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Review Article

Variable efficacy of drotrecogin alfa (activated) in severe sepsis and septic shock: a meta-analysis

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Abstract: In this meta-analysis, we aimed to assess the clinical efficacy of drotrecogin alfa (activated) (DAA) in severe sepsis and septic shock. A literature search on PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrails.gov until February 10, 2017 was used to identify the relevant randomized controlled trials. Data analysis was performed using Stata 14.0. Six eligible studies were included in this study. With respect to the 28-day all-cause mortality, DAA had no significant effect (relative risk (RR)=1.01, 95% confidence interval (95% CI): 0.85-1.2, I^2=70.1%, *P*=0.005). In addition, DAA showed no significant difference in the 90-day all-cause mortality (RR=1.09, 95% CI: 0.99-1.2, I^2=23.4%, *P*=0.271). DAA was also associated with an increased risk of serious bleeding (RR=1.43, 95% CI: 1.03-1.98, I^2=0.00%, *P*=0.606). Moreover, the pooled results of intracranial hemorrhage events showed no statistical significance (Peto odds ratio =1.21, 95% CI: 0.50-2.9, I^2=0.00%, *P*=0.897). No publication bias was observed for any of the outcomes, as evidenced by the symmetry of the funnel plots and Egger's test. Based on these results, DAA should be used carefully in the treatment of severe sepsis and septic shock in adults.

Keywords: Severe sepsis, septic shock, drotrecogin alfa, mortality, hemorrhage

Introduction

Sepsis is a life-threatening condition that occurs when the body response to infection damages its own tissues and organs [1]. Common signs and symptoms include fever, increased heart rate, increased respiratory rate, and confusion [2]. Symptoms of established sepsis include confusion, metabolic acidosis (which may be accompanied by faster breathing that can lead to respiratory alkalosis), hypotension because of decreased systemic vascular resistance, higher cardiac output, and dysfunction of blood coagulation, wherein clotting may lead to organ failure. Severe sepsis is associated with impaired organ function or insufficient blood supply. Insufficient blood supply may manifest as hypotension, high blood lactate, or low urine output [3]. Sepsis accounts for millions of deaths worldwide every year, and is the most common cause of death in hospitalized patients [4, 5]. The risk of death from sepsis, severe sepsis, and septic shock is approximately 30, 50, and 80%, respectively [6-8].

Sepsis is caused by an immune response triggered by an infection [4]. It has been postulated that removal of the inflammatory mediators and/or bacterial toxins from the bloodstream could result in a beneficial down regulation of the overactive immune response that mediates end-organ damage in patients with septic shock [9-11]. The infections leading to sepsis are usually bacterial; however, fungal and viral infections can result in sepsis as well. Gram-negative bacteria were previously considered the most common cause of sepsis; however, in the last decade, gram-positive bacteria, most commonly staphylococci, are believed to account for more than 50% of the cases of sepsis [12]. Sepsis is attributed to a combination of factors related to the particular invading pathogen(s) and to the status of the host immune system [13, 14]. The early phase of sepsis, character-

ized by excessive inflammation (sometimes resulting in a cytokine storm), may be followed by a prolonged period of decreased functioning of the immune system. Both phases may be fatal [14, 15].

Drotrecogin alfa (activated) (DAA) is a recombinant form of human activated protein C, which is produced from its inactive precursor, protein C, by thrombin coupled to thrombomodulin [16]. The conversion of protein C to activated protein C may be impaired during sepsis because of the down regulation of thrombomodulin by the inflammatory cytokines. Reduced levels of protein C are found in the majority of patients with sepsis, and are associated with an increased risk of death [17]. DAA, or recombinant human activated protein C, has antithrombotic, anti-inflammatory, and profibrinolytic properties. DAA was approved for the treatment of severe sepsis in 2001 based on the results of the Prospective Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) study [9]. In this meta-analysis, we aimed to evaluate the efficacy of DAA in severe sepsis and septic shock using the 28-day and 90-day all-cause mortality as primary endpoints, and severe bleeding and intracranial hemorrhage as secondary outcomes.

Materials and methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [18], and was conducted in accordance with the Cochrane Collaboration's systematic review framework [19].

