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Original Article

Efficacy and safety of prophylactic intravenous dexmedetomidine on opioid-induced cough: a systematic review and meta-analysis

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Abstract: Background: Opioid is widely used during general anesthesia but undesirable coughing can occur after an intravenous injection. Previous literature has examined the efficacy of administration of dexmedetomidine for the management of opioid-induced cough (OIC), but these results have been inconsistent. Therefore, the effectiveness and safety of prophylactic intravenous dexmedetomidine on OIC needs further investigation. Methods: A comprehensive literature search was performed to identify all randomized controlled trials (RCTs) that compared dexmedetomidine with normal saline about the reduction in the incidence of OIC. I^2 statistics were used to assess statistical heterogeneity, and fixed or random effects models were chosen to calculate the pooled risk ratio (RR) and 95% confidence interval (CI). The funnel plot, Begg test, and Egger test were used to assess potential publication bias. Results: We summarized 14 RCTs with a total of 2514 participants. Overall, prophylactic dexmedetomidine reduced the incidence of OIC [pooled RR=0.416; 95% CI: 0.353 to 0.491; P=0.096; heterogeneity test, I^2=34.9%]. Sub-group analysis indicated a significant reduction in the incidence of fentanyl-induced cough (FIC) and remifentanil-induced cough (RIC). Further sub-group analysis indicated that the lowest effect dose of dexmedetomidine for preventing the prevalence of OIC was 0.1 μg/kg. Dexmedetomidine used for preventing OIC is relatively safe. Conclusions: Our available data confirmed the effectiveness and safety of prophylactic dexmedetomidine for the prevention of OIC during induction. The lowest effective dose of dexmedetomidine on the risk of OIC appeared to be 0.1 μg/kg. Due to existed potential publication bias, larger RCTs are warranted.

Keywords: Dexmedetomidine, opioid-induced cough, fentanyl-induced cough, remifentanil-induced cough, meta-analysis

Introduction

Since Bohrer [1] and his colleagues first reported that administering fentanyl through a central venous catheter evokes the cough reflex, it has become well-known that remifentanil and fentanyl used for induction of anesthesia can provoke a cough. Generally, the incidence of opioid-induced cough (OIC) has been reported to be approximately 26-31% after remifentanil administration [2-4] and 18-65% after fentanyl injection [5-8].

Studies revealed that risk factors of fentanyl-induced cough (FIC) include young age, absence of cigarette smoking, and anesthetic factors, including the absence of epidurally administered lidocaine and the absence of a priming dose of vecuronium, however, it was unaffected by gender, the presence of either bronchial asthma or chronic obstructive pulmonary disease, or prior use of atropine [4, 8, 9]. Although OIC is transient, self-limiting and benign for most patients, sometimes coughing can increase intracranial, intraocular, and intra-abdominal pressures and thus it may become spasmodic or explosive, and life threatening requiring immediate intervention [7, 10, 11].

Although there were approaches of suppressing cough by limiting the peak plasma concentration of fentanil and remifentanil [7, 12-14] or by a huffing maneuver [15] before induction of anesthesia, pharmacological agents have been

Table 1. Characteristics of randomized controlled trials

Study (author, year, country)	Sample Size (n)	Age (years)	Coughing patients in the control group (%)	Intervention	Incidence of cough (%)	Opioid type and dose	Opioid time point of injection	Opioid speed of injection	Jadad Score
Sun et al. 2013 (China)	240	18-58	16/60 (26.7)	Saline	26.7	Sufentanil 0.5 μg/kg	5 min after intervention	Over 3 s	4
				Dexmedetomidine 0.1 μg/kg	6.7				
				Dexmedetomidine 0.25 μg/kg	5				
				Dexmedetomidine 0.5 μg/kg	6.7				
Zhou et al. 2013 (China)	280	18-65	32/70 (45.7)	Saline	45.7	Fentanyl 4.0 μg/kg	Immediately after intervention	Within 3 s	3
				Dexmedetomidine 0.5 μg/kg	34.2				
				Dexmedetomidine 0.75 μg/kg	21.4				
				Dexmedetomidine 1.0 μg/kg	18.6				
Wu et al. 2013 (China)	240	18-60	21/60 (35)	Saline	35	Sufentanil 0.2 μg/kg	Before intubation	NA	3
				Dexmedetomidine 1.0 μg/kg (rate: 0.07 $\mu g \cdot kg^{-1} \cdot min^{-1}$)	11.7				
				Dexmedetomidine 1.0 μg/kg (rate: 0.1 μg·kg-1·min-1)	10				
				Dexmedetomidine 1.0 μg/kg (rate: 0.2 μg·kg-1·min-1)	6.7				
Guo et al. 2013 (China)	80	27-65	15/40 (37.5)	Saline	37.5	Fentanyl 3.0 μg/kg	After intervention	Within 5 s	3
				Dexmedetomidine 0.5 μg/kg	7.5				
An et al. 2013 (China)	80	20-65	22/40 (55)	Saline	55	Sufentanil 0.5 μg/kg	After intervention	Within 5 s	4
				Dexmedetomidine 1.0 μg/kg	22.5				
Ma et al. 2013 (China)	300	20-50	30/60 (50)	Saline	50	Fentanyl 4.0 μg/kg	After intervention	Within 2 s	4
				Dexmedetomidine 0.1 μg/kg	26.7				
				Dexmedetomidine 0.25 μg/kg	23.3				
				Dexmedetomidine 0.5 μg/kg	20				
				Dexmedetomidine 1.0 μg/kg	20				
Yu et al. 2012 (China)	220	18-65	45/110 (40.9)	Saline+Saline	40.9	Fentanyl 3.0 μg/kg	2 min after intervention	Within 2 s	3
				Saline+Dexmedetomidine 0.5 μg/kg	22.7				
He et al. 2012 (China)	300	18-60	61/100 (61)	Saline	61	Fentanyl 4.0 μg/kg	Immediately after intervention	Less than 2 s	4
				Dexmedetomidine 0.5 μg/kg	40				
				Dexmedetomidine 1.0 μg/kg	18				
Chen et al. 2012 (China)	100	20-60	29/50 (58)	Saline	58	Fentanyl 4.0 μg/kg	After intervention	Within 3 s	3
				Dexmedetomidine 0.5 μg/kg	22				
Yu et al. 2012 (China)	424	18-65	27/106 (34.9)	Saline	34.9	Fentanyl 2.5 μg/kg	After intervention	Within 2 s	3
				Dexmedetomidine 0.1 μg/kg	13.2				
				Dexmedetomidine 0.25 μg/kg	21.7				
				Dexmedetomidine 0.5 μg/kg	22.6				
Liu et al. 2012 (China)	90	18-60	22/45 (48.9)	Saline	48.9	Sufentanil 0.3 μg/kg	After intervention	Within 3 s	3
				Dexmedetomidine 0.5 μg/kg	24.4				
Zhou et al. 2012 (China)	160	25-55	16/40 (40)	Saline	40	Fentanyl 5.0 μg/kg	After intervention	5 s	2
				Dexmedetomidine 0.5 μg/kg	10				
				Dexmedetomidine 0.8 μg/kg	10				
				Dexmedetomidine 1.0 μg/kg	5				
Zhou et al. 2011 (China)	60	24-68	17/30 (56.7)	Saline	56.7	Fentanyl 4.0 μg/kg	After intervention	Within 3 s	2

