Annals of Medicine and Medical Research

Research Article
Published: 17 Oct, 2022

Effects of Dexmedetomidine on Organ Function and Mortality in Patients with Sepsis: A Systematic Review and Meta-Analysis

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Abstract

Background: Dexmedetomidine has been widely used clinically as a sedative drug. Studies have shown that dexmedetomidine not only has a sedative effect but can also have the protective effects on organ function by ameliorating stress in septic patients.

Methods: By searching the PubMed, Embase, The Cochrane Library, and Web of Science databases, we collected prospective controlled trials that evaluated patients with sepsis who were treated with dexmedetomidine sedation, from the establishment of the database to December 23rd, 2020. RevMan 5.3 software was used for the meta-analysis. Binary variables were expressed by the Odds Ratio (OR) and 95% Confidence Interval (95% CI), and continuous variables were expressed as the Mean Differences (MD) and 95% CI.

Results: We included 11 articles, including 10 randomized controlled studies and 1 prospective cohort study. A total of 1,245 patients with sepsis were included the meta-analysis results showed that dexmedetomidine did not reduce the sequential organ failure assessment score (MD= -0.63, 95% CI: -1.3~0.03, P=0.06), but it did reduce the score of kidney (MD= -0.56, 95% CI: -1.00~ -0.12, P=0.01). Dexmedetomidine significantly reduced the serum creatinine (MD= -0.35, 95% CI: -0.57~ -0.13, P=0.002) and cystatin C levels (MD= -0.59, 95% CI: -0.90~ -0.29, P<0.001), but it did not reduce the proportion of patients on continuous renal replacement therapy (OR=1.23, 95% CI: 0.70~2.17, P=0.47). Dexmedetomidine significantly reduced the 24-h vasopressor requirements (MD= -0.49, 95% CI: -0.68~ -0.31, P<0.001), but it did not significantly reduce the 24-h plasma lactic acid level (MD= -0.05, 95% CI: -0.35~ -0.25, P=0.77). The use of dexmedetomidine had no effect on the duration of mechanical ventilation (MD= -0.03, 95% CI: -1.13~1.06, P=0.95). Dexmedetomidine reduced the short-term mortality of patients with sepsis (OR= -0.58, 95% CI: 0.45~0.75, P<0.001) but no effect on the length of intensive care unit stay (MD= -0.08, 95% CI: -0.67~0.52, P=0.80).

Conclusion: Dexmedetomidine can improve the renal function and reduce the mortality in septic patients, with no significant effects on other organ functions. Our results provided a promising therapeutic direction that requires further investigation.

Trial registration: Registration number is CRD42021231867 in PROSPERO.

Keywords: Dexmedetomidine; Sepsis; Stress; Mortality; Organ function; Meta-analysis

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Received Date: *26 Sep 2022*
Accepted Date: *12 Oct 2022*
Published Date: *17 Oct 2022*

Citation:
Zhao W, Zhao C, Liu L, Gao Z, Chen Y, Hu Z. Effects of Dexmedetomidine on Organ Function and Mortality in Patients with Sepsis: A Systematic Review and Meta-Analysis. Ann Med Medical Res. 2022; 5: 1049.

Abbreviations

DEX: Dexmedetomidine; RCT: Randomized Controlled Trial; ICU: Intensive Care Unit; CRRT: Continuous Renal Replacement Therapy; TNF-α: Tumor Necrosis Factor α; IL-1: Interleukin-1; IL-6: Interleukin-6; SOFA: Sequential Organ Failure Assessment; APACHE II: Acute Physiology and Chronic Health Evaluation II

Introduction

Sepsis should be defined as life-threatening organ dysfunction caused by a dysregulated host response to infection. Its pathogenesis includes the simultaneous activation of early proinflammatory and anti-inflammatory responses and affects many non-immunological pathways and systems, such as the cardiovascular system, neurological systems, and hormonal pathways, and there are significantly abnormal biological changes in energy, metabolism and coagulation. It is essentially a

stress reaction [1].

Acute stress can cause the activation of the locus coeruleus-noradrenergic neuron sympathetic-adrenal medulla system and excitement of the hypothalamic-pituitary-adrenal cortex axis, which results in the significant release of norepinephrine and adrenaline. Studies have shown that high levels of norepinephrine are associated with multiple organ dysfunction and mortality [2] in septic patients.

The locus coeruleus is the main part of the human body that is responsible for regulating wakefulness and is the main part of the brain that synthesizes norepinephrine. It is also the origin of the medulla-spinal noradrenergic pathway and has extensive connections with the limbic system and cerebral cortex. Dexmedetomidine (DEX) is a highly selective α2 receptor agonist that mainly acts as a sedative and has analgesic effects by the activation of the pontine locus coeruleus, medulla oblongata and spinal cord neuron α2A receptors [3]. From the pharmacology, DEX would provide greater improvement in clinical outcomes [4] by alleviating the stress response [3,5,6] through inhibiting the activity of locus coeruleus neurons and the noradrenergic pathway [7]. However, there are no high-quality clinical research reports on the impact of DEX on the organ function and mortality of patients with sepsis. This article aims to objectively evaluate the effects of DEX on the organ function in sepsis by using a meta-analysis that synthesizes multiple clinical studies.

Methods

Inclusion criteria

1) **Patients:** Adult patients (age ≥ 18 years old) diagnosed with sepsis or septic shock. Other patients were excluded.

2) **Intervention:** DEX sedative treatment in the experimental group.

3) **Control:** The control group was treated with sedative drugs other than DEX.

4) **Outcomes:** The main outcome indicators included the case fatality rate. Other indicators included the Intensive Care Unit (ICU) hospitalization time, organ function damage (central, kidney, heart, liver, digestion, blood, breathing), and changes in inflammatory factors. Studies that did not obtain the final outcome indicators were excluded.

5) **Research:** This meta-analysis included prospective randomized controlled trials, quasi-randomized controlled trials, and a prospective cohort study. Animal experiments, retrospective studies, crossover clinical studies, reviews, individual case reports, and studies where the full text was not available were also excluded.