Search strategy

We searched four electronic databases, namely PubMed, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrails.gov, until February 10, 2017 for eligible randomized controlled trials (RCTs) that have evaluated the effectiveness of DAA in severe sepsis and septic shock. We searched PubMed using the following terms: ("Sepsis" [tiab] OR "Shock, Septic" [Mesh] OR "shock" [tiab]) AND ("drotrecogin alfa activated" [Supplementary Concept] OR "activated protein C "[tiab] OR "protein C" [tiab] OR "APC" [tiab] OR "APC alfa" [tiab] OR "rh APC" [tiab]) AND random*. EMBASE was searched using the following terms: ('drotrecogin'/exp OR 'activated protein C'/exp) AND ('sepsis'/exp OR 'septic shock'/exp). Both the Cochrane Central Register of Controlled Trials and Clinical Trials. gov were searched using the unrestricted term, "drotrecogin".

Literature selection and exclusion

A thorough literature search was conducted to retrieve all RCTs that have evaluated the efficacy of DAA in adult with severe sepsis or septic shock via investigation of one of the following outcomes: 1) 28-day all-cause mortality, 2) 90-day all-cause mortality, 3) severe bleeding, or 4) intracranial hemorrhage. The 28-day and 90-day all-cause mortality were pooled as the primary outcomes, while the severe bleeding and intracranial hemorrhage were seen as a secondary outcomes.

Patients were eligible for the trial if they had severe sepsis, which was defined as the presence of a suspected or known infection and sepsis-induced dysfunction of at least one organ (cardiovascular, renal, respiratory, hematologic, or unexplained metabolic acidosis), and a low risk of death. Studies were excluded according to the following criteria: 1) if the study was a duplicate; 2) the data could not be extracted or obtained through contact with the author, and 3) it was not study DAA as primary treatment drug.

Data extraction and quality assessment

The relevant information, including the study design, patient characteristics, interventions, comparisons, and outcomes, was independently extracted and entered into a database by two investigators. When relevant research information was missing, particularly the study design and outcome information, we contacted the original authors for clarifications.

Two investigators independently evaluated the methodological quality of the eligible trials by using the Cochrane Collaboration's tool for assessing the risk of bias (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other sources of bias) [19]. Disagreements between the two authors on data extraction and quality assessment

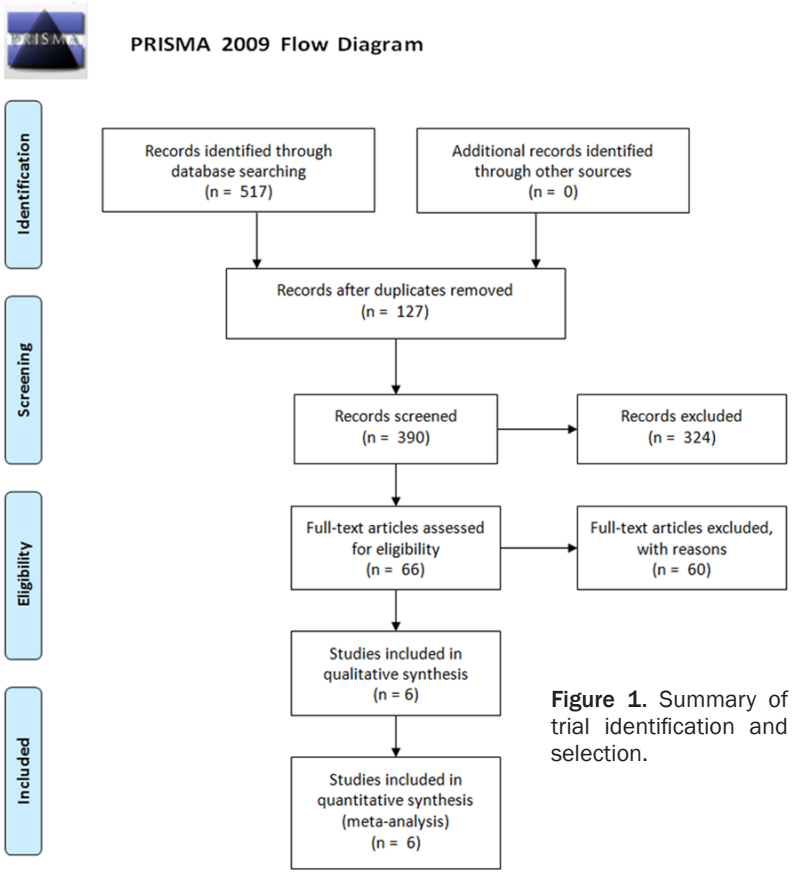

Figure 1. Summary of trial identification and selection.

were resolved by discussion. If the dispute persisted, other senior investigators were consulted to attain consensus.

