

# A systematic review and meta-analysis of the safety and efficacy of remifentanil and dexmedetomidine for awake fiberoptic endoscope intubation

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## Abstract

**Background:** Awake fiberoptic endoscope intubation (AFOI) is the primary strategy for managing anticipated difficult airways. Adequate sedation, most commonly being achieved with remifentanil and dexmedetomidine, is integral to this procedure. This meta-analysis aimed to compare the safety and efficacy of these 2 sedatives.

**Methods:** We conducted electronic searches in Embase, Web of Science, PubMed, Google Scholar, Medline, Springer, and Web of Science with no language restrictions. Studies comparing safety and efficacy between the sole use of remifentanil and dexmedetomidine among patients who underwent AFOI were included. Eight randomized controlled trials, comprising 412 patients, met the inclusion criteria. The primary outcomes were first attempt intubation success rate and incidence of hypoxia. The secondary outcomes were the Ramsay Sedation Scale score at intubation, memory recall of endoscopy, and unstable hemodynamic parameters during intubation.

**Results:** Dexmedetomidine significantly reduced the incidence of hypoxemia during AFOI (risk ratio: 2.47; 95% confidence [CI]: 1.32–4.64) compared with remifentanil; however, the first intubation success rates were equivalent (risk ratio: 1.12; 95% CI: 0.87–1.46). No significant differences between the 2 sedatives were found for the Ramsay Sedation Scale score at intubation (mean difference: –0.14; 95% CI: –0.66–0.38) or unstable hemodynamic parameters during intubation (risk ratio: 0.83; 95% CI: 0.59–1.17). Dexmedetomidine reduced memory recall of endoscopy (risk ratio: 1.39; 95% CI: 1.13–1.72).

**Conclusions:** While both remifentanil and dexmedetomidine are effective for AFOI and well-tolerated, dexmedetomidine may be more effective in reducing the incidence of hypoxemia and memory recall of endoscopy.

**PROSPERP registration number:** CRD42020169612.

**Abbreviations:** AFOI = awake fiberoptic endoscope intubation, DEX = dexmedetomidine, PRISMA = Systematic Reviews and Meta-analysis, RCTs = randomized controlled trials, REM = remifentanil.

**Keywords:** dexmedetomidine, endoscopy, intratracheal, intubation, meta-analysis, remifentanil

## 1. Introduction

The awake fiberoptic endoscope intubation (AFOI) technique is the gold standard for the management of patients with predicted difficult airways, especially prior to general anesthesia induc-

tion.<sup>[1]</sup> Nevertheless, the improper application of AFOI can lead to unstable hemodynamics, patient discomfort, and treatment failure; thus, the success of this technique is highly dependent on operator proficiency and a safe sedation scheme.<sup>[2]</sup>

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Z-hT and QC contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are publicly available.

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Controlled sedation and analgesia are integral to AFOI, as deep sedation can cause respiratory depression, while shallow anesthesia may result in a rough cough and extreme discomfort.<sup>[3]</sup> The ideal sedation outcome is to keep the patient quiet with their eyes closed under spontaneous breathing, maintain low sensitivity to nausea and vomiting, and allowing for them to be awakened if necessary.<sup>[2,3]</sup> Safety and comfort are the main concerns in the rational use of sedative agents.

The most commonly used sedative agents in operating theaters include benzodiazepines, ketamine, propofol, sevoflurane, remifentanyl (REM), and dexmedetomidine (DEX).<sup>[2–7]</sup> In non-difficult airway cases, such as selective bronchoscopy, a combination of 2 sedatives can be used to meet procedural needs,<sup>[8]</sup> but the combination of these drugs during AFOI can result in severe respiratory depression. For safety purposes, the agents chosen for sedation should be short-acting, easily titratable, and have minimal suppression of spontaneous ventilation.<sup>[9]</sup>

Different sedative agents have been shown to have their own advantages and disadvantages, and this has been the focus of a number of prior studies. For instance, several randomized controlled trials (RCTs),<sup>[10,12–14]</sup> case report,<sup>[11]</sup> and systematic reviews<sup>[15,16]</sup> have demonstrated that DEX is superior to midazolam, fentanyl, sufentanil, and propofol when used during AFOI. While previous studies have compared DEX with REM for AFOI, the results have been inconclusive.<sup>[17–24]</sup> Thus, we undertook this systematic review and meta-analysis to investigate whether AFOI with DEX would lead to better safety and efficacy when compared with REM.