Search

We searched PubMed, the Cochrane Library, Web of Science and Embase. The final search was done on December 23rd, 2020. The following keywords were used: "Sepsis, Bacteremia, Shock, Septic, Systemic Inflammatory Response Syndrome, Pyemia, Pyohemia, Pyaemia, Septicemia, Bloodstream Infection, Septic Shock, Dexmedetomidine, MPV-1440, MPV 1440, MPV1440, Precede, Dexmedetomidine Hydrochloride, Hydrochloride, Dexmedetomidine". The reference sections of the found studies were also screened for additional publications.

Study selection and data extraction

The retrieved documents were sorted, and two independent researchers, who had received training, excluded any irrelevant studies based on their title and abstract. The reviewers read the relevant literature, determined the inclusion or exclusion of the studies, and retrieved the original text. The quality evaluation and data were extracted from the included studies. If there were differences between the reviewers regarding the incision of studies, the reviewers discussed the study between themselves, and if a conclusion could not be reached through negotiation, a third researcher was asked to provide assistance.

The extracted data included (1) the general information of the study: Title, author, publication date, and source of the study. (2) The research characteristics of the study: The type of research design, inclusion criteria, exclusion criteria, number of people included, average age, SOFA score, APACHE II score, intervention measures, and outcome indicators.

Quality assessment

The quality of Randomized Controlled Trial (RCT) was evaluated using the risk of bias evaluation tool recommended by the Cochrane Collaboration. These included (1) the random allocation method; (2) allocation plan concealment; (3) the blinding method; (4) completeness of the resulting data; (5) selective reporting of research results; and (6) other sources of bias. Items were judged as "high-risk, low-risk, and unclear." The remaining studies used the Newcastle Scale (NOS) to assess the risk of bias in the included literature, including the study object selection, comparability between the groups, and outcome measurement. The NOS range was 0-9 points.

Statistical analysis

We used RevMan 5.3 software for the meta-analysis. An inverse variance model with a 95% confidence interval was used to analyze the continuous outcomes. The Risk Ratio (RR) and 95% Confidence Intervals (CIs) were used to analyze the dichotomous outcomes. A *P* value of less than 0.05 was considered significant. Significant heterogeneity was identified when the *P* value as determined by the chi-square test was less than 0.10 and when I^2 was greater than 50%. A fixed-effect model was employed to calculate the pooled effect when there was no statistically significant heterogeneity. Otherwise, a random-effects model was used. Publication bias was evaluated by a funnel plot.

Results

Study selection

A total of 891 related documents were retrieved: 434 titles in Embase, 221 in Web of Science, 165 in PubMed, and 71 in Cochrane. After excluding duplicate documents, 705 articles were retained, the titles and abstracts were screened, and then 42 full-text articles were selected for further analysis. The remaining documents included 18 review articles, 8 retrospective articles, 4 duplicate articles, 1 animal study, and 11 remaining articles. Articles were included in the study, 10 were RCTs and 1 was a prospective cohort study. The retrieval flow chart is shown in Figure 1. A total of 1,245 patients with sepsis were enrolled. There were 620 patients in the experimental group and 625 patients in the control group. Due to the diversity of the included literature, a comprehensive description was applied to some of the experimental results. The basic characteristics of the included literature are shown in Table 1.

Study characteristics and quality

A total of 10 RCT studies and 1 prospective cohort study were

Table 1: Basic characteristic of the included documents.

Study	Country	Number of Cases	Sex Male/ Female		Age		Apache II		SOFA		Intervention		Outcome
			DEX	Control	DEX	Control	DEX	Control	DEX	Control	DEX	Control	
Memis D [8]	Turkey	40	-	-	-	-	20 (4.7)	18.10 (5.7)	-	-	DEX	Midazolam	③, ⑪, ⑦, ⑩, ⑩
Memis D [9]	Turkey	40	14/6	13/7	60 (31-80)	54 (25-75)	22 ± 5	20 ± 8	4.5 ± 2.8	4.0 ± 2.9	DEX	Propofol	②, ④, ⑧, ⑨
Tasdogan [10]	Turkey	40	11/9	14/6	58 (21-78)	50 (19-74)	18 ± 4	19 ± 5	4.0 ± 2.5	4.2 ± 1.8	DEX	Propofol	④, ⑤, ⑦, ⑪
Pandharipande PP [11]	USA	63	18/13	13/19	60 (46-65)	58 (44-66)	30 (26-34)	29 (24-32)	10 (9-13)	9 (8-12)	DEX	Others	④, ①, ⑨
Kawazoa Y [12]	Japan	201	63/37	64/37	68 (14.9)	69 (13.6)	23 (18-29)	22 (16-29.5)	8(6-11)	9 (5-11)	DEX	Others	④, ①, ⑤, ⑩
Chen LL [13]	China	80	-	-	-	-	-	-	-	-	DEX	Others	⑥, ⑪
Miyamoto K [14]	Japan	111	40/20	29/22	7.0 ± 14.3	72.1 ± 12.3	23 (19-29)	27 (20-32)	10 (8-12)	11 (8-12)	DEX	Others	③, ①, ⑨, ⑩
Ding J [15]	China	283	97/34	110/42	55.0 ± 10.8	55.2 ± 11.3	18.87 ± 4.30	18.67 ± 4.3	-	-	DEX	Propofol	④
Nikashima T [18]	Japan	104	30/24	33/17	70. 7 ± 15.1	71.4 ± 13.2	29 (25-39)	30 (25-33)	9 (7-11)	11 (9-13)	DEX	Others	④, ⑥, ①, ⑩
Liu JQ [17]	China	200	58/42	57/43	54 (35-71)	57 (31-66)	29 (22-36)	29 (26-37)	11 (8-12)	10 (8-13)	DEX	Propofol	④, ⑤, ⑥, ①, ⑪
Cioccari L [16]	Australia	83	29/15	28/11	67. 7 ± 12.4	62.9 ± 16.8	62.9 ± 16.8	62.9 ± 16.8	-	-	DEX	Others	②, ③, ④, ⑨

Note: ① 28-day mortality rate; ② ICU mortality rate; ③ mortality during hospitalization; ④ ICU hospitalization time; ⑤ mechanical ventilation time; ⑥ renal function; ⑦ gastrointestinal function; ⑧ liver function; ⑨ circulation; ⑩ SOFA score; ⑪ inflammatory factors

included. The RCT studies were all determined to be either a low or a medium risk of bias. Seven random sequence generation methods were all computer generated [9-12,14,17,18], 7 studies had proposed allocation methods, 3 studies were randomized by envelopes [8-10], and 4 studies were uniformly allocated by the center [11,12,14,18]. Only 4 studies were double-blinded studies [11,12,14,18], while the others were not blinded. The results of the studies were not affected by blinding. All 10 studies reported on predesigned research outcome indicators, and none of the experiments ended early. The research risk bias is shown in Figure 2 and Figure 3, and one study is a prospective cohort study [15]. The NOS score was 8 and the studies were divided into high-quality studies, among which the study object selection was 3 points, the comparability was 2 points, and the outcome was 3. The non-observed outcome indicators at the beginning of the study could not be determined and were given 0 points.

