attenuate Postoperative Inflammatory Response in the Adult Surgical Patients with General Anaesthesia? A Meta-analysis of Randomized Controlled Trials Studies

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ABSTRACT

Objective: *The study was done to investigate the postoperative anti-inflammatory effects of dexmedetomidine (DEX) in various surgical procedures.*

Methods: *A search of randomized placebo-controlled trials for intra-operative DEX use in adults was conducted. The primary outcome was postoperative concentrations of interleukin-6 (IL-6) and tumour necrosis factor-alpha (TNF-α); secondary outcomes were: intra- and post-operative hypotension and bradycardia.*

Results: *A total of seven randomized controlled trials involving 424 patients with different types of surgeries were analysed. The pooled standardized mean difference (SMDs) were -0.33 (95% CI:-0.41, -0.25, $p < 0.001$) and -0.22 (95% CI:-0.35, -0.09, $p = 0.001$) for TNF-α, -51.02 (95% CI:-52.83, -49.21, $p < 0.001$) and -19.67 (95% CI:-21.15, -18.19, $p < 0.001$) for IL-6 at the end of surgery and the first day after surgery, respectively.*

Conclusion: *This meta-analysis showed that intra-operative DEX reduces postoperative concentrations of IL-6 and TNF-α at the end of surgery and the first day after surgery. Future studies should further explore the anti-inflammatory effects of DEX in detail.*

Keywords: Cytokines, dexmedetomidine, inflammation, meta-analysis, surgery

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INTRODUCTION

It is reported that more than 230 million patients receive major surgical procedures worldwide each year (1). Major surgery invariably evokes an inflammatory response and this leads to postoperative complications. Thus, modulation of inflammation is of great importance to reduce the incidence of postoperative complications. Dexmedetomidine (DEX), a highly selective α_2-adrenoceptor agonist, has significant sympatholytic effects which can reduce norepinephrine release and attenuate stress reaction. Several studies (2–10) have reported that DEX impacts intra and postoperative secretion of cytokines. However, the results disagree with each other. Thus, it remains unclear whether DEX has an anti-inflammatory effect on surgical insult. One meta-analysis regarding the anti-inflammatory effects of DEX has been published recently (11). However, it had a poorly homogeneous population including children (12) and non-surgical patients (13) and a non-single contrast such as placebo and propofol (3, 14). Moreover, the assessment of the impact of these confounding factors was overlooked. Thus, we undertook a meta-analysis of randomized controlled trials to evaluate the anti-inflammatory effect of DEX compared with placebo on the levels of cytokines (IL-6 and TNF-α) in adult surgical patients in the early postoperative period.

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SUBJECTS AND METHODS

A systematic search was performed in PubMed, EMBASE and CENTRAL, up to April 13, 2016. In addition, the reference lists of the retrieved full articles were manually searched. The search strategies used the following Medical subject heading terms and corresponding key words: "dexmedetomidine" and (immunity OR inflammation OR cytokines). No language restriction was imposed.

Inclusion criteria: (i) study population: adult patients undergoing surgery; (ii) intervention: DEX intravenous administration; (iii) comparison intervention: placebo or no intervention; (iv) outcome measure: the plasma levels of IL-6 and TNF-α and (v) study design: Randomized Controlled Trial (RCT).

Data extraction

The following data were extracted from the identified studies: first author, year of publication, number of patients (DEX/control), patient characteristics, surgery and anaesthesia characteristics, regimens of DEX administration (dosage, timing, length of infusion), study design, measuring methods of the cytokines and outcomes data.

Risk-of-bias assessment

All the studies were subjectively reviewed and scored as high, low, or unclear risk of bias to the criteria in accordance with guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0).

Grading quality of evidence

The quality of the evidence was evaluated for primary and secondary outcomes according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology for risk of bias, inconsistency, indirectness, imprecision, and publication bias, classified as very low, low, moderate, or high. Summary tables were constructed using the GRADE Profiler (version 3.6, GRADEpro).

Statistical analyses

Relative risks (RRs) were calculated with 95% confidence intervals (CIs) for dichotomous outcomes and mean differences (MDs) with 95% CIs for continuous outcomes. Heterogeneity across studies was quantified using the I^2 statistic; $I^2 > 50\%$ indicated significant heterogeneity. Outcome data were pooled using a fixed-effects model accounting for clinical heterogeneity. Except where otherwise specified, $p < 0.05$ was considered statistically significant. All statistical analyses were performed using RevMan 5.3 (Nordic Cochrane Centre).