## 2. Materials and methods

### 2.1. Protocol and registration

This meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) Statement guidelines.<sup>[25]</sup> The protocol of this systematic review was registered with the International Prospective Register of Systematic Reviews (CRD42020169612). Ethical approval was unnecessary as the study protocol consists only of a systematic review and did not involve private patient data.

### 2.2. Literature search

The literature search was conducted by 2 independent reviewers. In the case of disagreements on study eligibility, the opinion of a third reviewer was obtained. A total of 7 electronic databases (Embase, PubMed, Google Scholar, Medline, Springer, and Web of Science) were searched up to April 20, 2020 with combinations of the following keywords

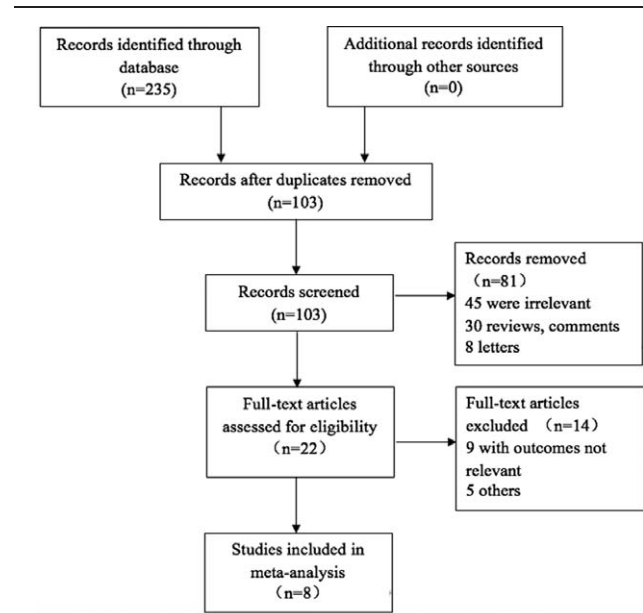
“remifentanyl,” “dexmedetomidine,” “awake intubation,” “awake fiberoptic intubation,” and “intubation.” The search strategy was limited to RCTs conducted on human participants. The including studies were limited to those published in English.

### 2.3. Eligibility criteria

Studies were included if they were

1. RCTs and
2. compared REM and DEX in adult patients undergoing AFOI.

We excluded RCTs comparing other sedatives, local infiltration anesthesia, or thyrocriocentesis. Case reports, review articles, and animal experiments were also excluded.



**Figure 1.** PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

### 2.4. Trial selection

The methodological quality of each included study was evaluated by 2 independent reviewers; a third reviewer was consulted if disagreements arose. The results of the trial selection process are presented in the PRISMA flowchart (Fig. 1).

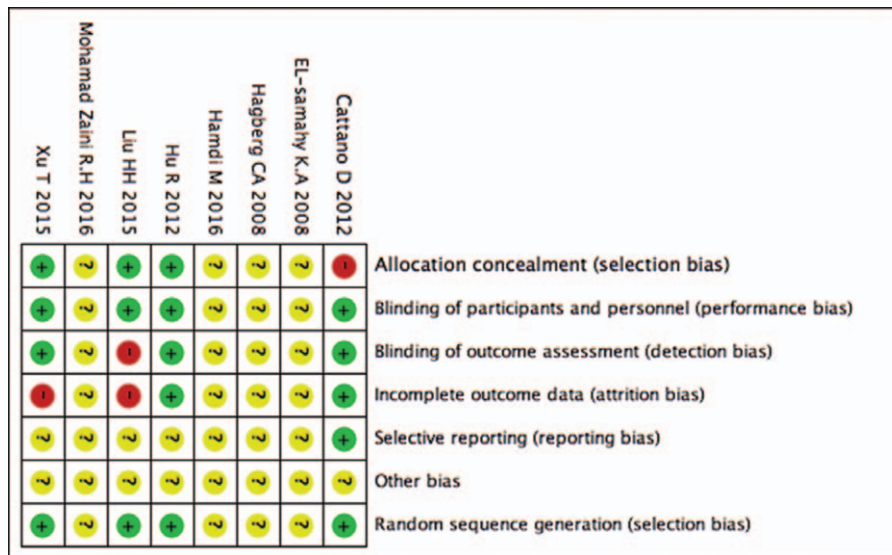
### 2.5. Risk of bias assessment

The Cochrane Collaboration Risk of Bias Tool was used to evaluate the quality of each RCT in terms of selection, performance, detection, attrition, and reporting bias (Fig. 2). Two authors assessed the RCTs independently and assigned quality scores after reaching a consensus. A third author was consulted when an agreement could not be reached. RCT quality scores were not a factor for trial exclusion.

