



# The Effect of Dexmedetomidine on the Prognosis of Mechanically Ventilated Patients with Sepsis: A Meta-Analysis of Randomized Controlled Trials

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## Abstract

**Background:** Dexmedetomidine (Dex), as a new and highly selective  $\alpha_2$  adrenergic receptor agonist, has been widely used in mechanically ventilated patients. In the present study, we used meta-analysis to study the effect of Dex on the prognosis of mechanically ventilated patients with sepsis.

**Methods:** We searched PubMed, Cochrane clinical trial, EMBASE, Web of Science, and Chinese biomedical literature database to analyze relevant literature published from January 2000 to January 2021. We conducted the quality evaluation and data extraction for studies that met the inclusion criteria. RevMan 5.3 software was used to perform a meta-analysis of the 28-day mortality, hospital mortality, the length of ICU stay, and other adverse indicators.

**Results:** Ten randomized controlled trials (RCTs) that met the inclusion criteria were finally included, including 9 RCTs in English and one in Chinese, with a total of 892 patients. Our meta-analysis results found that in mechanically ventilated patients with sepsis, Dex could significantly reduce the length of ICU stay ( $P=0.02$ ), but did not reduce the patients' 28-day mortality ( $P=0.06$ ), hospital mortality ( $P=0.17$ ) and ventilator-free days ( $P=0.33$ ). Furthermore, our meta-analysis results also found that Dex had no significant effect on the respiratory rate ( $P=0.53$ ), heart rate ( $P=0.02$ ), mean arterial pressure ( $P=0.63$ ), the level of creatinine ( $P=0.82$ ) and continuous renal replacement therapy ( $P=0.39$ ) in mechanically ventilated patients with sepsis.

**Conclusion:** In mechanically ventilated patients with sepsis, Dex can reduce the length of ICU stay, but which cannot reduce the 28-day mortality, hospital mortality, and ventilator-free days.

**Keywords:** Dexmedetomidine; Sepsis, Mechanical ventilation; Mortality; Meta-analysis

## Introduction

With the accelerated aging of the population, the incidence of sepsis is on the rise year by year (1). Millions worldwide suffer from sepsis every year, and the mortality rate is as high as 25 % (2). Despite the continuous development and improve-

ment of treatment measures for sepsis, the fatality rate remains high (3). Due to its complex and unpredictable condition, and increased medical costs, many studies currently focus on what treatment measures can be taken to reduce the



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mortality of patients with sepsis, including fluid resuscitation, anti-infection, mechanical ventilation, etc. , and in which sedation and analgesia are also an essential part of the treatment of patients with sepsis(4).

Dexmedetomidine (Dex) is a new and highly selective  $\alpha_2$  adrenergic receptor agonist, with sedative and anti-anxiety effects by acting on the  $\alpha_2$  adrenergic receptor in the locus coeruleus area of the brainstem. Compared with other sedative drugs, Dex not only has good sedative and analgesic effects, but also has a less inhibitory effect on respiratory and circulatory functions (5). At present, the clinical application of Dex is receiving increasing attention. Studies showed that Dex can inhibit inflammatory responses in animals and humans, including organ protection (6, 7). Dex had a significantly lower risk of delirium and coma, and which can shorten the time of mechanical ventilation and improve survival (8). In patients with sepsis, Dex does not improve the mortality of patients with sepsis (9).

Dex has shown certain advantages and application value in the clinical application of patients with sepsis, but there are significant differences in current research. Therefore, we aimed to search related randomized controlled trials (RCTs) for meta-analysis to clarify the effect of Dex on the prognosis of mechanically ventilated patients with sepsis.

## Methods

### *Trial Identification*

We searched PubMed, EMBASE, Cochrane clinical trial, Web of Science, and Chinese biomedical literature database, and collected relevant literature data published in journals from January 2000 to January 2021. The search keywords we used were "dexmedetomidine," "sepsis," "septic shock," and "mechanical ventilation," and the language was limited to English and Chinese. The literature inclusion criteria we developed were 1) The clinical trials were designed as RCTs, and there was no significant difference between the

baseline level of the experimental group and the control group; 2) The study population was adults (age>18); 3) Diagnostic criteria it met the diagnostic definition of the international sepsis guidelines, and the patients used mechanical ventilation during treatment; 4) The experimental group was treated with Dex, and the control group was treated with other sedative drugs, including: midazolam, propofol, lorazepam or placebo, all administration methods were intravenous pumping, and Dex sedation time was longer than 24 hours. Exclusion criteria: 1) Animal experiments; 2) Non-RCTs; 3) Repeated RCTs; 4) Incomplete literature data.