RESULTS

Study identification and selection

The initial search returned 65 relevant publications, of which 46 were excluded for duplicate studies and other reasons, on the basis of the titles and abstracts (Fig. 1). The remaining 19 publications were retrieved for full text. Of this number, 12 were excluded: eight did not provide enough available data, two were for propofol control, one was on intranasal use, and one was on regional anaesthesia. Thus, seven RCTs were included in the final analysis (6–10, 15, 16).

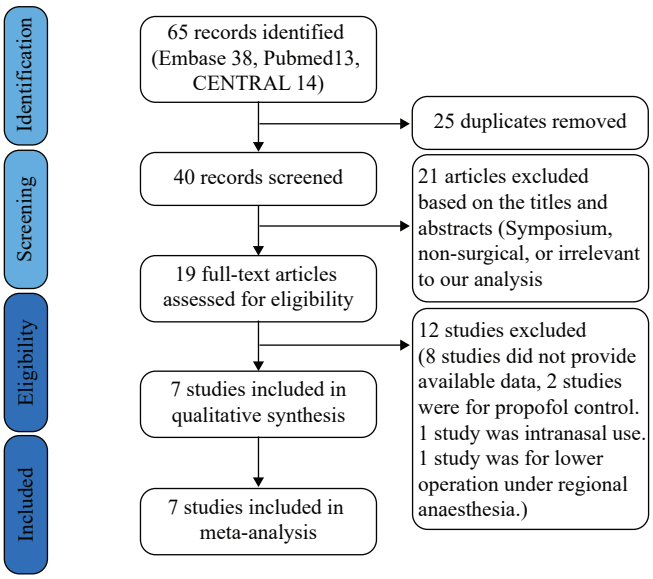

Fig. 1: Search strategy and flow chart for this meta-analysis.

Study characteristics

The main characteristics of the seven included RCTs are presented in Table 1. These studies were published between 2012 and 2015. The sample sizes ranged from 30 to 100 patients (total of 424). The populations were adults who had various operations under general anaesthesia. All of these patients received intravenous administration of DEX intra-operatively, and none was administered after surgery.

Risk of bias assessment

Overall, three trials were categorized as being at low risk of bias. An adequate randomized sequence was generated in six trials and appropriate allocation concealment

Table 1: Characteristics of randomized controlled trials included in the meta-analysis. Data are presented as mean ± SD unless indicated otherwise.

First author, year	Patients No. (I/C)	Surgery type	Duration of surgery (I/C) min	Anaesthesia methods	Duration of Anaesthesia (I/C) min	Intervention protocol	Study design
Bekker 2013	54(26/28)	lumbar fusion	230.6 ± 84.7/ 227.3 ± 93.4	propofol + fentanyl	304.0 ± 85.9/ 295.9 ± 102.2	IR: 0.5 ug/kg.h till 20 min BES	double-blind RCT
Li 2013	60(30/30)	radical nephrectomy	105 ± 12/ 102 ± 10	propofol + remifentanil + vecuronium	124 ± 18/ 120 ± 16	LD: 1 ug/kg (15min), IR:0.2-0.5 ug/kg.h	double-blind RCT
Liu 2013	60(30/30)	valve replacement	not reported	propofol + sevoflurane + fentanyl + vecuronium	not reported	LD:1 ug/kg, IR:0.4 ug/kg.h	non-blind RCT
Ding 2015	100(50/50)	robot-assisted laparoscopicradical prostatectomy	not reported	propofol + sevoflurane + remifentanyl + cisatracurium	not reported	0.8 ug/kg.h for 10 min, 0.4 ug/kg.h till 30 min BES	double-blind RCT
Yacout 2012	30(15/15)	major abdominal surgery	194.0 ± 13.26/ 192.0 ± 17.2	general anaesthesia (no details)	206.33 ± 15.06/ 204.67 ± 16.95	LD:1 ug/kg (> 10 min), IR: 0.5 ug/kg.h till the end of surgery	double-blind RCT
Wang 2015	40(20/20)	radical gastrectomy	136.7 ± 35.9/ 127.8 ± 27.6	propofol + isoflurane + fentanyl + cisatracurium	not reported	LD:0.5 ug/kg (> 10 min), IR:0.4 ug/kg.h TILL 30 min BES	single-blind RCT
Xu 2014	80(40/40)	hip-replacement surgery	126 ± 14/ 123 ± 12	propofol + sevoflurane + sufentanyl + cisatracurium	not reported	LD:1 ug/kg (10min), IR:0.2 ug/ kg.h till the end of surgery	double-blind RCT