### 2.6. Data extraction

Data were retrieved independently by 2 reviewers, and subsequently cross-checked. Differences in opinions were resolved by consensus through discussion and consultation with a third reviewer. Extracted data included author names, publication year, number of patients in each group, intubation type, and details of local anesthetic, REM, and DEX usage (Table 1).

Some studies (e.g., conference abstracts) met our selection criteria but did not report sufficient data. For instance, some of these studies did not present their outcome data as mean and standard deviation or standard error of the mean and 95% confidence interval (CI); in these cases, we sent e-mails to request the original data from the corresponding authors. If a reply was not received, the mean was considered to be equivalent to the median, and the standard deviation was approximated to be the interquartile range divided by 1.35 or the range divided by 4. Hypoxia was defined as a pulse oximetry saturation <90%, and unstable hemodynamic parameters included hypertension, hypotension, tachycardia, and bradycardia.



**Figure 2.** Evaluation of risk of bias for each included study. Green circle indicates low risk of bias, red circle indicates high risk of bias, yellow circle indicates unclear risk of bias.

**2.7. Outcomes**

The primary outcomes were the success rate of intubation on the first attempt, and the incidence of hypoxia during intubation. Secondary outcomes included the Ramsay Sedation Scale (RSS) score, unstable hemodynamic parameters during intubation, and memory recall of endoscopy.

**2.8. Statistical analysis**

Revman 5.3 software (Oxford, UK), provided by the Cochrane Collaboration, was used for all statistical analyses. Each continuous outcome was expressed as a mean difference (SD with 95% CI). The relative risk (with 95% CI) was determined for dichotomous data. The level of heterogeneity was determined via the  $\chi^2$  test *P* value and the *I*<sup>2</sup> value. A fixed effects model was

performed in cases of data heterogeneity (*P* > .1 or *I*<sup>2</sup> < 50%), and a random effects model was performed in cases of data homogeneity (*P* < .1 or *I*<sup>2</sup> > 50%). Publication bias was assessed using the Egger test, with *P* > .05 indicating no statistically significant publication bias. Sensitivity analysis was also utilized to evaluate the stability of article results.

**3. Results**

**3.1. Literature search**

The literature search identified a total of 235 potentially relevant studies, with 8 qualifying RCTs (comprising 412 patients) meeting our inclusion criteria (Fig. 1).<sup>[17–24]</sup> All 8 RCTs compared REM with DEX during AFOI.

**Table 1**

**Trial characteristics.**

Study	Year	No. patients	Intubation type	Local anesthesia	Dexmedetomidine, infusion rate	Remifentanyl, infusion rate
Cattano D	2012	30	AFOI 22 oral /8 nasal	4%lidocaine	a loading dose of 0.4 mcg/kg followed by an infusion of 0.7 mcg/kg/h	a loading dose of 0.75 mcg/kg followed by an infusion of 0.075 mcg/kg/min
Hu R	2012	40	AFOI nasotracheal	7%lidocaine	a loading dose (1.5 lg/kg) infused over 10min followed by 0.7 lg/kg/h	TCl: initial 3.0 ng/ml, than 0.5 ng/ml
Liu HH	2015	90	AFOI	2% lidocaine	1 $\mu$ g/kg infused over 10 min, followed by 0.3 $\mu$ g/kg/h	a loading dose of 0.15 $\mu$ g/kg/min over 5 min, followed by 0.1 $\mu$ g/kg/min
Xu T	2015	68	AFOI	Lidocaine 200mg	1 $\mu$ g · kg <sup>-1</sup> over 10 min followed by 0.7 $\mu$ g · kg <sup>-1</sup> h <sup>-1</sup>	TCl: 2.5 ng ml <sup>-1</sup> , increased to 3 ng ml <sup>-1</sup> 10 min later
Hagberg CA	2008	30	AFOI	4% lidocaine	0.4 $\mu$ g/kg over 10 minutes followed by an infusion 0.7 $\mu$ g/kg per hour	a bolus of 0.75 $\mu$ g/kg over 10 minutes, followed by 0.075 $\mu$ g/kg per minute
Hamdi M	2016	40	AFOI	5% idocaine 3 sprays ateach nostril	bolus of 0.4 $\mu$ gkg <sup>-1</sup> followed by an infusion at a rate of 0.7 $\mu$ gkg <sup>-1</sup> h <sup>-1</sup>	bolus 0.75 $\mu$ gkg <sup>-1</sup> followed by an infusion at a rate of 0.075 $\mu$ gkg <sup>-1</sup> min <sup>-1</sup>
Mohamad Zaini RH	2016	64	AFOI	unclear spray as you go	0.5 mcg/kg over 10 min followed by 0.5–0.7 mcg/kg/h	TCl: 0.5–1 ng/ml
EL-samahy KA	2008	50	AFOI	none	1 $\mu$ g.kg <sup>-1</sup> in bolus over10min, followed by a continuous infusion of 0.7 $\mu$ g.kg <sup>-1</sup> .h <sup>-1</sup> .	0.75 $\mu$ g.kg <sup>-1</sup> in bolus administered over30s, followedbya continuous infusion of 0.075 $\mu$ g.kg <sup>-1</sup> .min <sup>-1</sup>