				Dexmedetomidine 1.0 μg/kg	23.3				
Sun et al. 2011 (China)	240	18-55	15/60 (25)	Saline	25	Sufentanil 0.5 μg/kg	After intervention	3 s	3
				Dexmedetomidine 0.1 μg/kg	7				
				Dexmedetomidine 0.25 μg/kg	7				
				Dexmedetomidine 0.5 μg/kg	5				

All interventions were administered intravenously.

Table 2. Baseline patient characteristics

Study	Age Mean (S.D.)	Female (%)	Weight (kg) Mean (S.D.)	ASA I/II (n)	Smoking (%)
Sun et al. 2013 (China)	39.65 (13.06)	50.6	65.1 (11.95)	127/31	24.7
Zhou et al. 2013 (China)	39.48 (12.09)	59.3	64.18 (10.63)	215/65	NA
Wu et al. 2013 (China)	40 (11.56)	42.5	60 (9.57)	NA	NA
Guo et al. 2013 (China)	NA	NA	NA	NA	NA
An et al. 2013 (China)	43.3 (7.27)	51.3	62.7 (7.45)	64/16	NA
Ma et al. 2013 (China)	41.4 (5.58)	NA	58.8 (6.65)	NA	NA
Yu et al. 2012 (China)	34.7 (9.8)	50.5	70.15 (11.63)	166/34	NA
He et al. 2012 (China)	39.75 (12.46)	38.2	65.5 (10.66)	396/104	31.6
Chen et al. 2012 (China)	44 (8.06)	51	58.4 (4.9)	NA	NA
Yu et al. 2012 (China)	44.5 (12.76)	55.9	64.25 (11.56)	296/128	NA
Liu et al. 2012 (China)	NA	NA	NA	NA	NA
Zhou et al. 2012 (China)	NA	NA	NA	NA	NA
Zhang et al. 2011 (China)	NA	NA	NA	NA	NA
Sun et al. 2011 (China)	35.75 (10.4)		59.75 (10.64)	NA	NA

ASA: American Society of Anesthesiologists Class; S.D.: standard deviation; NA: not available.

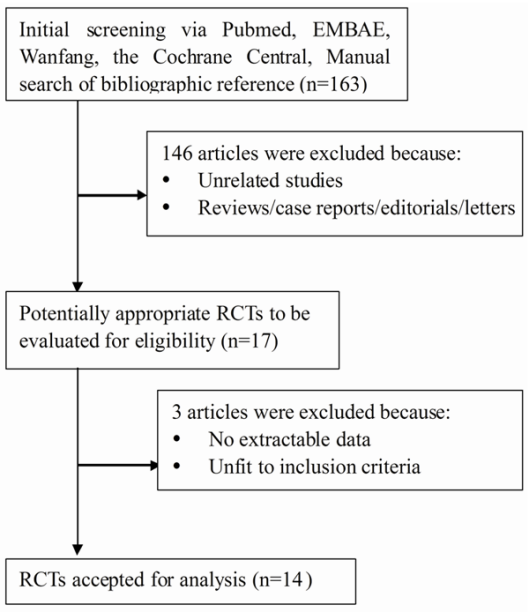

Figure 1. Flow chart of meta-analysis. RCT, randomized controlled trial.

reported to reduce OIC, and it has been reported that terbutaline [16], salbutamol [17], ephedrine [8], clonidine [18], ketamine [19], dexamethasone [20] and lidocaine [3, 6, 8, 21, 22] are effective in reducing FIC or remifentanil-induced cough (RIC).

Dexmedetomidine, a α2-adrenoceptor (α2-AR) agonist with sedative, analgesic and anxiolytic actions, has been widely used in the anesthetic setting and in intensive care and may have the potential of reducing the incidence of OIC. However, its impact on OIC remains inconclusive [23-36]. Therefore, we conducted a meta-analysis of randomized controlled trials (RCTs) in order to evaluate the efficacy of dexmedetomidine on OIC, as well as its safety.