Organ function

Impact on the sequential organ failure assessment score (SOFA score): Three articles reported the results of the patients' total SOFA scores [12,14,18]. The total SOFA scores between the two groups of patients with different sedative drugs was not statistically significance (MD= -0.63, 95% CI: -1.3~0.03, P=0.06; P=0.009, I^2=55%). Two studies evaluated the respiratory system, circulatory system, blood, liver, kidney, and central nervous system [14,18] and showed there were significantly difference between the two groups in the scores of kidney. Our meta-analysis on the kidney scores found that the kidney score in the DEX group was significantly lower than that in the other sedatives groups (MD= -0.56, 95% CI: -1.00~ -0.12, P=0.01; P=0.06, I^2=53%) (Figure 4, 5).

Kidney function:

Effect on serum creatinine level: A meta-analysis of serum creatinine was performed. Compared with other sedative drugs, DEX can significantly reduce the serum creatinine level in patients with sepsis (MD= -0.35, 95% CI: -0.57~ -0.13, P=0.002; P<0.001, I^2=95%) (Figure 6).

Effect of the serum cystatin C level: There were two studies describing the level of serum cystatin C [13,17]. The effect of DEX could significantly decreased the level of cystatin C (MD= -0.59, 95% CI: -0.90~ -0.29, P<0.001; P<0.001, I^2=96%) (Figure 7).

Impact on the application of continuous renal replacement therapy (CRRT): Two studies reported the use of CRRT [17,18]. Compared with other sedative drugs, DEX did not significantly reduce the proportion of patients with sepsis who had CRRT (OR=1.23, 95% CI: 0.70~2.17, P=0.47; P=0.40, I^2=0%) (Figure 8).

Impact on the duration of mechanical ventilation: There were four papers reported the mechanical ventilation time [10,12,16,17] and three papers reported the number 28-day ventilator-free days [11,12,18]. We conducted a meta-analysis on each of these factors. Compared with other sedative drugs, DEX did not reduce the time needed for mechanical ventilation (MD= -0.03, 95% CI: -1.13~1.06, P=0.95; P=0.04, I^2=64%). The experimental group had a longer time without mechanical ventilation (MD=6.38, 95% CI: 0.31-12.46, P=0.04; P=0.02, I^2=76%) (Figure 9, 10).

Impact on circulation function: Two studies reported the application of DEX to vasoactive drugs in 24 h [11,16]. Compared with other sedative drugs, DEX reduced the amount of vasoactive drugs used in the patients with sepsis (MD= -0.49, 95% CI: -0.68~ -0.31, P<0.001; P=0.69, I^2=0%), but studies included were biased. There were two studies reporting the changes in the 24-h lactic acid level of the patients [9,14]. There was no significant difference in the levels of serum lactic acid between the patients sedated with DEX compared with the patients sedated with other sedative drugs (MD= -0.05, 95% CI: -0.35~ -0.25, P=0.77; P=0.89, I^2=0%) (Figure 11, 12).

Other results: One study reported the effect of the sedatives on liver function [9]. The literature results showed that there was no significant difference in the effects of the two groups on the levels of alanine aminotransferase and bilirubin in patients at 24 h. One study reported a change in the pH in the gastric mucosa [8]. Compared with other sedative drugs, DEX had no significant effect on the pH in the gastric mucosa. One article evaluated the intra-abdominal pressure of patients with sepsis [10]. The DEX group significantly reduced intra-abdominal pressure after intestinal obstruction. One study reported the effect on the patients' cardiac function [15]. Compared with other

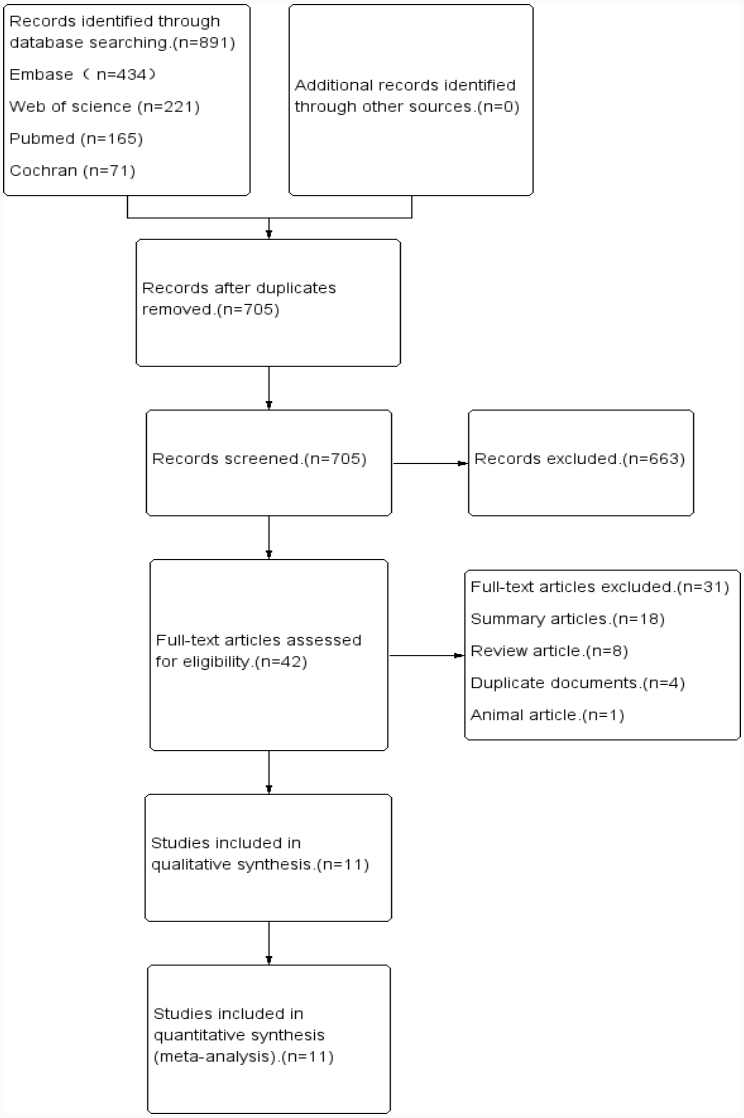

Figure 1: Flow chart of literature inclusion.