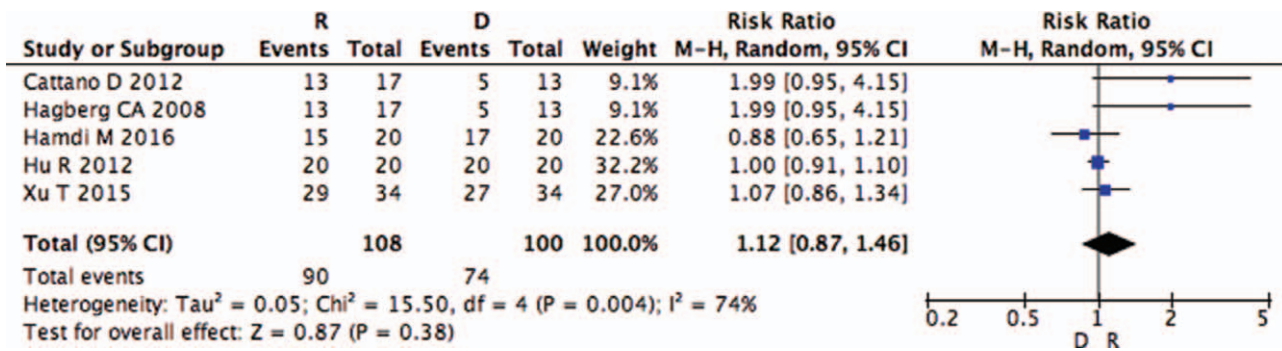


Figure 3. Forest plot of the meta-analysis: success rate of intubation at the first attempt between 2 agents.

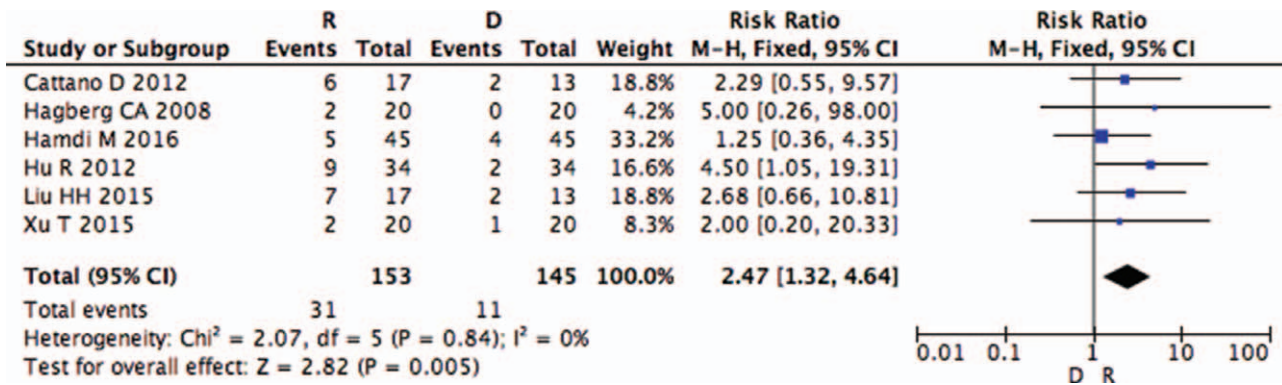


Figure 4. Forest plot of the meta-analysis: incidence of hypoxia during intubation between 2 agents.