Notes: IR: infution rate; LD: loading dose; BES: before the end of surgery.

was reported in five trials. Six trials were conducted in a blinded fashion. All trials reported on the numbers and reasons for withdrawal or dropout and were free of other bias. An overview of the risk of bias is summarized in Fig. 2.

Primary outcome

Only six RCTs provided available data on IL-6 and TNF-α. The aggregated results suggested that the administration of DEX was associated with a significant reduction in the levels of IL-6 and TNF-α. The overall mean 95% CI difference of IL-6 at the end of surgery and the first day after surgery was -51.02 (95% CI: -52.83, -49.21) and -19.67 (95% CI:-21.15, -18.19) pg/mL, respectively ($p < 0.00001$). The overall mean (95% CI) difference of TNF-α at the end of surgery and the first day after surgery was -0.33(95% CI:-0.41, -0.25) and -0.22 (95% CI:-0.35, -0.09) pg/mL, respectively ($p < 0.01$), [Figs. 3, 4]. The test for heterogeneity was significant (three of six p-values < 0.00001; I2 > 90%).

Secondary outcomes

Dexmedetomidine was not associated with hypotension in the process of the trials (three RCTs; RR 1.41, 95% CI: 0.73, 2.71; $p = 0.3$; p for heterogeneity = 0.61, Fig. 5), bradycardia (two RCTs; RR 1.32, 95% CI: 0.79, 2.21; $p = 0.29$; p for heterogeneity = 0.49, Fig. 6). There was no evidence of heterogeneity for these secondary outcomes (all p-values > 0.1; I2 = 0%).

Quality of evidence

The GRADE evidence profiles for the primary and secondary outcomes are shown in Tables 2 and 3. The quality of evidence was moderate for levels of IL-6 and TNF-α at the end of surgery and the first day after surgery. It was also moderate for occurrences of hypotension and bradycardia.

Sensitivity analyses

Subsequently, sensitivity analyses were performed to explore the source of this significant heterogeneity and to observe the influence of various exclusion criteria on the combined estimates. Exclusion of two studies in which inhalation anaesthetics did not apply in general anaesthesia, yielded similar results of IL-6 at the end of surgery and the first day after surgery (MD -56.08, 95% CI: (-58.07, -54.09) pg/mL, $p < 0.00001$ and MD -22.81, 95% CI: (-26.82, -18.80) pg/mL, $p < 0.00001$, respectively, with substantial evidence of heterogeneity [I2 = 99%, $p < 0.00001$; and I2 = 94%, $p < 0.00001$, respectively] (7, 10). After exclusion of two studies with low loading dose (< 1 ug/kg), the results of IL-6 on the first day after surgery were still maintained (MD-18.72 pg/mL, 95% CI: 20.24, -17.20);) yet, heter-