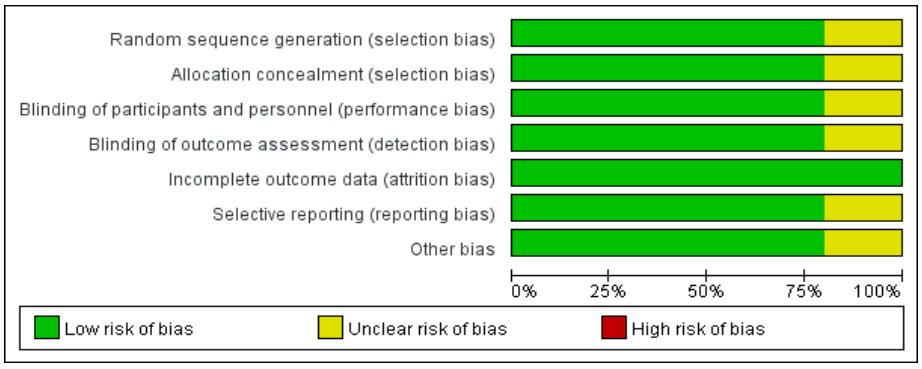

Figure 2: The risk of bias in the included studies.

sedative drug groups, the concentration of Creatine Kinase (CK-MB) in the DEX group was significantly lower, but the serum Troponin T (cTnT) was not significantly reduced.

Mortality

Five studies evaluated the 28-day mortality [11,12,14,17,18], 4 studies evaluated the ICU mortality [8-10,16], and 3 studies reported the mortality during hospitalization [14,16,18]. We defined short-term mortality including 28-day mortality, ICU mortality, and the mortality during hospitalization. At the same time, we conducted a subgroup analysis for mortality. DEX, as compared to other sedation drugs, was shown to improve the short-term mortality of patients (OR= -0.58, 95% CI: 0.45~0.75, P<0.001; P=0.62, I^2=0%), as shown in Figure 13. The funnel chart for inclusion in the study was basically

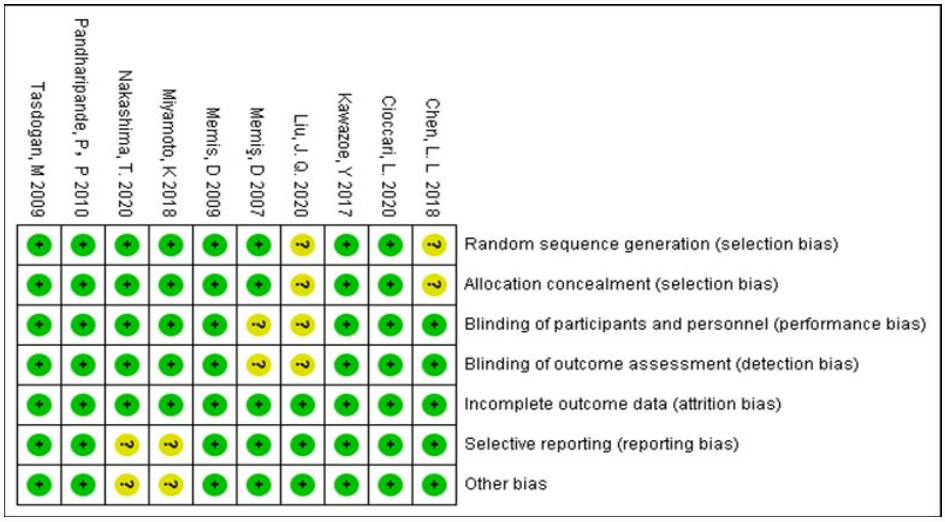

Figure 3: Summary of the risk of bias in the included studies.