### 3.2. Study quality

Four studies did not have a high risk of bias for any of the evaluated criteria, while the other 4 studies had almost elements with unclear risk of bias due to abstract only (Fig. 2).

### 3.3. Success rate of intubation on the first attempt

Five studies measured the success rate of intubation on the first attempt (n=208).<sup>[17-21,24]</sup> Although 2 studies reported that REM improved the first intubation attempt success rate, the results of the meta-analysis indicated that there was no significant difference between REM and DEX (95% CI: 0.87-1.46; I<sup>2</sup>=74%; P=.38). However, there was a large degree of heterogeneity (Fig. 3). The Egger test did not show obvious evidence of publication bias (P=.093).

### 3.4. Incidence of hypoxia

The incidence of hypoxia during intubation was reported in 6 studies (n=298).<sup>[17-21,24]</sup> DEX was associated with a lower incidence of hypoxia during AFOI (95% CI: 1.32-4.64; I<sup>2</sup>=0%; P=.005) (Fig. 4). The Egger test for publication bias (P=.215) and sensitivity analysis did not significantly alter these results.

### 3.5. Level of sedation

Four studies assessed the level of sedation using the RSS score during intubation (n=228).<sup>[17-20]</sup> RSS scores were not significantly associated with either the use of DEX or REM (95% CI: -0.66 to 0.38; I<sup>2</sup>=70%; P=.60) (Fig. 5). The Egger test showed evidence of publication bias (P=.008).

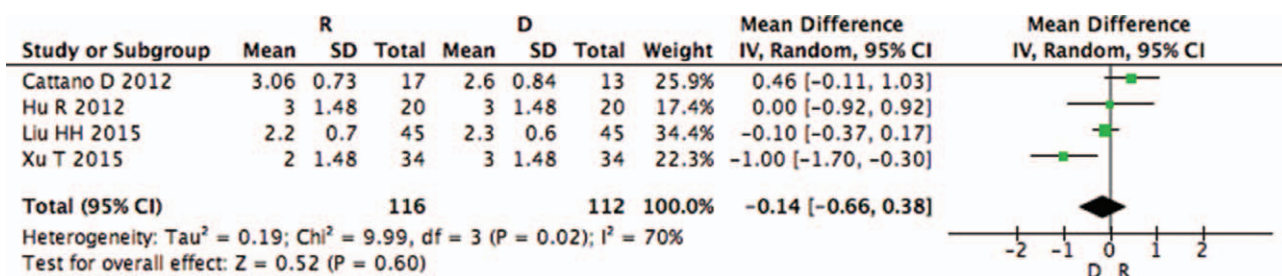


Figure 5. Forest plot of the meta-analysis: level of sedation during intubation between 2 agents.



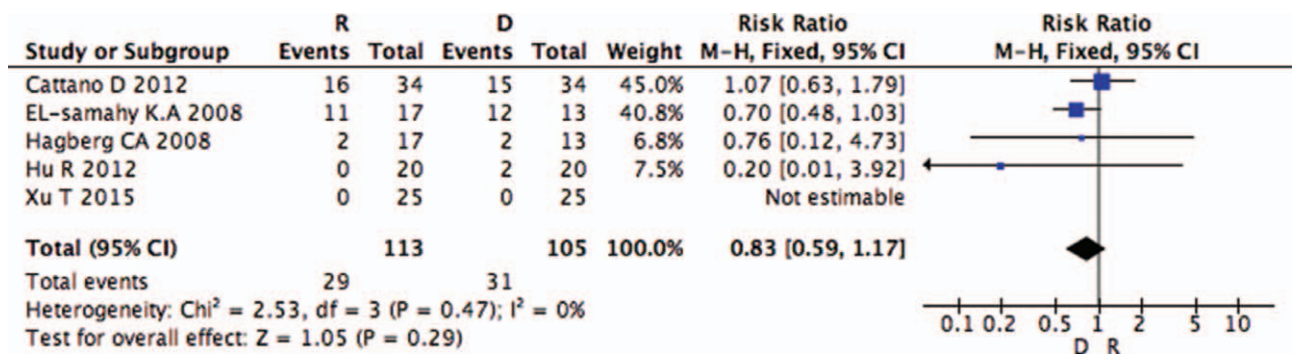


Figure 6. Forest plot of the meta-analysis: unstable hemodynamic parameters during procedures between 2 agents.