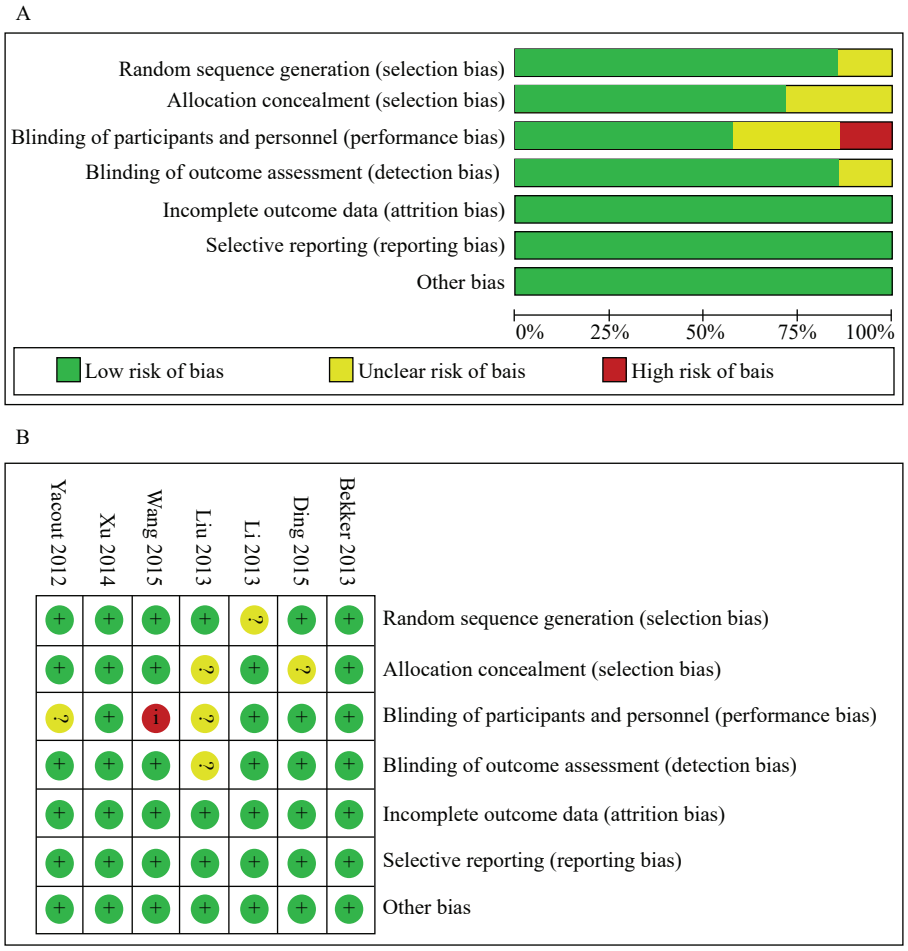

Fig. 2: Risk of bias analysis. A: Risk of bias graph, B: Risk of bias summary.

Table 2: GRADE evidence profile for levels of IL-6 and TNF-α

Quality assessment							No. of patients		Effect		Quality	Importance
No. of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	DEX group	CON group	Relative (95% CI)	Absolute		
IL-6 - pre-anaesthsia (Better indicated by lower values)												
4	randomised	no serious	serious[2]	no serious	no serious	none	115	115	-2.72 to 1.06	-0.83	Moderate	Critical
IL-6 - End of surgery (Better indicated by lower values)												
5	randomised	no serious	serious[2]	no serious	no serious	none	135	135	-57 to -12.98	-34.99	Moderate	Critical
IL-6 - POD1 (Better indicated by lower values)												
6	randomised	Randomised	serious[2]	no serious	no serious	none	185	185	-32.38 to -16.86	-24.62	Moderate	Critical
TNF-α - pre-anaesthsia (Better indicated by lower values)												
4	randomised	no serious	serious[2]	no serious	no serious	none	150	150	-0.2 to 0.46	0.13	Moderate	Critical
TNF-α - End of surgery (Better indicated by lower values)												
4	randomised	no serious	serious[2]	no serious	no serious	none	120	120	-2.69 to -0.13	-1.41	Moderate	Critical
TNF-α - POD1 (Better indicated by lower values)												
4	randomised	no serious	serious[2]	no serious	no serious	none	120	120	-1.35 to 0.24	- 0.56	Moderate	Critical