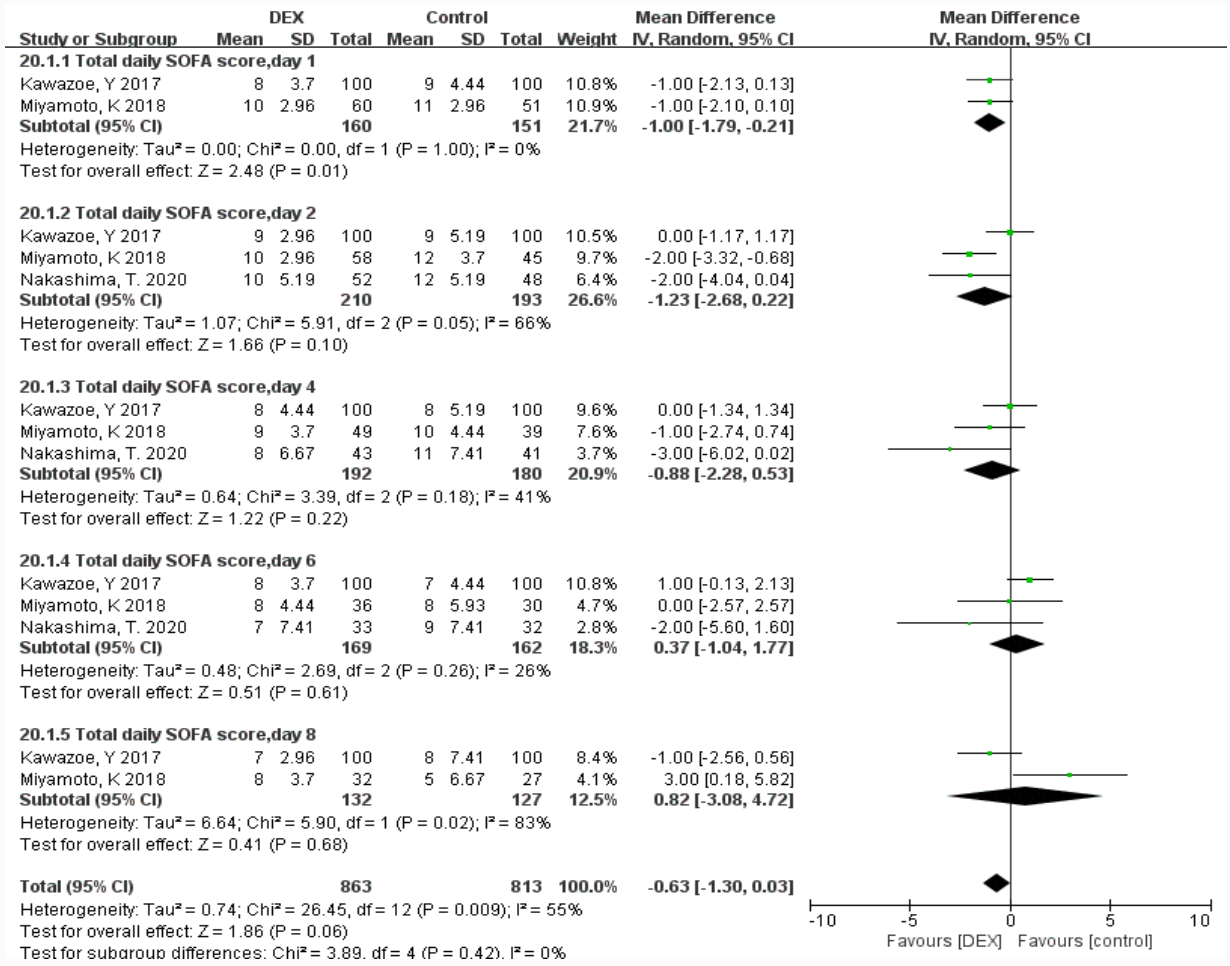

Figure 4: Meta-analysis of the total SOFA score of the two groups of sedative drugs.

symmetrical, suggesting that there was less publication bias, as shown in Figure 14.

Impact on the length of stay in the ICU

Eight studies reported the length of stay in the ICU [9-12,14-17]. The difference between the two groups was not statistically significant (MD= -0.08, 95% CI: -0.67~0.52, P=0.80; P=0.11, I^2=41%). Therefore, compared with other sedative drugs, DEX had no effect on the length of ICU stay of patients with sepsis, as shown in Figure 15.

Discussion

As we know, this meta-analysis comprehensively analyzed the

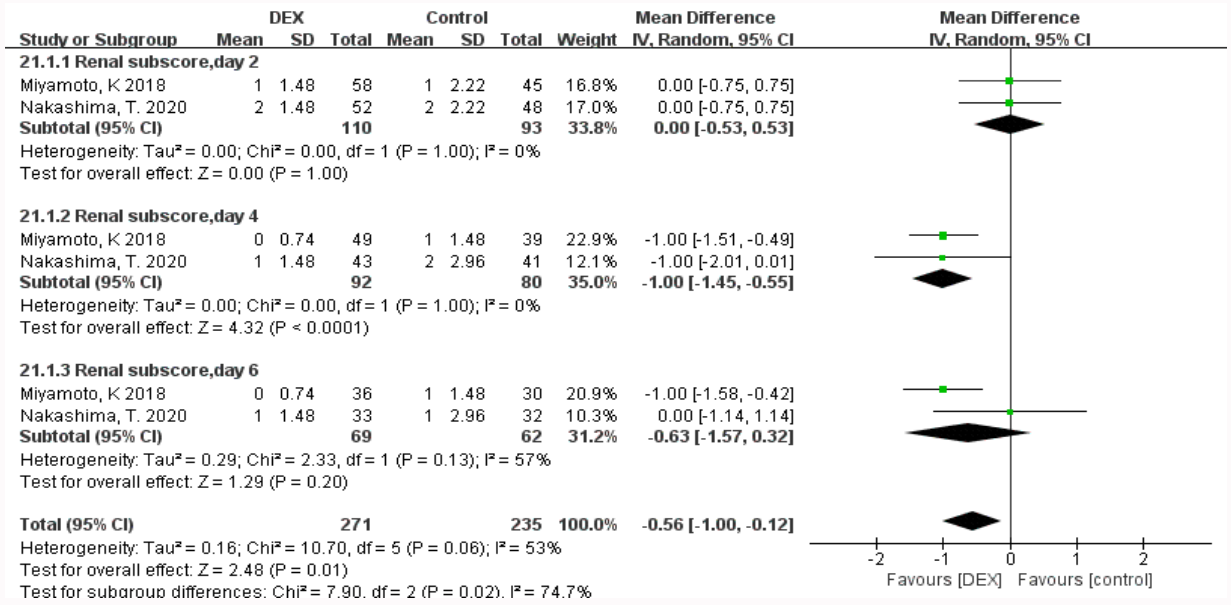

Figure 5: Meta-analysis of the two groups of sedative drugs on the renal SOFA scores of patients with sepsis.

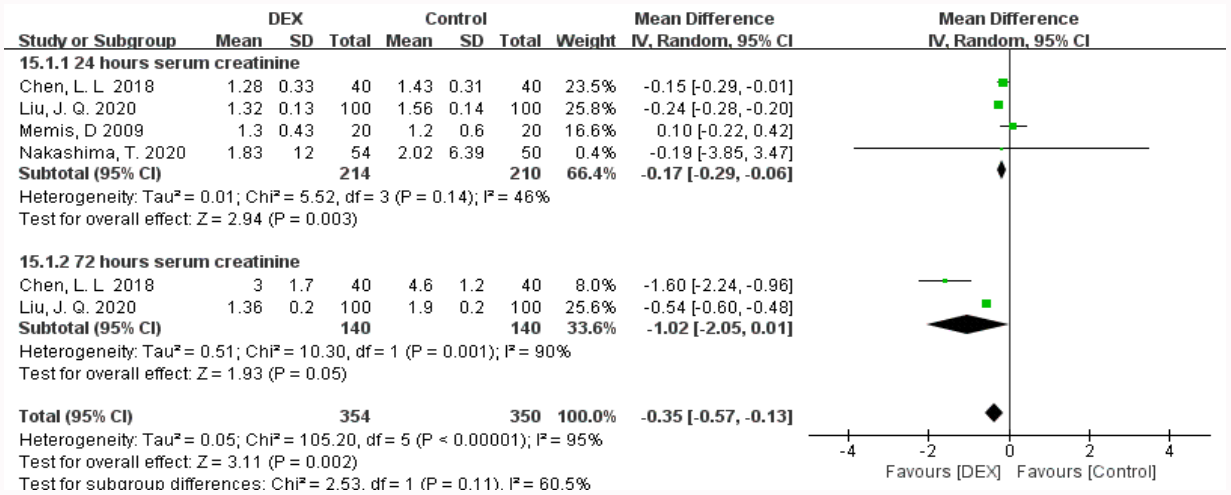

Figure 6: Meta-analysis of the comparison of serum creatinine levels between the two sedation groups.