### 3.6. Unstable hemodynamic parameters

Five RCTs (n=218) investigated the incidence of unstable hemodynamic parameters (hypertension, hypotension, tachycardia, and bradycardia) during AFOI.<sup>[18,19,21,22]</sup> DEX did not reduce the incidence of unstable hemodynamic parameters (95% CI: 0.59–1.17;  $I^2=0\%$ ;  $P=.29$ ) (Fig. 6). The Egger test for publication bias ( $P=.120$ ) and sensitivity analysis did not significantly alter the summarized results.

### 3.7. Postoperative events

Postoperative recall of the endoscopy procedure was assessed with various methods in the included studies. Four studies (n=228) utilized a similar evaluation for memory recall of the endoscopy procedure, and were included in the meta-analysis.<sup>[17-20]</sup> DEX was associated with a lower postoperative recall of endoscopy compared to REM (95% CI: 1.13–1.72;  $I^2=27\%$ ;  $P=.002$ ) (Fig. 7). The Egger test for publication bias ( $P=.352$ ) and sensitivity analysis did not significantly alter the summarized results.

## 4. Discussion

The present meta-analysis was the first to evaluate the safety and efficacy of DEX vs REM when used as the sole sedative agent during AFOI. After analyzing the combined results of 8 RCTs, we found that DEX was associated with a lower incidence of hypoxemia and memory recall of endoscopy compared to REM. The success rate of first intubation was high for both drugs, and no significant difference was observed.

While the AFOI technique has a long track record of success and has been continuously refined over the past decade, the choice of sedative remains a matter of debate. This issue has been especially pertinent during the coronavirus disease pandemic, which has put anesthesiologists at a high risk of nosocomial infection. Thus, it has become increasingly important to reduce aerosol generation during AFOI. This may be achieved by optimizing the intubation procedure to reduce the number of required intubation attempts, and shorten the duration of intubation to improve patient cooperation. Potential measures need to be urgently evaluated and incorporated into detailed intubation plans for the treatment of patients with difficult airway.<sup>[26]</sup>

Although the AFOI technique can be performed safely without the use of sedatives,<sup>[27,28]</sup> they are still recommended to reduce anxiety and promote airway tolerance.<sup>[9]</sup> Nevertheless, it is not easy to achieve a balance between providing an adequate level of sedation for intubation, and reducing the risk of adverse effects. For instance, the co-administration of sedative agents can often result in over-sedation. The use of DEX or REM as the sole sedative agent, however, has been associated with low risks of airway obstruction and over-sedation, as well as high levels of patient satisfaction.<sup>[29]</sup>

REM is a selective  $\mu$ -receptor agonist with a rapid onset and offset of effect. It is a commonly used opioid that can suppress coughing and cardiovascular responses caused by tracheal manipulation.<sup>[30,31]</sup> Xu et al compared DEX and REM for sedation during AFOI using a Shikani optical stylet, and reported that the proportion of patients with coughing after intubation in the DEX group was twice that in the REM group. This was

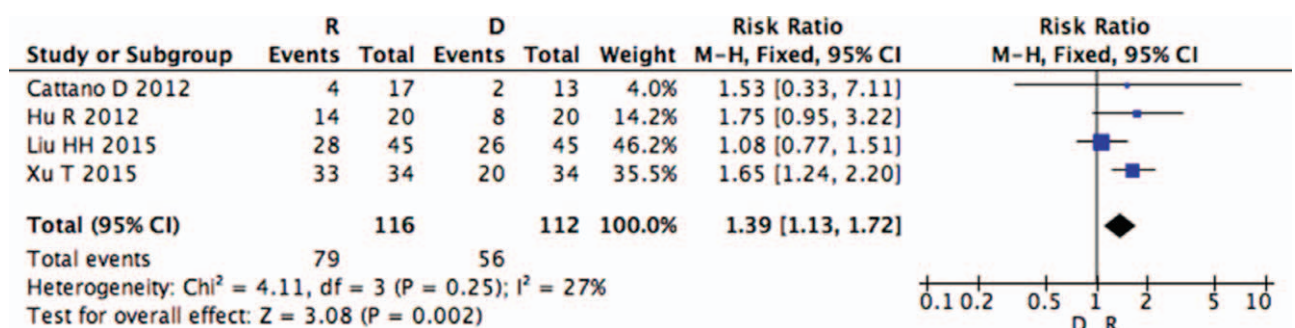


Figure 7. Forest plot of the meta-analysis: postsurgical recall of endoscopy procedure between 2 agents.