Statistical analysis

To describe the main dichotomous data [20], we used the relative risk (RR), 95% confidence interval (95% CI), and $P \leq 0.05$. For the event rates below 1%, the Peto odds ratio (OR) was employed according to the Cochrane handbook [19]. All outcome data were processed using STATA 14.0 software. We performed a statistical test for heterogeneity and adopted $I^2 > 50\%$ as evidence for heterogeneity, according to the Cochrane handbook. Data were homogeneous under the fixed effects model. If the data were still heterogeneous, and the number of included studies was few, we used the random effects model.

The symmetry of a funnel plot [21] was used to qualitatively determine whether there was publication bias or not. In a funnel plot, larger studies provide a more precise estimate of the intervention effect at the spout of the funnel, whereas smaller studies with less precision form the cone end of the funnel. Asymmetry in the funnel plot indicates potential publication bias. Finally, the Egger's test was used for quantitative detection of bias [22].

Results

Characteristics of individual studies

We identified 517 publications in the electronic databases (**Figure 1**). Employing the selection criteria summarized in the Materials and methods section, we obtained quantitative data for our meta-analysis after reading all the titles, abstracts, and full texts. Six eligible studies [23-28] were included in our final analysis. The six eligible studies included 6661 patients. There were 798 of 3364 (23.72%) and 759 of 3297 (23.02%) deaths in the DAA and control groups, respectively, on day 28. On day 90, 543 of 1464 (37.1%) and 498 of 1467 (34%) deaths were observed in the DAA and control groups, respectively. Regarding severe bleeding, 95 of 3175 (3%) and 55 of 2754 (2%) patients developed severe bleeding in the DAA and control groups, respectively. In addition, 11 of 3011 (3.65%) and 9 of 3010 (2.99%) patients suffered from intracranial hemorrhage in the DAA and control groups, respectively. The characteristics of each individual study are shown in **Table 1**.

Quality of the included studies

The risk of bias in the included studies was strictly evaluated. Details on the methodological approach are shown in **Table 2**.

28-day all-cause mortality

The DAA group in all included studies [23-28] showed no advantage in the primary endpoint of 28-day all-cause mortality, compared to the

Table 1. Characteristics information of the included studies

Study	Year	Country	Population	Gender (female%)	Mean age	Diabetes (%)	Mean APACHE II Score	Vasopressor (%)	Protein C Deficiency (%)	Sample (I/C)	Interventions	Control	Outcomes
Povoa [23]	2015	Portugal	Patients diagnosed with septic shock	42.41	64.9	25.1	23.5	NA	NA	414/442	DAA (at a dose of 24 ug per kilogram of body weight per hour) for 96 hours	Saline placebo	①②
Annane [24]	2013	France	Adults with persistent septic shock and no contraindication to DAA	34.50	63.0	64.0	NA	NA	NA	208/203	DAA (at a dose of 24 ug per kilogram of body weight per hour) for 96 hours	Saline placebo	①②
Ranieri [25]	2012	USA	Adults with infection, systemic inflammation and shock receiving fluids and vasopressors above threshold dose for 4 hours	43.60	63.1	24.4	25.3	100.00	39.92	846/834	DAA (at a dose of 24 ug per kilogram of body weight per hour) for 96 hours	Saline placebo	①②③④
Abraham [26]	2005	USA	Adults with severe sepsis and APACHE II Score <25 or single-organ failure	42.60	58.7	NA	18.2	47.72	NA	1316/1297	DAA (at a dose of 24 ug per kilogram of body weight per hour) for 96 hours	Saline placebo	①③④
Bernard [27]	2001	USA	Adults with seystemic inflammation and prgan failure due to acute infection	43.02	60.5	21.5	24.8	73.60	39.10	490/480	DAA (at a dose of 24 ug per kilogram of body weight per hour) for 96 hours	Saline placebo	①③④
Bernard [28]	2001	USA	Adults with severe shock	36.10	59.3	22.3	17.3	69.40	50.00	90/41	DAA (at a dose of 12, 18, 24 or 30 ug per kilogram of body weight per hour) for 48 or 96 hours	Saline placebo	①③