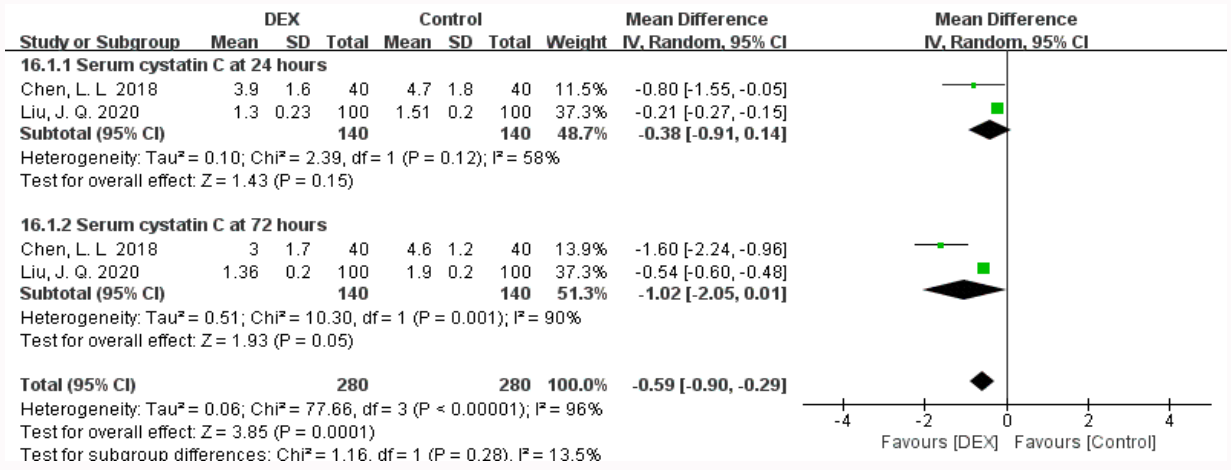

Figure 7: Meta-analysis of the effects of sedation on the level of cystatin C in the two groups.

Figure 8: Meta-analysis of DEX's application to the CRRT ratio.

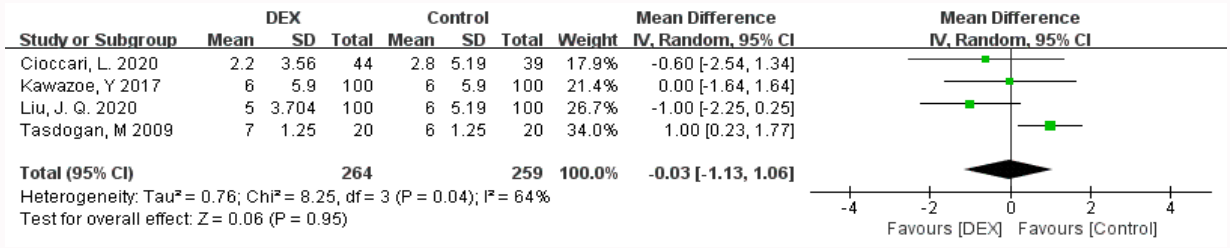

Figure 9: Meta-analysis of DEX on the duration of mechanical ventilation in patients with sepsis.

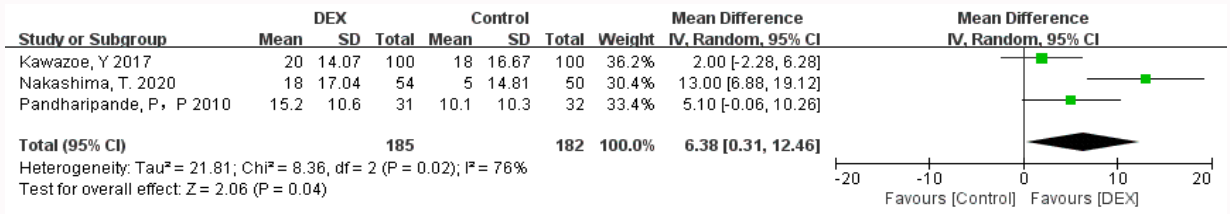

Figure 10: Meta-analysis of DEX on the 28-day ventilator-free days in patients with sepsis.

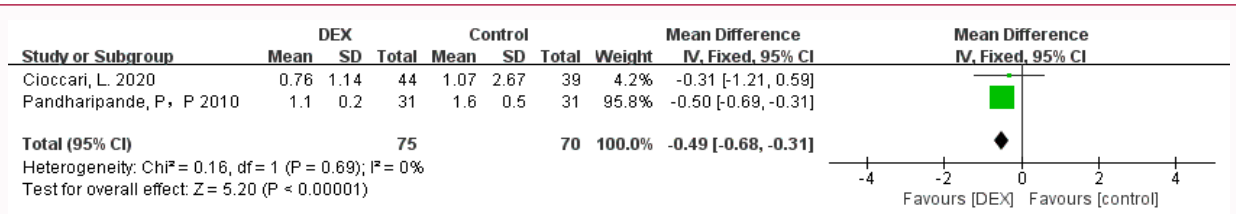

Figure 11: A meta-analysis of the 24-hour vasoactive drug application of the two groups of sedative drugs.