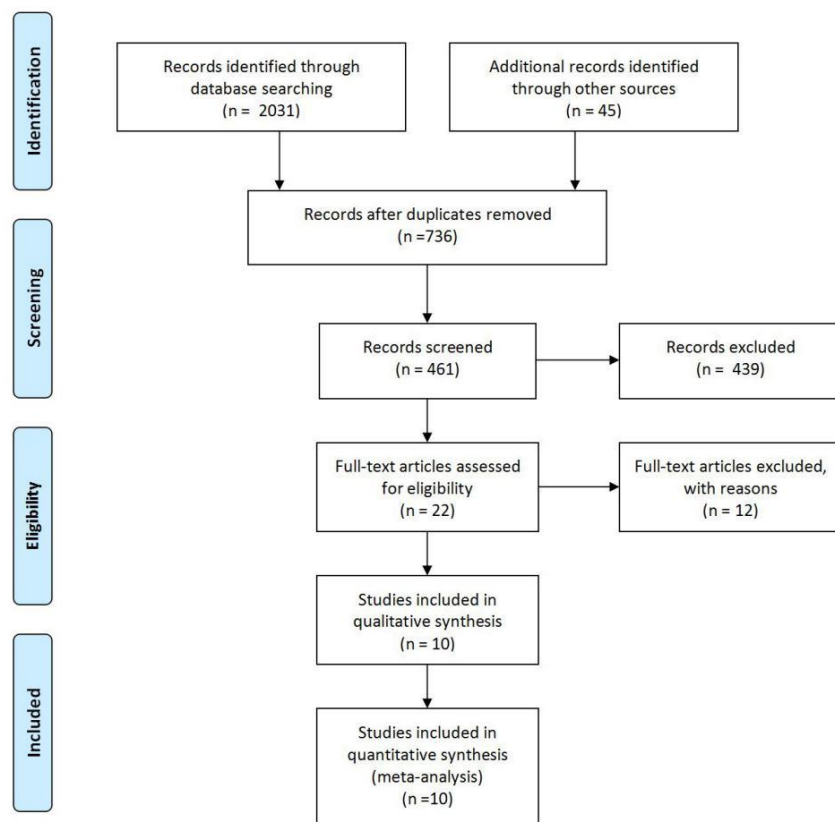
### *Data Abstraction*

Two evaluators who independently selected the research, imported the retrieved documents into the management software, followed the document inclusion process, excluded duplicate records, read article titles and abstracts, and excluded non-related research, and searched for the full text of the remaining literature (Fig. 1). The relevant data of the study was extracted according to the necessary data extraction table of the literature. The general information included: the title of the literature, the research object, the method, the sample size, the intervention measures, and the quality control, etc. (Table 1). The primary outcomes were 28-day mortality and Hospital mortality, the secondary outcomes were the length of ICU stay and ventilator-free days. Other indicators of development were respiratory rate, heart rate, mean arterial pressure, the level of creatinine, and continuous renal replacement therapy (CRRT). The two reviewers cross-checked the included studies. If there were a disagreement, they would discuss it together, and if necessary, used a third party to help resolve the dispute.

Our study was approved by the Ethics Committee of Luodian Hospital. This study did not involve human trials, so the patient's informed consent was not required.



PRISMA 2009 Flow Diagram



From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *PLoS Med* 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Fig. 1: Flowchart of literature screening

### Risk of Bias Assessment

We used the Cochrane risk bias assessment tool to evaluate the quality of the included RCTs. The evaluation content had the method of random allocation, whether to use the blinding, whether to hide the allocation plan, whether to report a loss to follow-up, and whether to conduct intent to treat, whether to report results selectively. For each item, "high risk of bias," "unclear risk of bias," and "low risk of bias" were used for judgment.