Notes: [1]low sample, [2]different target populations

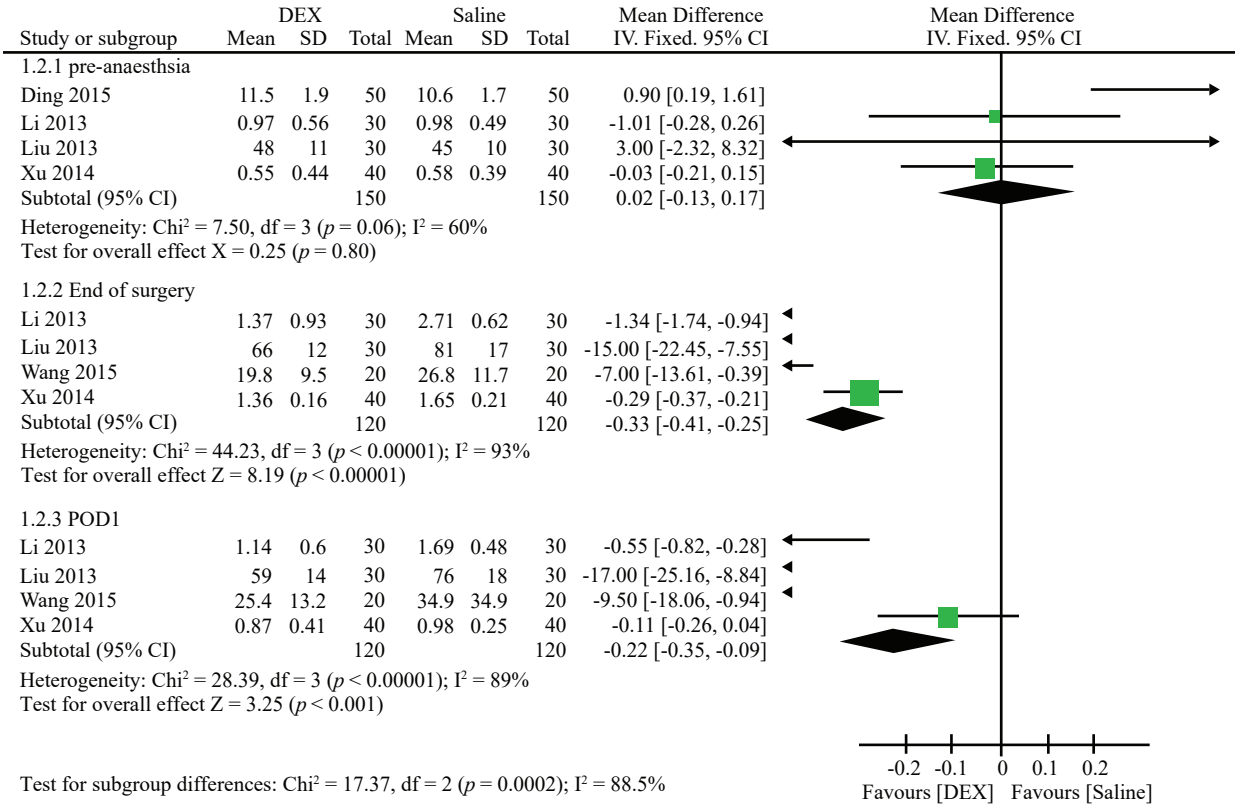

Fig. 3: Forest plot of the effect of DEX *versus* saline on the difference of serum/plasma IL-6 level among various surgical patients.