Methods

Search strategy

We performed a systematic search of Pubmed, Embase, Wanfang and the Cochrane Central Register of Controlled Trials through April 2014 for relevant studies of association between prophylactic intravenous dexmedetomidine and OIC. Search strategies for subject headings and

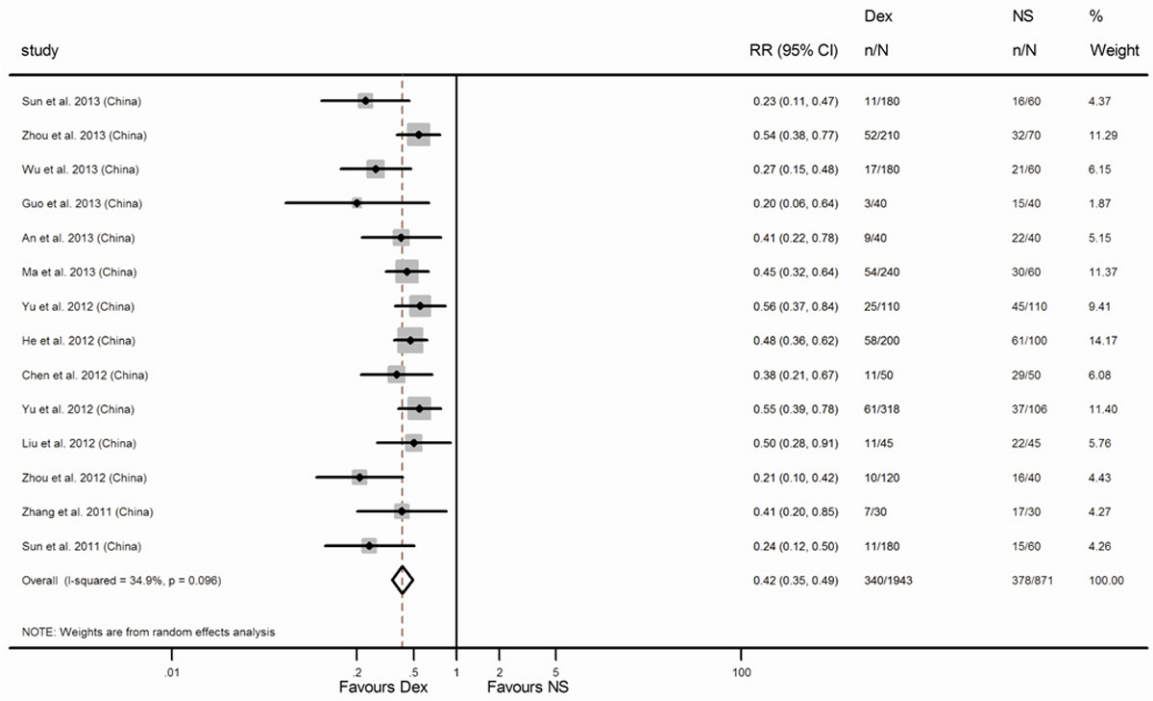

Figure 2. Dex on the incidence of OIC. Dex = dexmedetomidine, NS = normal saline.

key words as follows: (1) opioid, fentanyl, remifentanil, sufentanil, alfentanil; (2) dexmedetomidine, α2-adrenoceptor agonist, alpha 2-adrenoceptor agonist, α2-adrenergic receptor agonist, α2-AR agonist; (3) cough, coughing. A secondary reference review was conducted.

Inclusion and exclusion criteria

The eligible studies should match the following criteria: (1) study design: randomized controlled trial; (2) participants: patients underwent general anesthesia; (3) intervention: prophylactic intravenous dexmedetomidine; (4) comparator: placebo; (5) outcomes: the incidence of OIC and adverse events; (6) language restriction: no. We excluded trails that did not report any of the outcomes mentioned above. The titles, abstracts or full-texts were reviewed respectively.

Data extraction

We collected the following information from each eligible study: first author, year of publication, country of origin, sample size, age, gender, weight, smoking, American Society of Anaesthesiologists Class (ASA) classification, interventions, outcomes, and adverse events, presented in **Tables 1** and **2**. In extracting the data from three-arm studies with continuous data, it was desirable to combine two reported groups into a single group. The sample size, mean and SD of the combined group were calculated according to the formula described in the Cochrane Handbook of Systematic Reviews of interventions [37]. Independent investigators respectively calculated and tabulated the data with a standard extraction formula. Discrepancies were resolved via group discussion.

Quality assessment

A professional authority evaluated the methodological quality of included studies using the Jadad's score scale, [38] as shown in **Table 1**. The quality scale ranges from 0-5 points. Higher scores indicate better reporting. The studies are considered low quality if the Jadad score is ≤2 and high quality if the score is ≥3 [39]. Another specialist verified the evaluation accuracy.

Statistical analysis

We pooled data across studies and calculated the RR and associated 95% CIs for each dichotomous outcome. Heterogeneity across studies