### Statistical Analysis

We used RevMan 5.3 software for statistical analysis. We conducted a heterogeneity test on all

data included in RCTs before conducting a meta-analysis, and selected an appropriate effect model based on the results of the heterogeneity test, and determined whether to perform the meta-analysis. We judged whether there was heterogeneity through the Q test, and considered the magnitude of heterogeneity through the  $I^2$  test. If  $I^2 \leq 50\%$ , we used fixed-effects model analysis; if  $50\% < I^2 \leq 75\%$ , selected random-effects model analysis, and performed subgroup and sensitivity analysis if necessary. If  $I^2 > 75\%$ , considering that the heterogeneity was too considerable, the meta result evidence was low. The odds ratio (OR) and 95% confidence interval (CI) were used to ex-

press the count data. Measurement data are represented by mean difference (MD) and 95% CI. When  $P < 0.05$ , we considered the difference to be statistically significant.

## Results

### Trial Identification

According to the standards established by the literature retrieval strategy, we conducted computer searches on PubMed, Cochrane, EMBASE,

Web of Science, and the Chinese Biomedical Literature Database. The language was limited to English and Chinese. A total of 2076 documents were retrieved following the literature inclusion process standards. Finally, ten papers were screened out (9-18), of which 9 RCTs were in English (9-12, 14-18) and one was in Chinese (13), with a total of 892 patients (Fig. 1). The essential characteristics of the included studies show in Table 1.

**Table 1:** The essential characteristics of the 10 randomized controlled trials included in the meta-analysis  
 Dex: Dexmedetomidine; NA: Not Applicable; RASS: Richman agitation-sedation scale; RSS: The Ramsay Sedation Scale; CRRT: Continuous renal replacement therapy.

Study	Country	Population	Control patients	Dex patients	Comparator		Dex		Outcomes used in the meta-analysis	Sedation level
					Name	Dose	Loading dose	Infusion dose		
Memiş D et al. 2007 [9]	Turkey	Adult patients with sepsis requiring sedation and ventilation	20	20	Midazolam	0.1-0.5mg/kg/h	1.0µg/kg for 10 min	0.2-2.5µg/kg/h	Hospital mortality	RSS: <2.0
Kadoi Y et al. 2008 [10]	Japan	Adult patients with septic shock requiring sedation and ventilation	10	10	Propofol	1.0-3.0mg/kg/h	1.0µg/kg for 10 min	0.3-0.5mg/kg/h	Heart rate, Mean arterial pressure	RSS: 4
Tasdogan M et al. 2009 [11]	Turkey	Adult patients with severe sepsis requiring postoperative sedation and ventilation	20	20	Propofol	1.0-3.0mg/kg/h	1.0µg/kg for 10 min	0.2-2.5µg/kg/h	Hospital mortality, Respiratory rate	RSS: <2.0
Pandharipande PP et al. 2010 [12]	United Kingdom	Adult patients with sepsis requiring sedation and ventilation	32	31	Lorazepam	<10mg/h	NA	1.5mcg/kg/h	28-day mortality, ICU days, Ventilator-free days,	RASS: 0-5

Guo F et al. 2016 [13]	China	Adult patients (y > 18, and y < 80) with septic shock requiring sedation and ventilation	15	15	Propofol or midazolam	5.0mg/kg /h	NA	0.2-0.7µg/kg/h	Respiratory rate, Creatinine	28-day mortality, ICU days, Ventilator-free days	RASS: -2—-1
Kawazoe Y et al. 2017 [14]	Japan	Adult patients (y > 20) with sepsis requiring sedation and ventilation	101	100	Propofol or midazolam	1.0-3.0mg/kg /h	1.0µg/kg for 10 min	0.2-2.5µg/kg/h	28-day mortality, ICU days, Ventilator-free days, CRRT		RASS: -2—0
Miyamoto K et al. 2018 [15]	Japan	Adult patients (y > 20) with septic shock requiring sedation and ventilation	51	60	Placebo	1.0-3.0mg/kg /h	1.0µg/kg for 10 min	0.2-2.5µg/kg/h	Hospital mortality, Heart rate, Mean arterial pressure		RASS: -2—0
Liu J et al. 2020 [16]	China	Adult patients (y > 18) with septic shock requiring sedation and ventilation	100	100	Propofol	1.0-3.0mg/kg /h	1.0µg/kg for 10 min	0.2-0.3mg/kg/h	28-day mortality, ICU days, Ventilator-free days, Heart rate, Respiratory rate, Creatinine, CRRT		RASS: -2—0
Giocari L et al. 2020 [17]	Australia and other eight countries	Adult patients (y > 18) with septic shock requiring sedation and ventilation	39	44	Propofol or midazolam	0.6-9.6µg/kg /h	NA	0.6-4.2 µg/kg/h	Hospital mortality, ICU days, Ventilator-free days, Heart rate,		RASS: -3—1