I: Intervening group, C: Control group, DAA: Drotrecogin Alfa (activated), ①: 28-day all-cause mortality, ②: 90-day all-cause mortality, ③: Severe bleeding, ④: Intracranial hemorrhage, NA: Not obtainable.

Table 2. Risk of bias in included studies

Study	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Povoa [23]	2015	Low	Low	Low	Unclear	Low	Low	Unclear
Annane [24]	2013	Low	Low	Low	Low	Low	Low	Unclear
Ranieri [25]	2012	Low	Low	Low	Low	Low	Low	Low
Abraham [26]	2005	Low	Low	Low	Low	Low	Low	Low
Bernard [27]	2001	Low	Low	Low	Unclear	Low	Low	Unclear
Bernard [28]	2001	Low	Low	Low	Unclear	Low	Low	High

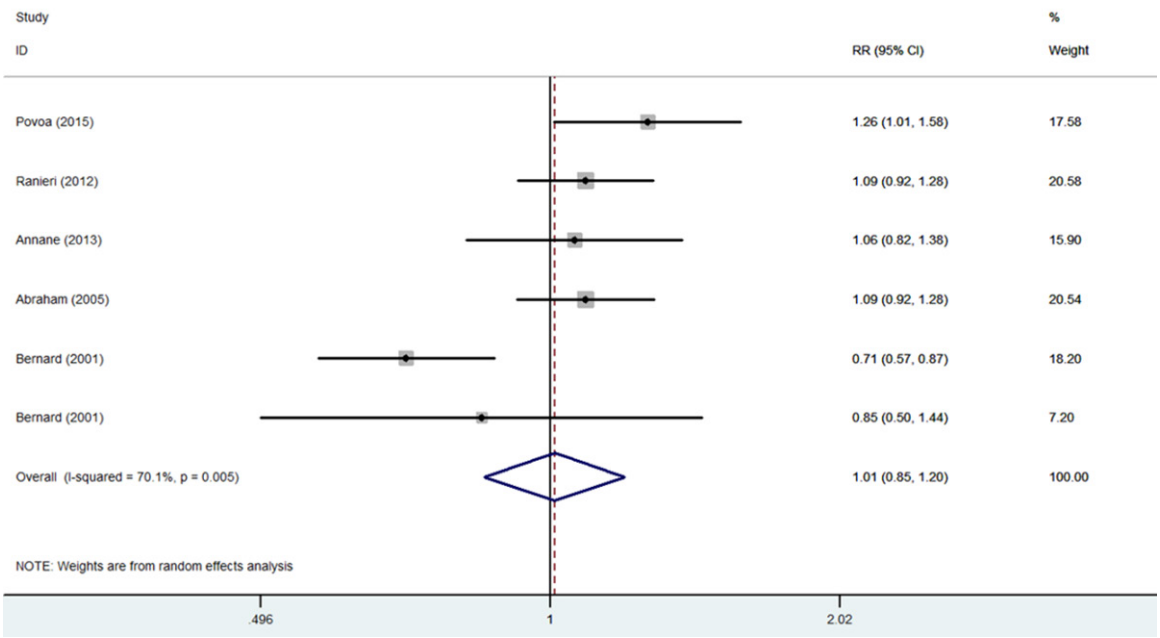

Figure 2. Forest plot of 28-day all-cause mortality.