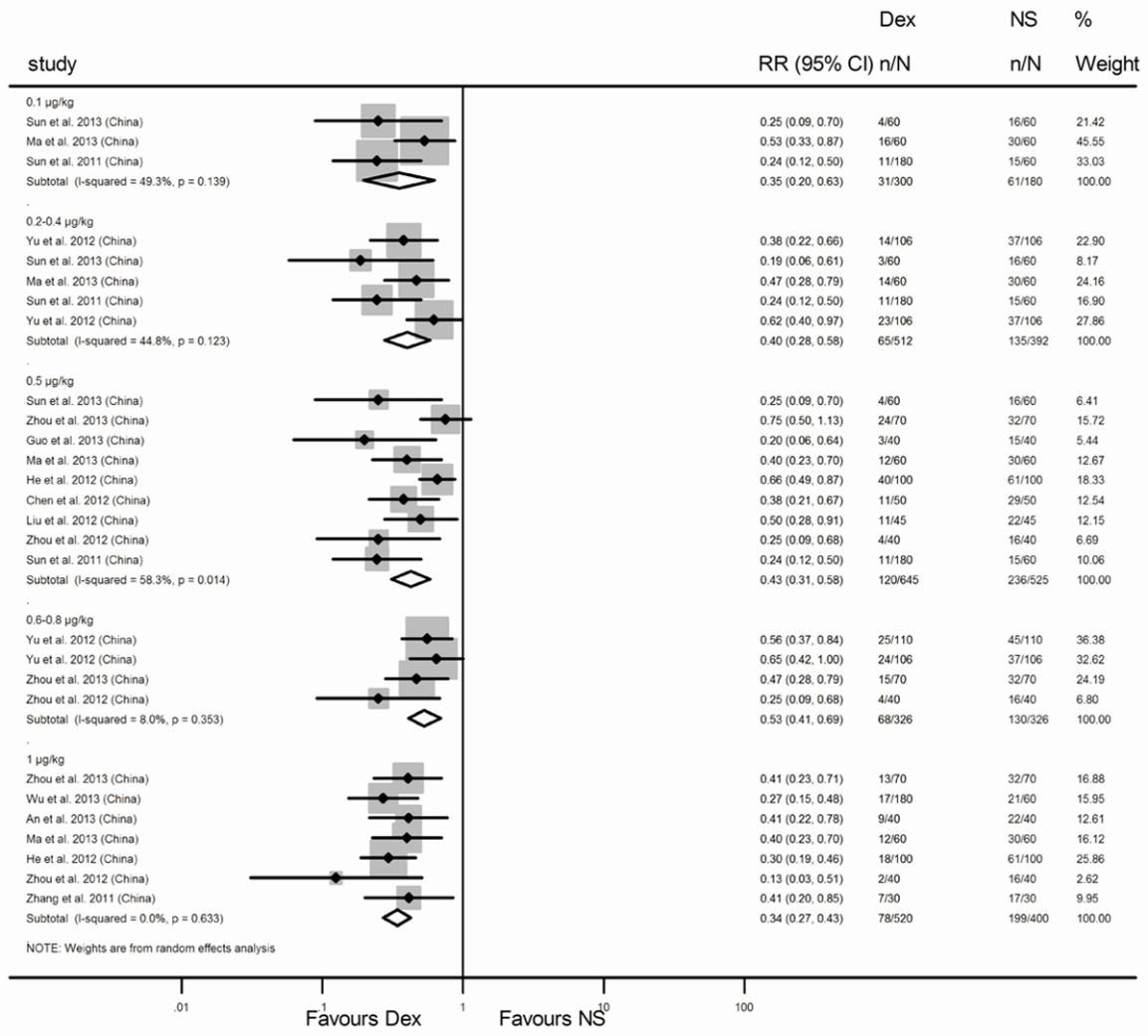

Figure 3. Dex on the incidence of OIC (grouped by dosage, random-effects model). Dex = dexmedetomidine, NS = normal saline.

was tested by using the I^2 statistic, which is a quantitative measure of inconsistency across studies [40]. An I^2 value greater than 50% indicates significant heterogeneity [41]. Considering that heterogeneity between studies, the random effects models were chosen to generate pooled effects.

We further conducted subgroup analyses and sensitivity analyses to explore possible explanations for heterogeneity. The possibility of publication bias was assessed using the Begg and Egger test [42, 43]. All analyses were performed using STATA version 11.2 (Stata Corp LP, College Station, TX). A value $P<0.05$ was considered statistically significant.

Results

Literature search

We initially retrieved 163 literatures from PubMed, Embase, Wanfang and the Cochrane Central Register of Controlled Trials (15 from Pubmed, 61 from Embase, 68 from Wanfang and 19 from the Cochrane Central). 14 independent studies that met the inclusion criteria were included in our final analysis [23-36]. The details of literature search and study selection are described in **Figure 1**.

Study characteristics

The characteristics of the 14 RCTs, published between 2011 and 2013, are presented in

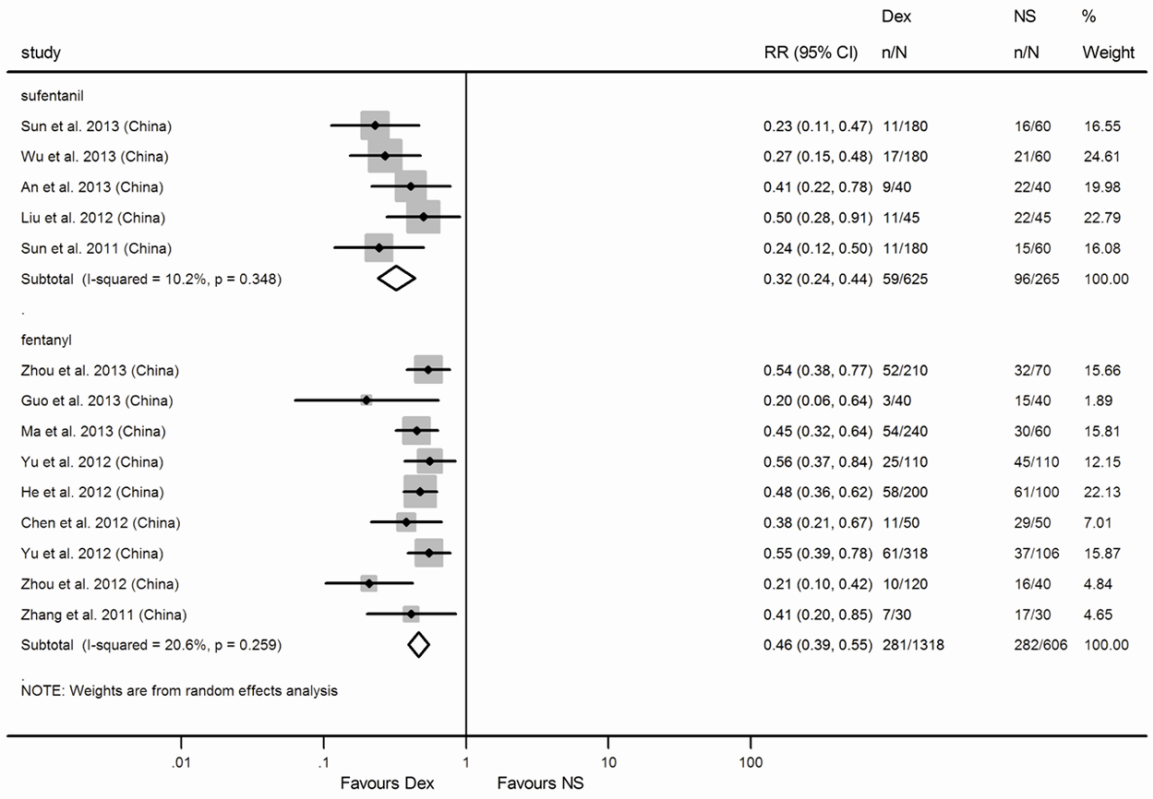

Figure 4. Dex on the incidence of OIC (grouped by opioid type, random-effects model). Dex = dexmedetomidine, NS = normal saline.