Nakashima T et al.2020 [18]	Japan	Adult patients (> 20) with severe sepsis requiring sedation and ventilation	50	54	Placebo	1.0-3.0mg/kg/h	1.0µg/kg for 10 min	0.2-2.5µg/kg/h	Mean arterial pressure, Creatinine, CRRT, Creatinine	RASS: -2-0
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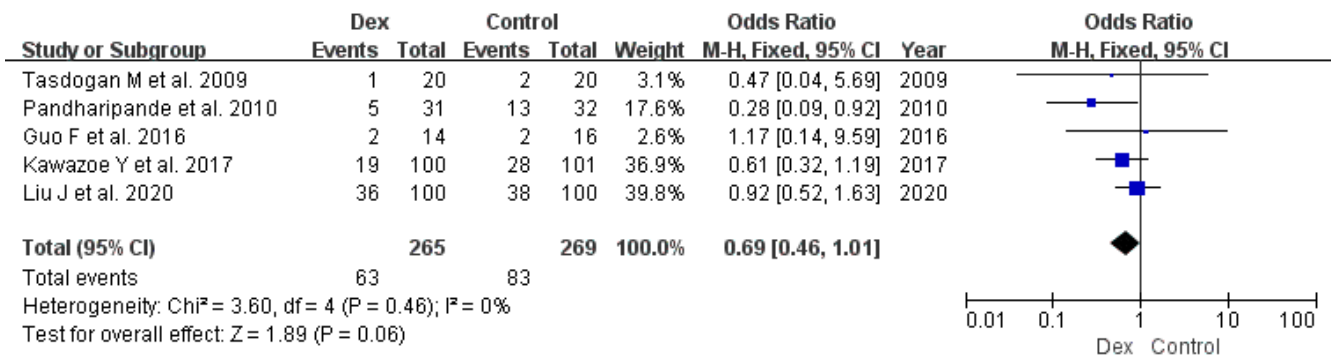
**Trial Characteristics and Quality Assessment**

All of the 10 RCTs used the random sequences, and 3 RCTs used the double-blind (14, 15, 18). Six RCTs did not explicitly mentioned blinding methods (10-13, 16, 17), and 1 RCT was not blinded (9). One RCT had incomplete outcome data (13), and 2 RCTs had selective reports (9, 16).

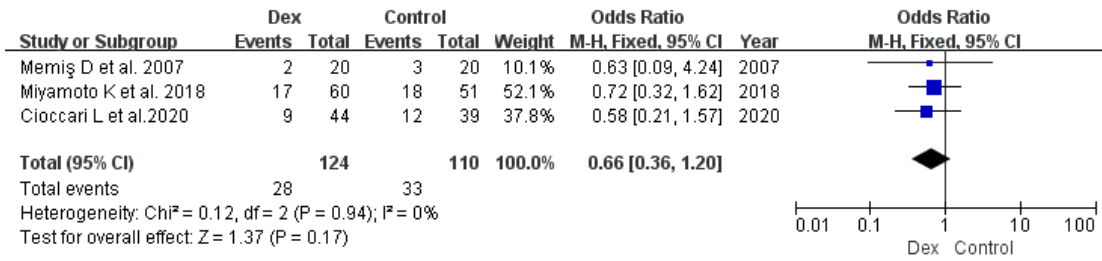
**Clinical outcomes**

Five RCTs reported the effect of Dex on the 28-day mortality of mechanically ventilated patients with sepsis (11-14, 16). A total of 534 patients included, and the results of the heterogeneity test

indicated that there was no apparent heterogeneity between the groups ( $P=0.46$ ,  $I^2= 0\%$ ). Using a fixed-effects model, and the consequences of our meta-analysis showed that Dex could not reduce the 28-day mortality of mechanically ventilated sepsis patients (Fig. 2,  $OR=0.69$ ,  $95\%CI=0.46\sim 1.01$ ,  $P=0.06$ ). 3 RCTs (9, 15, 17) reported the effect of Dex on the hospital mortality of septic patients, a total of 61 patients included. Using the fixed-effects model, and our meta-analysis results showed that the difference was not statistically significant (Fig. 3,  $OR=0.66$ ,  $95\%CI=0.36\sim 1.20$ ,  $P=0.17$ ).