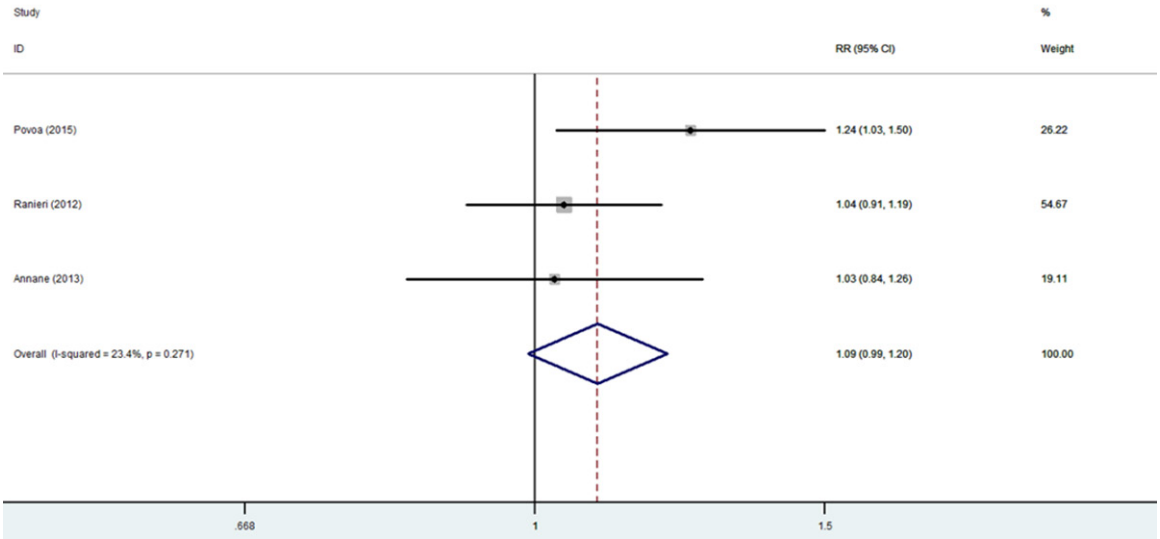

Figure 3. Forest plot of 90-day all-cause mortality.

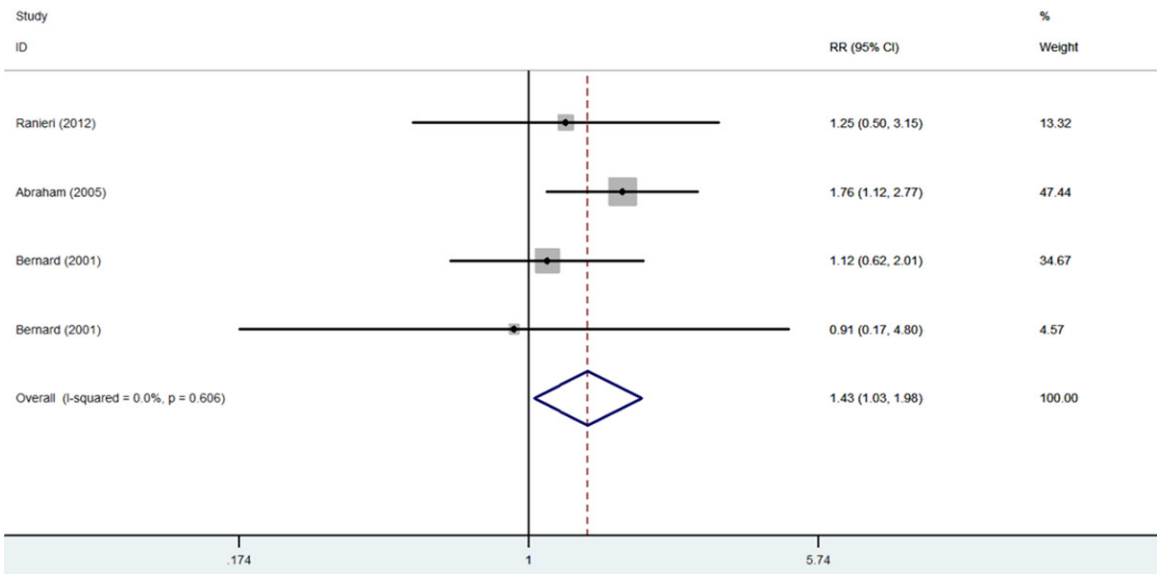

Figure 4. Forest plot of serious bleeding.