Table 1. All the studies were conducted in China. Four studies [23, 25, 27, 33, 36] investigated the remifentanil infusion, the other nine [24, 26, 28-32, 34, 35] studied the fentanyl injection. All the studies reported the incidence of OIC and five studies [23-25, 28, 36] also investigated the incidence of low blood pressure and severe sinus bradycardia induced by dexmedetomidine. The sizes of RCTs ranged from 60 to 424 (total 2514) participants. The dose range of fentanyl and remifentanil was 3.0-5.0 μg/kg and 0.2-0.5 μg/kg, respectively. The dose of dexmedetomidine was from 0.1 to 1.0 μg/kg and dexmedetomidine was all injected before opioid administration.

Dexmedetomidine with the incidence and severity of OIC

Intravenous dexmedetomidine was associated with a decreased risk of OIC: the pooled risk ratio (RR) of 0.416 [95% CI: 0.353 to 0.491], with moderate heterogeneity (P=0.096; I^2= 34.9%), as shown in **Figure 2**.

Sub-group analyses

To explore the study heterogeneity and dose effect of dexmedetomidine for preventing OIC, we also performed stratified analyses.

For analyzing the dose effect of dexmedetomidine, we divided the dose into five groups: 0.1 μg/kg, 0.2-0.4 μg/kg, 0.5 μg/kg, 0.6-0.8 μg/kg, 1 μg/kg. It seemed that dexmedetomidine can significantly reduce the incidence of OIC in all groups, as shown in **Figure 3**. That is to say, the lowest dose of dexmedetomidine for preventing the risk of OIC was 0.1 μg/kg.

After divide the opioid into remifentanil and fentanyl group, and found that the incidence of OIC was significantly reduced in two groups: pooled RR of 0.323 (95% CI, 0.239 to 0.437) and 0.464 (95% CI: 0.394-0.545), respectively, as shown in **Figure 4**.

Considering the methodological quality of include studies, we divided the studies into two groups: high quality group and low quality

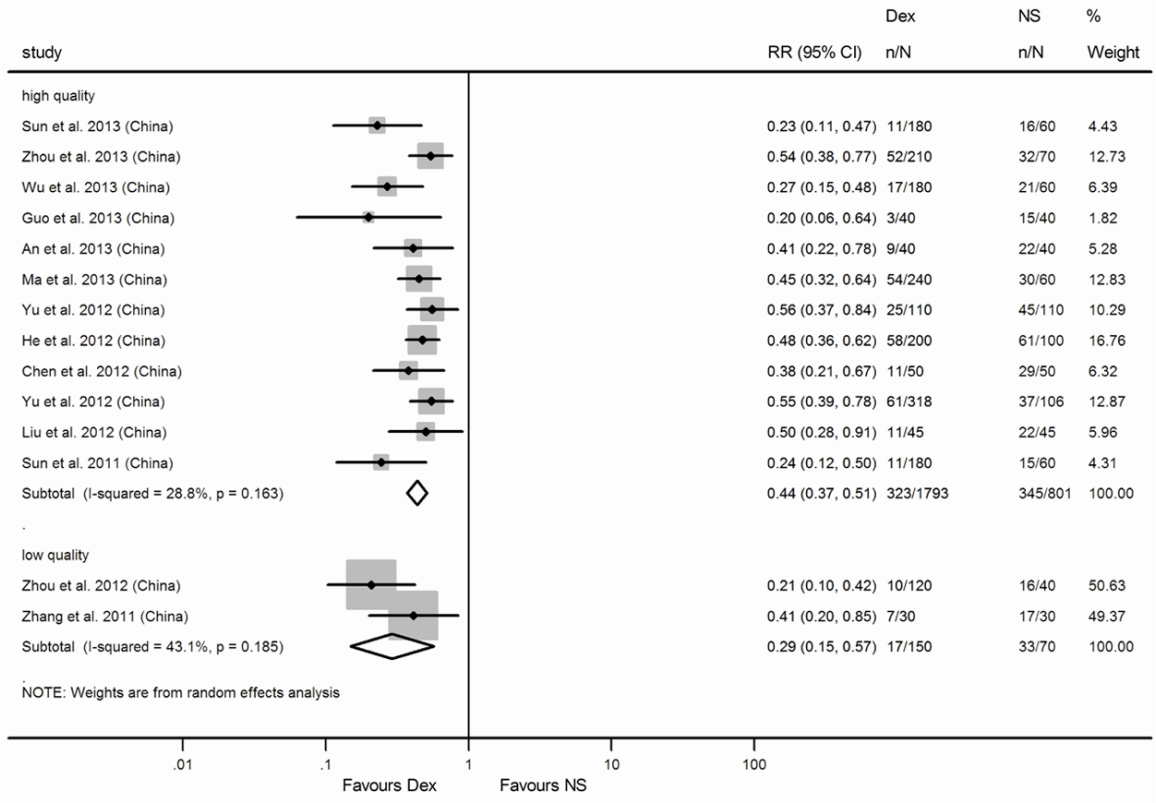

Figure 5. Dex on the incidence of OIC (grouped by quality score, random-effects model). Dex = dexmedetomidine, NS = normal saline.

group, we found that the incidence of OIC was significantly reduced in two groups: pooled RR of 0.435 (95% CI, 0.371-0.512) and 0.292 (95% CI: 0.150-0.569), respectively, as shown in **Figure 5**.

For analyzing the influence of publication language, we divided the studies into two groups: the English group and the Chinese group. It seemed that dexmedetomidine can significantly reduce the incidence of OIC in both groups: pooled RR of 0.437 (95% CI, 0.301-0.635) and 0.403 (95% CI: 0.331-0.492), respectively, as shown in **Figure 6**.