explained by the greater analgesic effect of REM, which resulted in a better tolerance of the tracheal tube.<sup>[19]</sup> However, no significant difference in the success rate of intubation on the first attempt was found between the REM and DEX groups in the present meta-analysis. A successful intubation requires that the patient be well sedated, and yet still be able to be aroused and cooperate under instruction.<sup>[32]</sup> The ability of both REM and DEX to provide an adequate level of sedation at the point of intubation could have accounted for the equivalent first-attempt intubation success rates.

DEX is a highly selective  $\alpha_2$ -adrenergic agonist with intrinsic sedative, anxiolytic, and sympatholytic effects.<sup>[33–35]</sup> While it has a rapid onset and equally rapid redistribution half-life with quick recovery, it only has modest efficacy as an analgesic. A number of case reports have indicated that DEX has little effect on respiration; while respiratory depression during the administration of DEX may be observed, it usually only occurs with the use of very large initial bolus doses (1.0 and 2.0  $\mu\text{g}/\text{kg}$  intravenously over 2 minutes),<sup>[36]</sup> or in patients with obesity. Our meta-analysis showed that REM was associated with a higher incidence of hypoxia during AFOI. REM-induced hypoxia is dose-related, and is mainly reflected by a decrease in respiratory rate and minute ventilation. The termination of REM infusion is associated with a quick and spontaneous recovery.<sup>[37]</sup> A previous study reported that REM sedation administered via target controlled infusion resulted in a lower incidence of apnea and respiratory depression compared with manual administration,<sup>[38–40]</sup> Although the adverse effects of REM on the respiratory system can be easily managed in most cases, it should be used with caution if airway obstruction is already evident before sedation.<sup>[41]</sup>

Excessive anxiety and airway manipulation triggers a mass release of catecholamines via sympathetic stimulation. This leads to an elevation in blood pressure, heart rate, and arrhythmia in patients with risk factors such as hypertension and coronary disease, and increases the risk of myocardial ischemia and infarction.<sup>[42,43]</sup> In the present study, we found no evidence to support the superiority of either DEX or REM in terms of hemodynamic stability. While the administration of REM can lead to hypotension and bradycardia,<sup>[30,31]</sup> its potent analgesic properties also reduce stimulation by the endoscopy and intubation procedures. The administration of DEX is mainly associated with hypertension, hypotension, and bradycardia caused by vasoconstriction<sup>[44]</sup>; nevertheless, with sufficient topical anesthesia and proper sedation, the hemodynamic change during AFOI can be reduced to a minimum. The hemodynamic sensitivity to DEX and REM increases with age and varies according to the patient's preoperative condition.

To the best of our knowledge, there is no standard assessment for patient satisfaction or memory recall of the intubation procedure. Four of the included studies used similar methods to evaluate these parameters, and the meta-analysis showed that DEX has a stronger amnesic effect and is associated with a lower postoperative recall of endoscopy than REM. Johnston et al reported that the use of REM as the sole sedative agent was associated with a 50% to 100% incidence of memory recall, even at high doses.<sup>[9]</sup> While the contents of the memories were not perceived by patients as unpleasant, the authors suggested that issues may arise in patients who are extremely anxious and desire a high degree of amnesia.

Two limitations are acknowledged in the present meta-analysis. First, the dosages of DEX and REM were different in

each of the included RCTs; this may be attributed to the lack of consensus regarding the optimal doses of these 2 sedative agents when used for AFOI. This variation in drug dose may have accounted for the high heterogeneity of the analyzed outcomes. Second, a subgroup analysis was not performed due to the small number of included studies.

## 5. Conclusions

Current evidence indicates that DEX and REM are both effective and well-tolerated in AFOI. While the efficacy of both sedative agents are equivalent, DEX has an advantage in terms of safety.

## Author contributions

All authors contributed equally to the manuscript and read and approved the final version of the manuscript.

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**Supervision:** Yong Wang, Wuhua Ma.

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**Visualization:** Zheng Yuan Xia.

**Writing – original draft:** Zhi Hang Tang, Qi Chen.

**Writing – review & editing:** Yong Wang, Wuhua Ma.

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