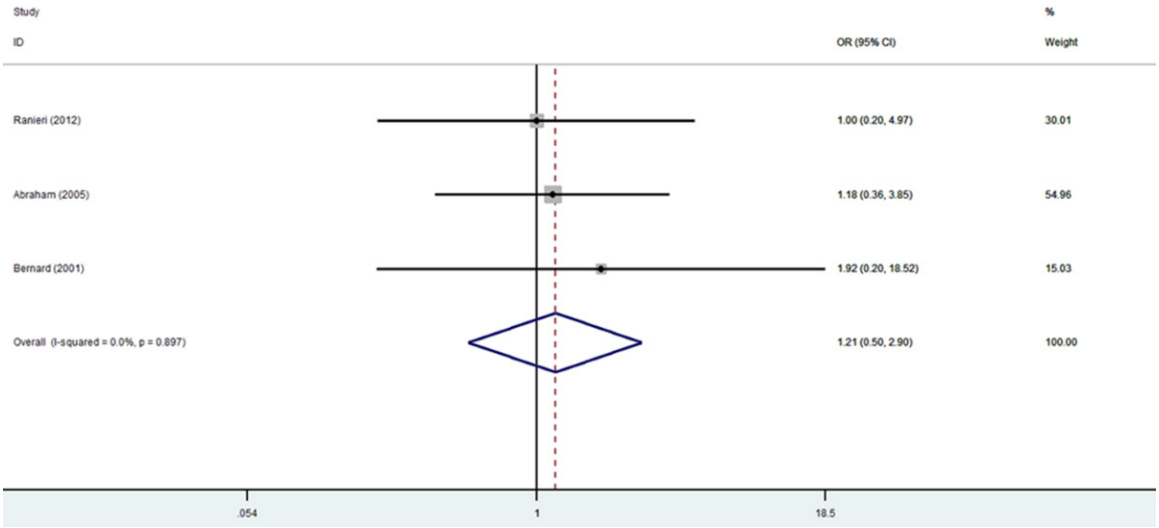

Figure 5. Forest plot of intracranial hemorrhage.

control group, with a pooled RR of 1.01 and 95% CI: 0.85-1.20 (forest plot in **Figure 2**). Significant heterogeneity was identified in this analysis (I^2=70.1%, *P*=0.005) using the random effects model.

90-day all-cause mortality

The effect of DAA on the 90-day all-cause mortality was assessed in three included studies [23-25]. DAA was not associated with an increase in mortality, with a pooled RR of 1.09 and 95% CI: 0.99-1.2 (forest plot in **Figure 3**). There was no heterogeneity (I^2=23.4%, *P*=0.271) using the fixed effects model.

Severe bleeding

Using the fixed effects model, it was shown that DAA was associated with an increase in serious bleeding (RR=1.43, 95% CI: 1.03-1.98, I^2=0.00%, *P*=0.606, forest plot in **Figure 4**).

Intracranial hemorrhage

Finally, we assessed the effect of DAA on preventing intracranial hemorrhage [25, 26, 28],

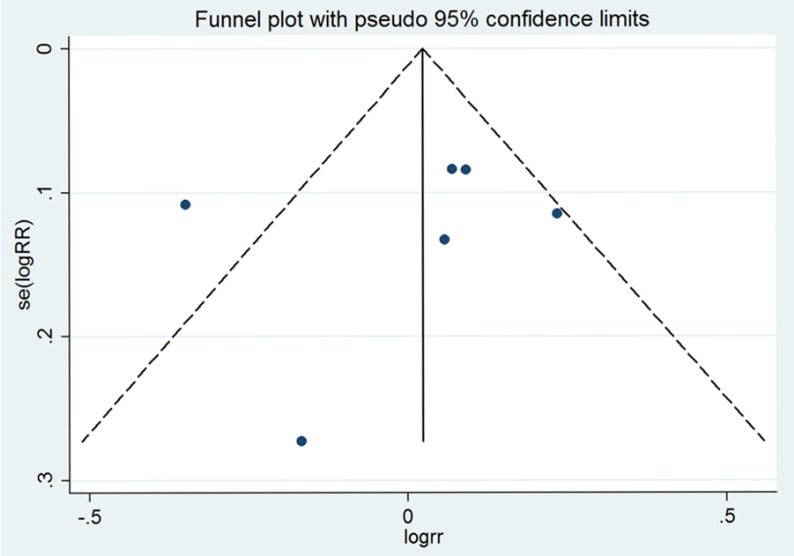

Figure 6. Funnel plot of 28-day all-cause mortality.