Adverse effect and safety of dexmedetomidine

Potential occurrence of adverse effects of dexmedetomidine such as low blood pressure and severe sinus bradycardia were reported in most of the studies. Although five studies [23-25, 28, 36] reported the incidence of low blood pressure, dexmedetomidine can maintain the stability of blood pressure: pooled RR=1.039; 95% CI: 0.497 to 2.176; P=0.039; I^2=60.4% (**Figure 7**). Five studies [23-25, 28, 36] reported that dexmedetomidine can induce severe sinus bradycardia: pooled RR=9.552; 95% CI: 1.536 to 59.396; P=0.008; I^2=70.9% (**Figure 8**). However, they can be solved by injection of atropine. Therefore, the dose of dexmedetomidine used for preventing OIC is relatively safe.

Sensitivity analyses

Sensitivity analysis excluding each included study at one time revealed that each individual study was consisted with the direction and size of the overall dexmedetomidine effect, as shown in **Figure 9** and **Table 3**.

Publication bias

Visual inspection of the Begg funnel plot indicated substantial asymmetry (**Figure 10**). The Begg rank correlation test and Egger linear regression test also supported the presence of publication bias (Begg's test, P=0.029; Egger's test, P=0.003).

Sensitivity analysis revealed that a single study involved in the meta-analysis was de-

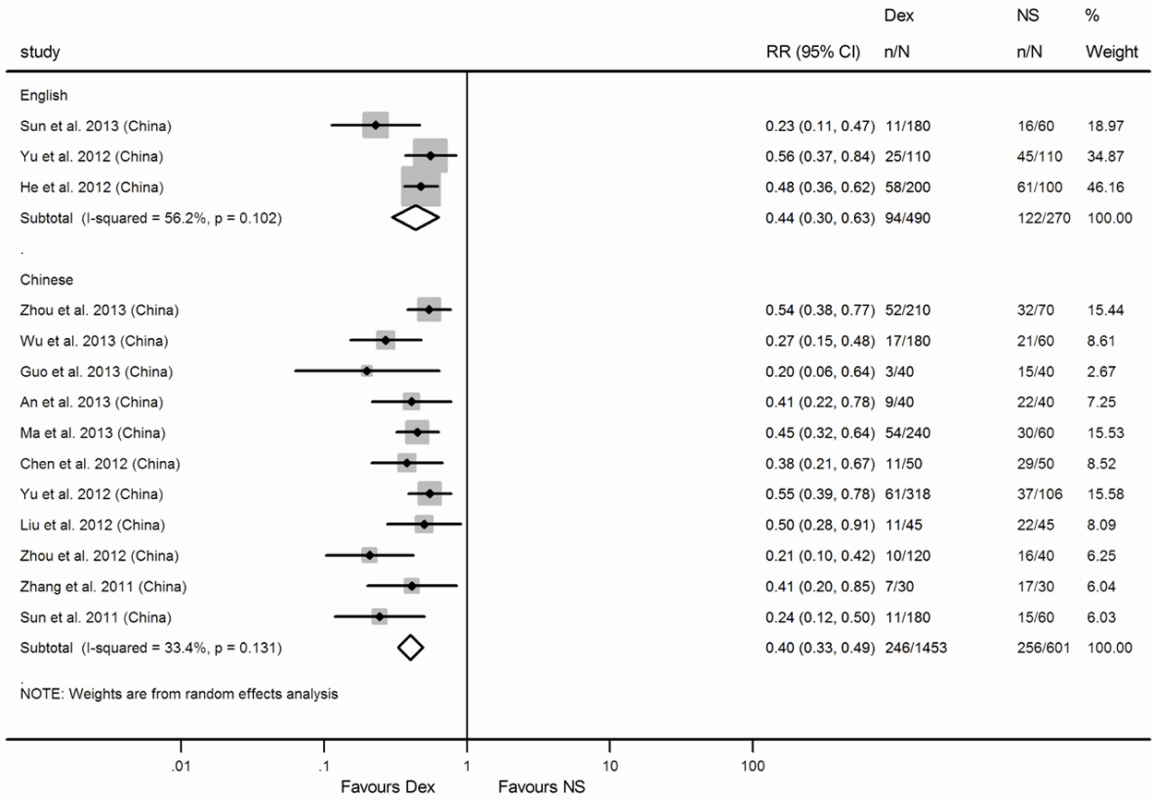

Figure 6. Dex on the incidence of OIC (grouped by language, random-effects model). Dex = dexmedetomidine, NS = normal saline.