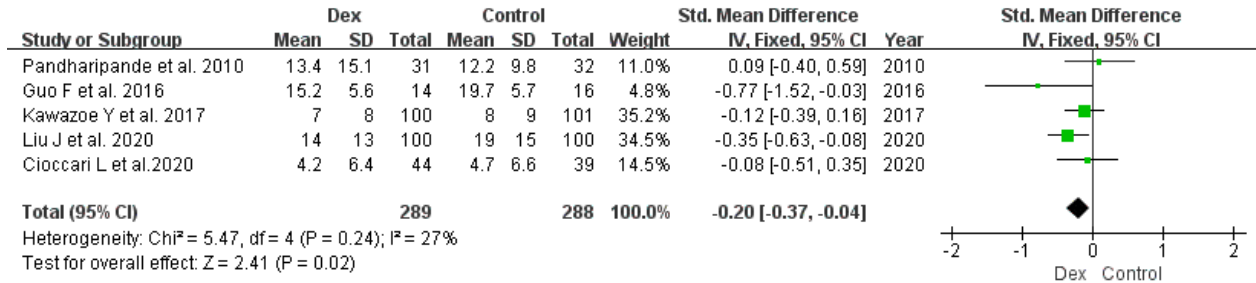
**Fig. 2:** The effect of dexmedetomidine on 28-day mortality in septic patients with mechanical ventilation.  $df =$  degrees of freedom, M-H = Mantel-Haenszel



**Fig. 3:** The effect of dexmedetomidine on hospital mortality in septic patients with mechanical ventilation. df = degrees of freedom, M-H = Mantel-Haenszel

Five studies (12-14, 16, 17) reported the effect of Dex on the length of ICU stay in patients with sepsis. A total of 577 patients included. Using the fixed-effects model analysis, our meta-analysis results showed that the difference was statistically significant (Fig. 4, MD=-0.20, 95%CI =-0.37~-0.04, P= 0.02). Meanwhile, the above 5 RCTs

(12-14, 16, 17) also reported the effect of Dex on the ventilator-free days of patients with sepsis. We used random-effects model analysis, and the results suggested that Dex did not impact on the ventilator-free days of patients with sepsis (MD=1.10, 95%CI=-1.11~3.32, P=0.33).



**Fig. 4:** The effect of dexmedetomidine on the length of ICU stay in septic patients with mechanical ventilation. df = degrees of freedom

Furthermore, we also meta-analyzed the effects of Dex on the respiratory rate, heart rate, mean arterial pressure, the level of creatinine, and CRRT in patients with sepsis. Among the 10 RCTs included, 3 RCTs reported the effect of DEX on the respiratory rate of patients with sepsis (11, 12, 16), and 4 RCTs reported the effect of DEX on the heart rate (14-17). 3 RCTs reported mean arterial pressure (10, 15, 17), 4 RCTs reported the level of creatinine (12, 16-18), and 3 RCTs reported continuous renal replacement therapy (14, 16, 17). After meta-analysis, we found that Dex had no significant effect on the respiratory rate (MD=-1.96, 95%CI=-8.10~4.19, P=0.53), heart rate (MD=-1.57, 95%CI=-8.95~5.81, P=0.02), mean arterial pressure

(MD=-0.74, 95%CI=-3.78~2.31, P=0.63), the level of creatinine (MD=-0.06, 95%CI=-0.62~0.49, P=0.82) and CRRT (OR= 0.82, 95%CI=0.51~1.30, P=0.39) in mechanically ventilated patients with sepsis.

**Publication bias**

To fully estimate the publication bias of the included studies, we drew funnel charts for the included studies. Our results showed that the scattered points of the 10 RCTs were inverted funnel-shaped symmetrically distributed on both sides of the effective line, all falling within the 95% linear range, suggesting that there was no publication bias.