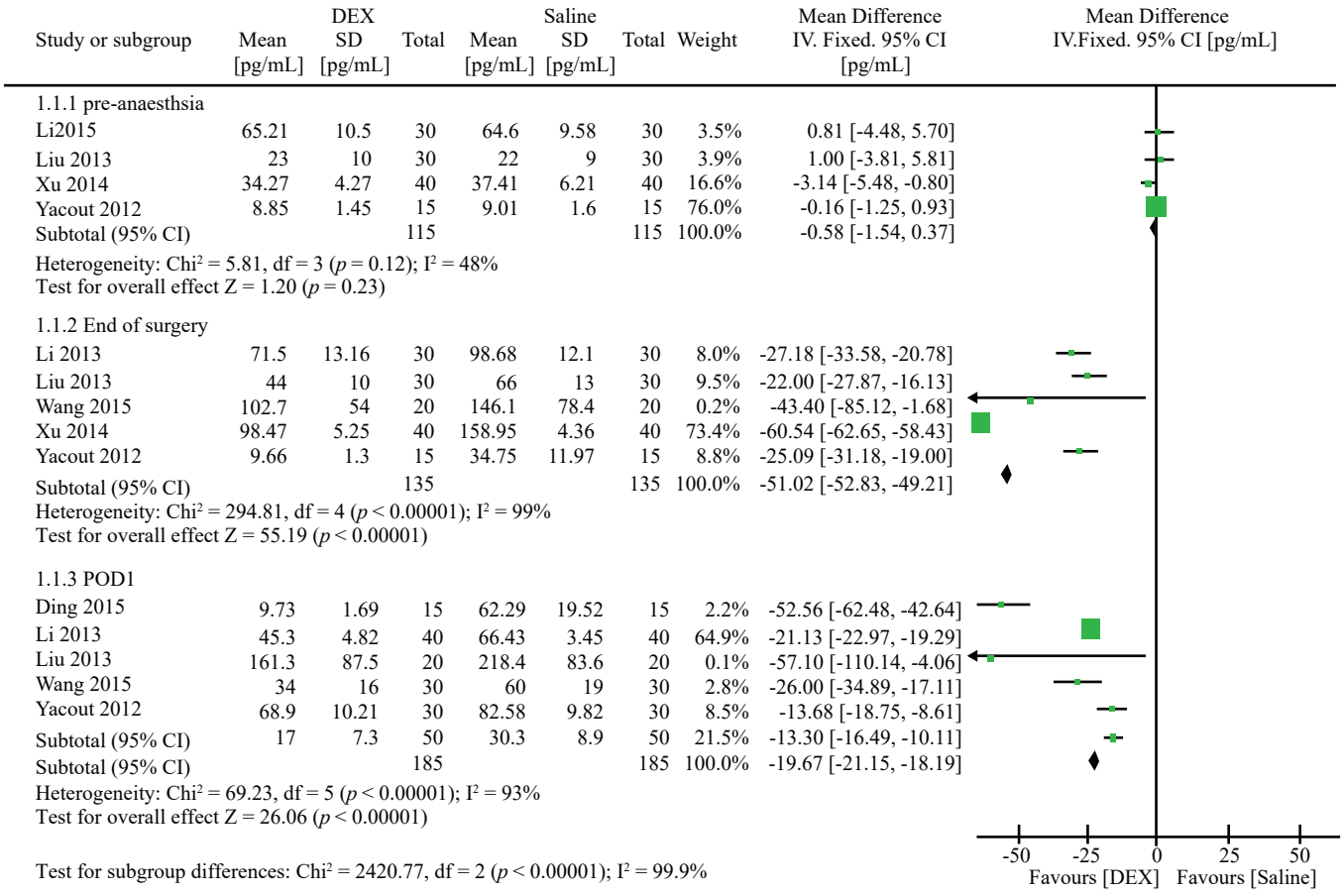

Fig. 4: Forest plot of the effect of DEX *versus* saline on the difference of serum/plasma TNF-α level among various surgical patients.

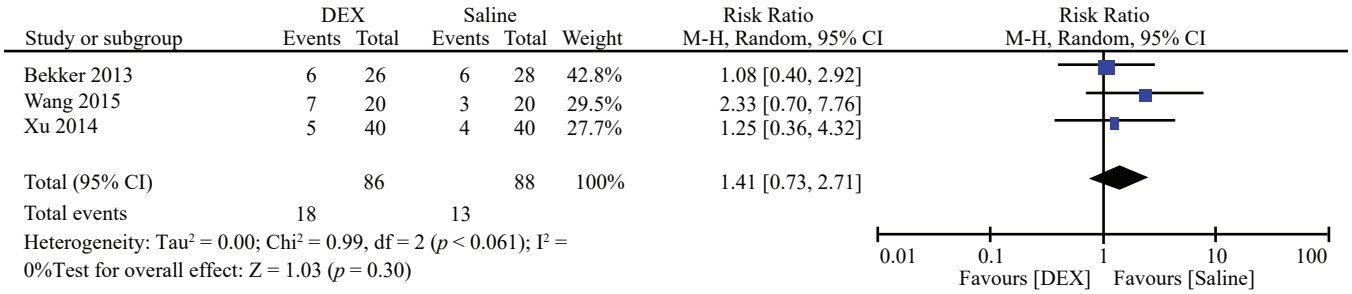

Fig. 5: Forest plot of the effect of DEX *versus* saline on the difference of hypotension.

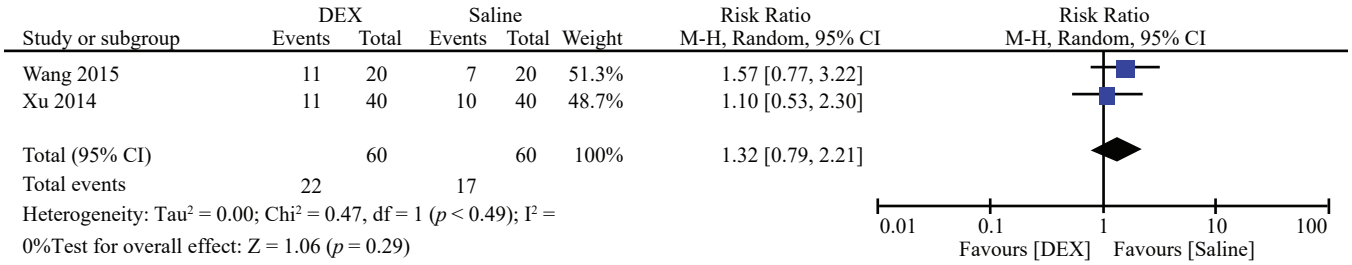

Fig. 6: Forest plot of the effect of DEX *versus* saline on the difference of bradycardia.