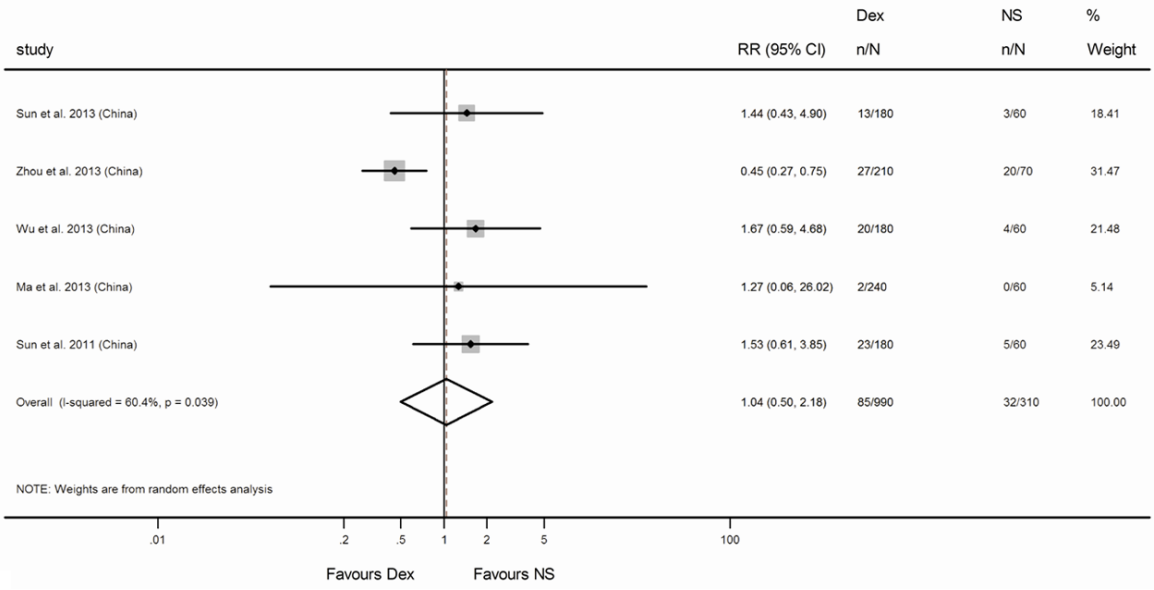

Figure 7. Dex on the incidence of OIC low blood pressure. Dex = dexmedetomidine, NS = normal saline.

leted each time did not influence the corresponding pooled RRs (**Figure 9** and **Table 3**), suggesting that our results are statistically robust.

Discussion

The relationship between prophylactic dexmedetomidine and OIC remains controversial. To

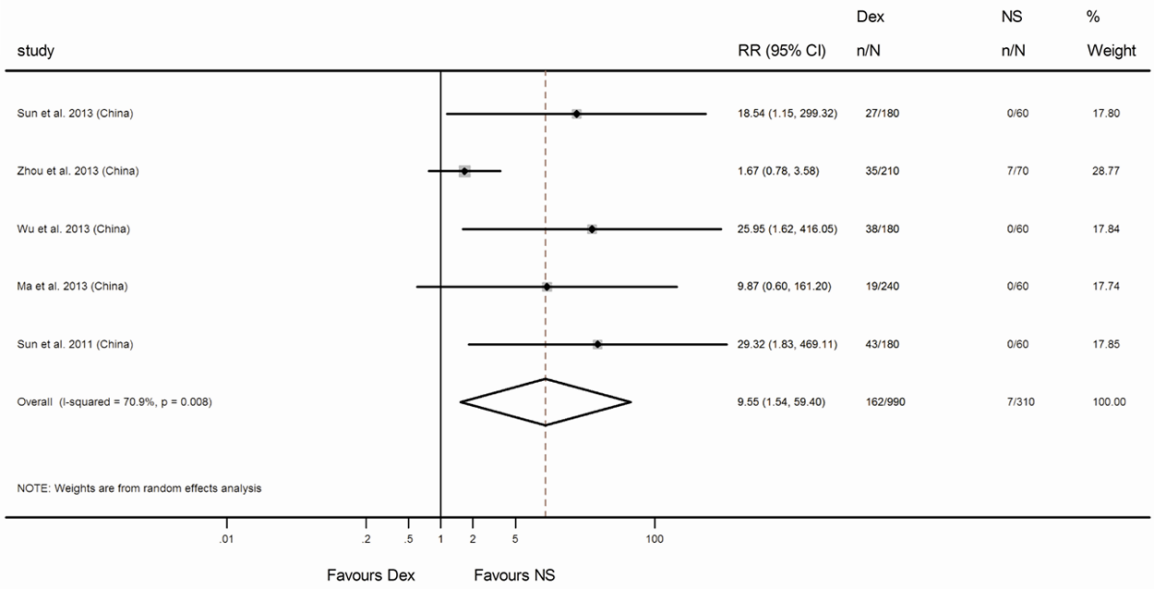

Figure 8. Dex on the incidence of severe sinus bradycardia. Dex = dexmedetomidine, NS = normal saline.

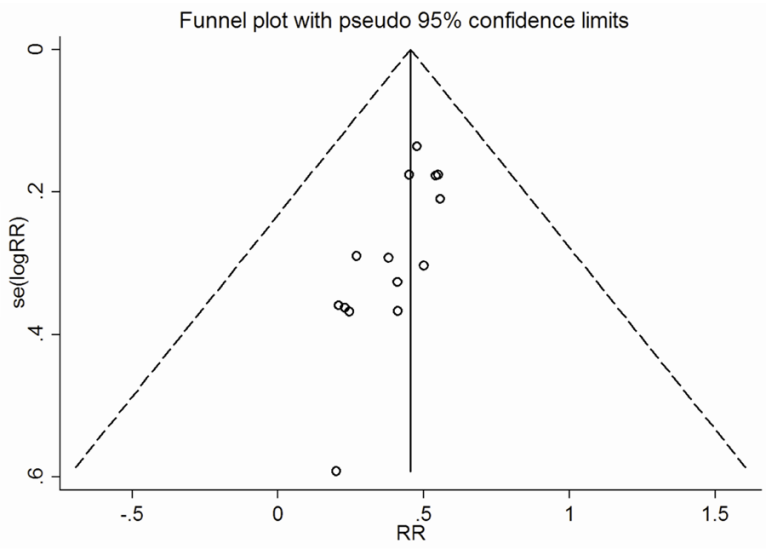

Figure 9. Funnel plot of studies included in the meta-analysis of DEX prevention in OIC (Egger' test, P=0.029; Egger' test, P=0.003). Dex = dexmedetomidine.

our knowledge, this is the first meta-analysis that investigated the association of dexmedetomidine with OIC, and we found dexmedetomidine can significantly reduce the incidence of OIC.

OIC is a common adverse event after opioid administration during general anesthesia. However, the mechanisms of OIC have not been elucidated. Various mechanisms proposed to explain OIC are as follows: (1) inhibition of central sympathetic outflow causing vagal predominance and inducing cough and reflex [16, 17, 44]; (2) pulmonary chemoreflex resulting from stimulation of C-fiber receptors (Juxta-capillary receptors) [5] or irritant receptors (rapidly adapting receptors) from deformation of the trachea-bronchial wall by tracheal smooth muscle constriction [22, 45]; (3) histamine release from lung mast cells [17]; (4) the sudden adduction of the vocal cords or supraglottic obstruction by soft tissue caused by opioid-induced muscle rigidity [46, 47].