## Discussion

With the increase of relevant research on the occurrence and development of sepsis, the current understanding of sepsis continuously deepens, and its clinical treatment measures are gradually improved (19). Nevertheless, due to the rapid progress of the disease, the whole mortality is still high, and medical expenses are expensive (20). At present, many studies focus on the field of treatment measures that can reduce the mortality of patients with sepsis, including fluid resuscitation, anti-infection, respiratory support, etc., and in which sedation and analgesia are also a part that cannot be ignored (21).

Dex, as a new and highly selective  $\alpha_2$  adrenergic receptor agonist, produces sedation and has fewer adverse effects. Animal studies have shown that Dex can reduce serum inflammatory factors in septic models and has organ protection (3). In clinical applications, Dex can produce a sedative effect similar to traditional sedative drugs (such as propofol or midazolam, etc.). It also has the function of inhibiting inflammation and organ protection (5). At present, Dex increasingly used in clinical applications, and it has gradually become the first choice for intensive care unit and surgical anesthesia.

Sepsis mainly characterizes by the uncontrolled inflammatory response and the release of a large number of inflammatory mediators, such as tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 (IL-1), interleukin-6 (IL-6), etc. (22). Dex could significantly down-regulate the concentration of inflammatory factors secreted by serum macrophages and monocytes, and improve the survival rate of endotoxin rats (23). It enhances mucosal immunity and bacterial clearance by promoting macrophage phagocytosis and bactericidal effects, and could effectively reduce the secondary infection rate in critically ill patients (24). However, the anti-inflammatory mechanism of Dex is not very clear, and which may be related to central sympathetic nerve block and cholinergic inflammation pathway (8).

Sepsis often first involves the central nervous system, leading to impaired brain self-regulation. Dex could activate the  $\alpha_2$  adrenal receptors in intracranial blood vessels to produce a major vasoconstrictor effect to reduce cerebral blood flow and significantly reduce intracranial pressure. Still, it did not significantly impact intracranial vascular resistance (25). When the body has circulatory dysfunction, the kidney is one of the most vulnerable organs. Dex used in coronary artery bypass grafting can reduce plasma neutrophil gelatinase-associated apolipoprotein levels on the first day after surgery, and reduce postoperative acute kidney injury, and improve the 30-day survival rate (26). It could significantly reduce intra-abdominal pressure (IAP) in critically ill patients for 24 hours or 48 hours, and has protective effects on breathing, cardiovascular, kidney, and central nervous system (27).

In the present study, we used meta-analysis to study the effect of Dex on the prognosis of mechanically ventilated patients with sepsis. Ten RCTs that met the inclusion criteria were finally included, including 9 in English and 1 in Chinese, with 892 patients. We found that in mechanically ventilated patients with sepsis, Dex could significantly reduce the length of ICU stay, but did not reduce the patients' 28-day mortality, hospital mortality, and ventilator-free days. Compared with the previously published meta-analysis (28), we have added a recently published RCT (16). Our result showed that Dex did not reduce the 28-day mortality of mechanically ventilated patients with sepsis. Many studies reported that the main adverse events of Dex are hypotension and bradycardia, and it has a special anterograde amnesia effect (5, 7, 8). However, our meta-analysis results suggested that in mechanically ventilated patients with sepsis, compared with other sedatives, Dex had no significant effect on the respiratory rate, heart rate, mean arterial pressure, the level of creatinine, and CRRT.

Our meta-analysis has the following limitations: 1) The number of studies included is few, and the number of samples is small, and the chance of false-positive results is high, which may bias the results. 2) Due to the small amount of literature,



we did not conduct a subgroup analysis of patients with sepsis, such as sepsis, severe sepsis, and septic shock. 3) The included literature of our meta-analysis are all RCTs, but the results of different literature are also quite different. 4) Among the RCTs studies we had, 3 RCTs (14, 15, 18) were from the same team, and 2 of them (15, 18) based on the results of the previous study (14). To avoid data duplication, we only used the data that appeared in the reviews, but which did not appear in the previous survey.

## Conclusion

In mechanically ventilated patients with sepsis, Dex can reduce the length of ICU stay, but it cannot reduce the 28-day mortality, hospital mortality, and ventilator-free days. Furthermore, compared with other sedatives, Dex has no significant effect on the respiratory rate, heart rate, mean arterial pressure, the level of creatinine, and CRRT in mechanically ventilated patients with sepsis.

## Journalism Ethics considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

## Acknowledgements

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## Conflict of interest

The authors declared that there was no conflict of interest.

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