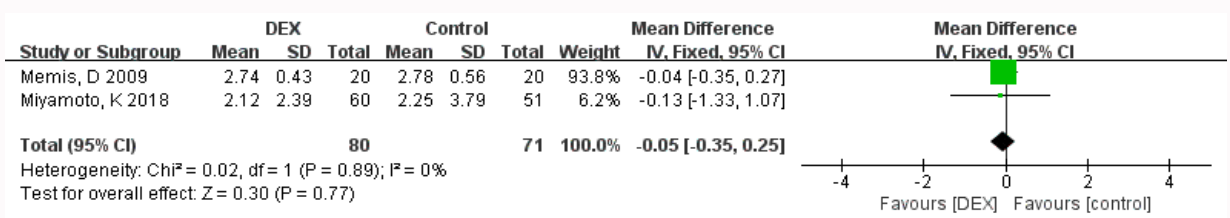

Figure 12: The 24-hour lactic acid situation of the two groups of sedative drugs.

effects of DEX on the organ functions and mortality in patients with sepsis firstly, and we conducted a systematic review. In our meta-analysis, a total of 11 articles were included, and the articles included 1,245 patients. It was found that compared with other sedative drug groups, DEX did not significantly decrease the SOFA score of patients with sepsis but did decrease the kidney score. DEX could significantly improve the renal function of septic patients. DEX did reduce the use of vasoactive drugs, but it did not reduce the patient's serum lactic acid level or the time of mechanical ventilation. DEX reduced the mortality of patients with sepsis, but it did not reduce the length of stay in the ICU.

A SOFA score of ≥ 2 points in patients with sepsis indicates the presence of acute organ dysfunction [19]. Three studies in our meta-analysis evaluated the effects of DEX on SOFA scores compared other sedative regiments. Although our results showed that DEX could not reduce the SOFA score compared with other sedatives, it did can reduce the score of renal function, suggesting the renal protective

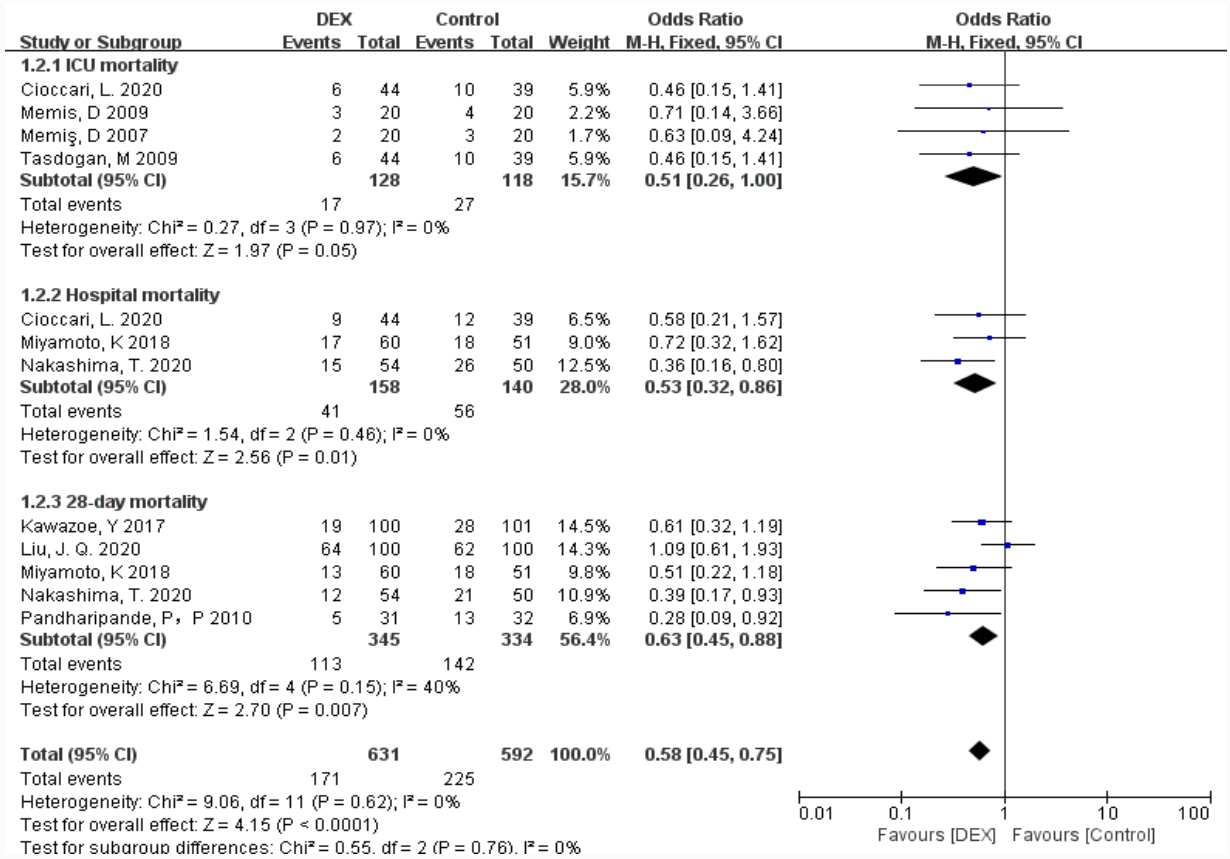

Figure 13: Meta-analysis of DEX on the fatality rate of patients with sepsis.