Considering the above referred mechanisms of OIC, many pharmacological measures were conducted to prevent OIC, such as terbutaline, salbutamol, ephedrine, clonidine, ketamine, and dexamethasone. Dexmedetomidine has sedative, analgesic, anti-sympathetic, and anti-shivering activities, and is able to inhibit the stress response while reducing the amounts of anesthetics and opioids used [48]. It is able to stabilize patients' hemodynamics without caus-

Table 3. Sensitivity analysis excluding individual study at one time

Study	Remaining RR	95% CI		*P*-value	I^2
Sun et al. 2013 (China)	0.433	0.369	0.506	0.165	27.80%
Zhou et al. 2013 (China)	0.402	0.336	0.480	0.106	34.50%
Wu et al. 2013 (China)	0.432	0.367	0.508	0.149	29.40%
Guo et al. 2013 (China)	0.424	0.360	0.499	0.113	33.70%
An et al. 2013 (China)	0.414	0.347	0.494	0.068	39.80%
Ma et al. 2013 (China)	0.407	0.338	0.491	0.068	39.90%
Yu et al. 2012 (China)	0.403	0.338	0.481	0.097	35.70%
He et al. 2012 (China)	0.416	0.353	0.491	0.096	34.90%
Chen et al. 2012 (China)	0.416	0.349	0.497	0.073	39.10%
Yu et al. 2012 (China)	0.401	0.336	0.479	0.112	33.80%
Liu et al. 2012 (China)	0.409	0.343	0.488	0.071	39.40%
Zhou et al. 2012 (China)	0.437	0.376	0.509	0.215	22.60%
Zhang et al. 2011 (China)	0.416	0.353	0.491	0.096	34.90%
Sun et al. 2011 (China)	0.429	0.365	0.505	0.138	30.80%

RR: risk ratio; CI: confidence interval.

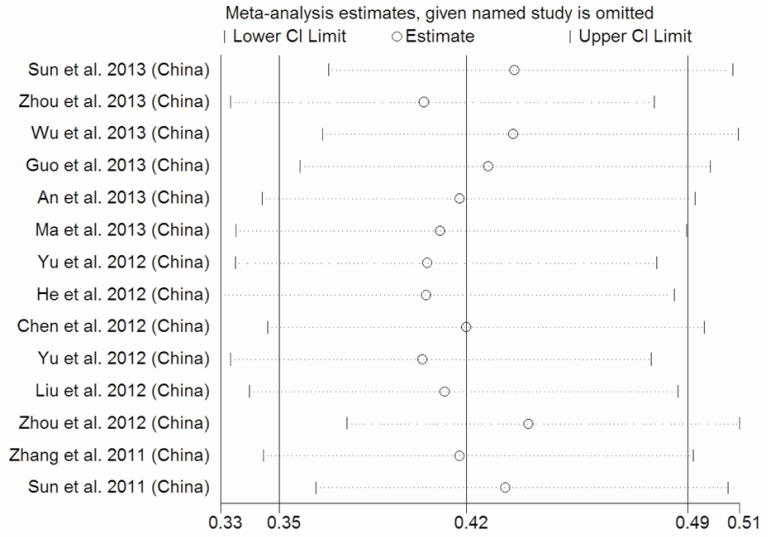

Figure 10. Sensitivity analysis evaluating the influence of each individual study (left side) on the overall estimate. The refmaining results with 95% confidence interval (CI) are presented.

ing respiratory depression [49, 50]. Therefore, the preoperative application of dexmedetomidine has been increasingly common.

The following factors may account for the possible mechanism of dexmedetomidine in inhibiting OIC. Firstly, the ability of α2-adrenoreceptor agonists to reverse the muscular rigidity induced by opioids in rats has been proven [51], and it is possible that the incidence of fentanyl-induced cough may be decreased by α2-adrenoreceptor agonists via reversal of the muscular rigidity induced by fentanyl [52]. Of note, the intravenous administration of dexmedetomidine effectively blocked histamine-induced bronchoconstriction in dogs [53], and it has been demonstrated that ketamine effectively reduced fentanyl-induced cough through relaxing histamine-associated tracheal smooth muscle contraction [54]. Clonidine prevents cough while reducing blood pressure moderately [55]; however, it may cause circulatory fluctuation, whereas a short duration of dexmedetomidine infusion has no effect on blood pressure. Though injection of dexmedetomidine may increase the risk of severe sinus bradycardia during anesthetic induction, the intravenous injection of atropine 0.5 mg helps to achieve a rapid return to the normal heart rate level. Therefore, dexmedetomidine used for preventing OIC is totally safe.

Therefore, we proposed that preventing OIC using drugs is of great importance, not only concerning with patients' comfortableness and safety, but also maintaining anesthesiologists' previous habits of using opioid during induction of anesthesia. Among these drugs, we recommended dexmedetomidine as the first choice, considering its effectiveness and other perioperative benefits. Dexmedetomidine 0.1 μg/kg is lowest effective dose to suppress OIC.

Further studies are needed due to some limitations in our meta-analysis. First, the number of some included studies was limited and the data was not complete. Second, bias analysis found funnel plots, Begg's test, and Egger's test suggested publication bias in this meta-analysis. Fourth, all the data were from adults,

we did not know the effectiveness of dexmedetomidine on OIC in children. Consequently, meta-analysis results for dexmedetomidine must be interpreted cautiously, because of the risk of unpublished negative results.

In summary, we have illustrated the effectiveness of prophylactic intravenous dexmedetomidine for the prevention the incidence of OIC in this meta-analysis. The lowest effect dose of dexmedetomidine seemed to be 0.1 μg/kg. The dosage of dexmedetomidine for preventing OIC was safe.

Based on this meta-analysis, high-quality randomized controlled studies of dexmedetomidine on both children and adults and other kinds of drug therapies for OIC should be investigated in the future.

Disclosure of conflict of interest

None.

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