Table 3: GRADE evidence profile for occurrences of hypotension and bradycardia

Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**
	Assumed risk	**Corresponding risk**			
Hypotension	Study population		OR 1.55	174	⊕⊕⊕⊖
	148 per 1000	212 per 1000 (108 to 372)	(0.7 to 3.42)	(3 studies)	moderate[1]
Bradycardia	Study population		RR 1.32	120	⊕⊕⊕⊖
	283 per 1000	374 per 1000 (224 to 626)	(0.79 to 2.21)	(2 studies)	moderate[1]

*The basis for the assumed risk (*eg* the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; RR: Risk ratio; OR: Odds ratio; [1]low sample.

ogeneity was still present: (I2 = 87%, $p < 0.0001$ (6, 9)]. Exclusion of two studies that were conducted in a non double-blind RCT design did not change the pooled results of IL-6 at the end of surgery and the first day after surgery (MD -54.10, 95% CI: (-56.01, -52.20) pg/mL, $p < 0.00001$ and MD-19.46, 95% CI: (-20.96, -17.96) pg/mL, $p < 0.00001$, respectively, with similar evidence of heterogeneity I2 = 99%, $p < 0.00001$; and I2 = 95%, $p < 0.00001$, respectively (9, 17).

Publication bias

For publication bias, the funnel plot was not assessed due to the small number (< 10) of RCTs included in each analysis.

DISCUSSION

This meta-analysis indicated that intraoperative DEX reduced the levels of IL-6 and TNF-α at the end of surgery and the first day after surgery. Interleukin-6 is a principal proinflammatory cytokine released as early as two to four hours and peaks about 12 hours after surgery and is a reliable indicator of the severity of inflammation and tissue injury. Tumour necrosis factor α (TNF-α) is also a proinflammatory cytokine and its increased production is an early feature of acute injury and also associated with several chronic inflammatory conditions. Thus, both IL-6 and TNF-α can predict the postoperative complications and lowering the levels of IL-6 and TNF-α can contribute to improvement of postoperative clinical outcomes.

Compared with previous meta-analysis (11), this study found some notable differences. First, to provide more credible evidence and minimize potential bias, only RCTs were included and the focus was on a specific patient population, namely: general-anaesthetized adults undergoing surgery who had not taken antipsychotic medications and anti-inflammatory drugs (*ie* steroids, non-steroid anti-inflammatory drugs, *etc*) for chronic use or treatment with alpha-2 agonists or antagonists recently. In addition, based on the previous meta-analysis, we included four other RCTs (6, 7, 9, 15) and excluded some studies with mixed intervention control and other interferences (3, 12–14). Though our meta-analysis was in line with the previous meta-analysis, this strict exclusion criteria added robustness to our main finding. Moreover, we also assessed the effect of DEX on cardiovascular stability and eliminated the security concerns for DEX use.

The results of the present study must be interpreted conservatively in light of a few potential limitations of the included trials. Firstly, there were some differences in the target populations (*eg*, gender, age, ethnicity, ASA grade, operation types and anaesthetic treatment) and intervention protocol (*eg*, treatment dosage and duration) of each study. Secondly, different measuring methods and samples were used for the determination of IL-6 and TNF-α. Thirdly, the pooled analyses were based on limited evidence and a medium sample size (30–100) patients.

CONCLUSION

The findings of this study suggests that intraoperative DEX can reduce the levels of IL-6 and TNF-α during the first day after surgery. However, the results should be interpreted with caution and further investigation is warranted.

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AUTHORS' NOTE

Wen-Qin Sun conceived the paper, oversaw the study and conducted the data analysis, wrote manuscript and approved the final version. Quan Zhou participated in the study design, data analysis and interpretation. Ai-Guo Zhou provided oversight for the study, critically revised the manuscript and approved the final version. Hong Mo participated in the data collection and interpretation. The authors declare that they have no conflicts of interest.