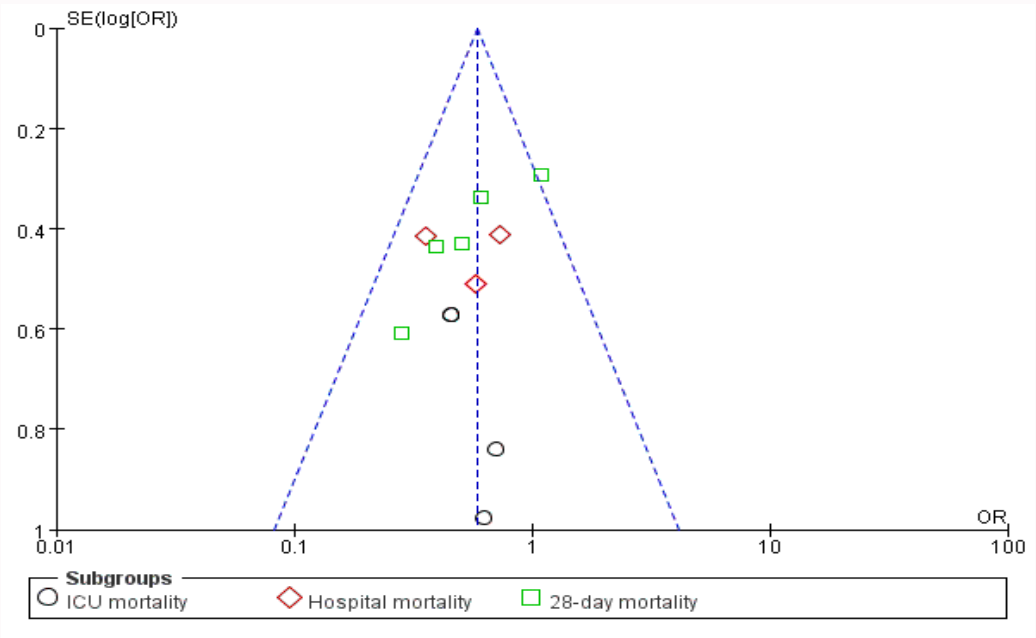

Figure 14: Funnel chart of DEX's evaluation of patients' fatality rate included in the literature.

effects of DEX. In addition, our meta-analysis from4 studies evaluated the effects of DEX on renal function in all of the 11 studies. We found that DEX reduced the serum creatinine and cystatin C levels compared with other sedatives, which further confirmed the protective effect of DEX on the kidney. Only one of the studies included in our meta-analysis reported the impact of DEX on heart and showed that DEX could reduce the level of cardiac injury biomarker compared with propofol and midazolam without providing the data about cardiac function. Our meta-analysis also showed that septic patients sedated with DEX had more free mechanical days and a lower mortality as

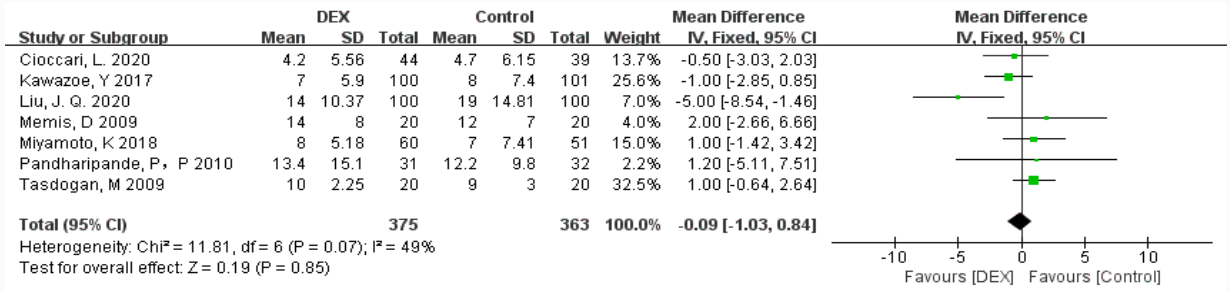

Figure 15: Meta-analysis of DEX on the length of stay in the ICU of patients with sepsis.

compared with those sedated with others.

The effects of DEX on septic patients' organ function and mortality may be due to its pharmacological mechanism, anti-stress response [20]. Although some degree of sympathetic activation is required for survival of a patient under the stressful conditions of sepsis, adrenergic overload has several underappreciated side effects that may impact negatively on final outcome. DEX can save on the need for exogenous norepinephrine by weakening the activity of sympathetic nerves which can decrease the level of norepinephrine in the endogenous blood and increase the sensitivity of vascular smooth muscle receptors to vasoactive drugs [21-23]. The result of our meta-analysis that DEX could decrease the norepinephrine requirements compared with other sedatives supported this mechanism.

'Inflammatory' shock constitutes the hallmark of sepsis [24]. Our meta-analysis illustrated that the levels of serum TNF-α and IL-1 in patients with sepsis sedated with DEX were lower remarkably than those sedated with other sedative regiments, which could have contributed to improved outcomes. The mechanism may be related to the neuroimmune interaction [25] (In supplementary materials).

Our meta-analysis did not find DEX could ameliorate other splanchnic organ functions, such as hepatic and gastrointestinal function. This difference may be due to the unique characteristics of kidney. Firstly, the density of sympathetic efferent nerves innervated in kidney is less than the other splanchnic organs, although all splanchnic organs are densely innervated [26]. That means renal blood flow could be reserved well a little bit than those of hepatic and gastrointestinal tract. Additionally, the kidney has the priority to get perfusion restored and more chance to recover its function as the kidney has relatively comprehensive autonomic regulation capacity in blood flow than other splanchnic organs [27]. These differences also reveal that the kidney has both vulnerability and certain self-protection in acute stress events, suggesting that the kidney may be used as the guiding organ for organ perfusion management in sepsis. From our meta-analysis, we could not find the improvements of DEX on the heart, maybe due to its some inhibition effects on myocardial function. We believe there must be more mechanisms to it than above mentioned [26]. Because the purpose of the study is not to discuss the mechanism, and there is a certain deviation due to the few articles included in our meta-analysis. Our results need to be further explored.

Advantages

To our knowledge, this article is the first comprehensive meta-analysis so far on the effects of DEX on organ function and mortality in patients with sepsis, and we also conducted a systematic review.

Limitations

(1) Although this meta-analysis showed that DEX has a certain effect of improving the kidney function, it did not significantly improve the functions of others. The specific mechanism is not clear and deserves further research.

(2) This meta-analysis found that DEX can reduce the dose of vasoactive drugs and reduce the level of inflammatory factors, but whether the reductions were related to the level of stress response and whether the reductions contributed to the protective effects on clinical outcomes are needed to be confirmed by further well-designed studies.

(3) The research protocols of the 11 studies were not completely consistent. The experimental group included patients who received DEX, but the control group included patients who received other sedative drugs including midazolam, propofol and lorazepam, which may have affected the final results.

Conclusion

In summary, the results of this meta-analysis show that, when compared with other sedative drugs, DEX can improve the renal function and mortality of septic patients may be associated with the reduction of vasopressor requirements and inflammatory levels by alleviate the stress response in sepsis. The reason why DEX failed to improve the function of other organs except that of kidney may lie in the unique characteristics of kidney. Our results provided a promising therapeutic direction that requires further investigation.

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