REFERENCES

1. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet 2008; **372:** 139–44.
2. Li Y, He R, Chen S, Qu Y. Effect of dexmedetomidine on early postoperative cognitive dysfunction and peri-operative inflammation in elderly patients undergoing laparoscopic cholecystectomy. Exp Ther Med 2015; **10:** 1635–42.
3. Tasdogan M, Memis D, Sut N, Yuksel M. Results of a pilot study on the effects of propofol and dexmedetomidine on inflammatory responses and intra-abdominal pressure in severe sepsis. J Clin Anesth 2009; **21:** 394–400.
4. Ueki M, Kawasaki T, Habe K, Hamada K, Kawasaki C, Sata T. The effects of dexmedetomidine on inflammatory mediators after cardiopulmonary bypass. Anaesthesia 2014; **69:** 693–700.
5. Wang ZX, Huang CY, Hua YP, Huang WQ, Deng LH, Liu KX. Dexmedetomidine reduces intestinal and hepatic injury after hepatectomy with inflow occlusion under general anaesthesia: A randomized controlled trial. Br J Anaesth 2014; **112:** 1055–64.
6. Ding L, Zhang H, Mi W, He Y, Zhang X, Ma X et al. Effects of dexmedetomidine on recovery period of anesthesia and postoperative cognitive function after robot–assisted laparoscopicradical prostatectomy in the elderly people. Zhong Nan Da Xue Xue Bao Yi Xue Ban 2015; **40:** 129–35.
7. Li H, Chen YH, Gong HJ. Effects of dexmedetomidine on inflammatory cytokines and renal function in patients underwent radical nephrectomy during perioperative period. J Jilin University Medicine Edition 2013; **39:** 588–91.
8. Liu HL, Qian YN. Effects of dexmedetomidine on perioperative inflammatory response in patients undergoing valve replacement. Chin J Applied Physiol 2013; **29:** 316–7.
9. Wang Y, Xu X, Liu H, Ji F. Effects of dexmedetomidine on patients undergoing radical gastrectomy. J Surg Res 2015; **194:** 147–53.
10. Yacout AG, Osman HA, Abdel-Daem MH, Hammouda SA, Elsawy MM. Effect of intravenous dexmedetomidine infusion on some proinflammatory cytokines, stress hormones and recovery profile in major abdominal surgery. Alexandria J Med 2012; **48:** 3–8.
11. Li B, Li Y, Tian S, Wang H, Wu H, Zhang A et al. Anti-inflammatory Effects of Perioperative Dexmedetomidine Administered as an Adjunct to General Anesthesia: A Meta-analysis. Sci Rep 2015; **5:** 12342.
12. Naguib AN, Tobias JD, Hall MW, Cismowski MJ, Miao Y, Barry N et al. The role of different anesthetic techniques in altering the stress response during cardiac surgery in children: a prospective, double-blinded, and randomized study. Pediatr Crit Care Med 2013; **14:** 481–90.
13. Zhang X, Wang J, Qian W, Zhao J, Sun L, Qian Y et al. Dexmedetomidine inhibits tumor necrosis factor-alpha and interleukin 6 in lipopolysaccharide-stimulated astrocytes by suppression of c-Jun N-erminal kinases. Inflammation 2014; **37:** 942–9.
14. Venn RM, Bryant A, Hall GM, Grounds RM. Effects of dexmedetomidine on adrenocortical function, and the cardiovascular, endocrine and inflammatory responses in post-operative patients needing sedation in the intensive care unit. Br J Anaesth 2001; **86:** 650–6.
15. Xu L, Hu Z, Shen J, McQuillan PM. Does dexmedetomidine have a cardiac protective effect during non-cardiac surgery? A randomised controlled trial. Clin Exp Pharmacol P 2014; **41:** 879–83.
16. Bekker A, Haile M, Kline R, Didehvar S, Babu R, Martiniuk F et al. The effect of intraoperative infusion of dexmedetomidine on the quality of recovery after major spinal surgery. J Neurosurg Anesthesiol 2013; **25:** 16–24.
17. Liu HL, Qian YN. Effects of dexmedetomidine on perioperative inflammatory response in patients undergoing valve replacement. Chin J Applied Physiol 2013; **29:** 316–7.

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