DAA did not prevent intracranial hemorrhage in patients with severe sepsis or septic shock (RR=1.21, 95% CI: 0.5-2.9, I^2=0.00%, *P*=0.897), using the fixed effects model (forest plot in **Figure 5**).

Publication bias

No publication bias was observed for any of the outcomes as evidenced by the symmetry of the funnel plots, as shown in **Figure 6**. The results of the Egger's test indicated no significant difference in alloutcomes: 28-day all-cause mortality (Bias =-1.247, 95% CI: -8.698-6.205, *P*=0.666), 90-day all-cause mortality (Bias =1.927, 95% CI: -7.523-6.869, *P*=0.755), severe bleeding (Bias =-1.107, 95% CI: -5.048-2.834, *P*=0.35), and intracranial hemorrhage (Bias =0.647, 95% CI: -10.156-11.45, *P*=0.586).

Discussion

Many approaches are used for treatment of sepsis, including fluid therapy, vasopressor therapy, supportive therapy, mechanical ventilation, and tight glycemic control. Administration of fluids, usually crystalloids, such as isotonic sodium chloride solution and lactated Ringer's solution, is the standard first-line treatment of severe sepsis. In a recent study examining early resuscitation to a defined goal, when sufficient fluids were administered within the first 6 hours after diagnosis of severe sepsis, mortality was significantly reduced [29]. Similarly, vasopressors are used to treat the disruption in the endothelial wall. Vasodilatation is counteracted with arterial constrictors, so that the increased constriction hopefully leads to improved perfusion [30]. A number of evidence-based supportive therapies can help minimize or prevent the worsening of injury induced by the pathophysiological sequelae of severe sepsis. These supportive measures include lung protective strategies, management of hyperglycemia seen in critical illness, and prevention of additional infections, particularly ventilator-associated pneumonia (VAP) [31]. Patients with sepsis are at greater risk for development of acute lung injury and acute respiratory distress syndrome (ARDS); thus, it is necessary to maintain mechanical ventilation in patients with sepsis. In 2000, the ARDS Network published a landmark study that showed the benefits of the lung protective strategies in patients with acute lung injury and ARDS [32, 33]. In addition, management of hyperglycemia in critically ill patients affects the mortality. In a study conducted on 1500 surgical intensive care unit (ICU) patients for a 12-month period, tight control of the blood glucose level, rather than the amount of insulin administered, had a beneficial effect [34].

In 2001, enthusiasm for the use of the PROWESS trial for treatment of sepsis peaked with the approval of DAA (Xigris®), a recombinant human activated protein C (rhAPC). These regulatory decisions were based on the results of the PROWESS trial, which demonstrated that treatment with DAA led to a 6.1% absolute risk reduction in 28-day mortality in patients with severe sepsis or septic shock, compared to placebo [27]. Since the original publication of the PROWESS trial, there has been much debate on the use of DAA. Four major limitations that decrease the use of this drug are 1) failure to diagnose high-risk severe sepsis and to determine which patients are appropriate candidates for treatment; 2) lack of understanding of the data supporting the efficacy of the drug; 3) failure to understand and manage the bleeding

risk in patients with sepsis; and 4) the cost associated with a novel treatment [30].

In this meta-analysis, we evaluated 6 clinical trials that included 6661 sepsis patients, aged >18 years old. In this study, DAA was associated with a statistically significant increase in severe bleeding. However, in terms of the 28-day and 90-day all-cause mortality and intracranial hemorrhage, the DAA group was not significantly superior to the control group. Therefore, it is noteworthy that although DAA is the most common drug currently used to control sepsis, caution should be used before its selection.

There remains some unease in the clinical and scientific communities about the use of DAA, particularly regarding the original study protocol and its efficacy and safety profile [35, 36]. Furthermore, our study has some limitations. First, only a few sample size based on the number of the included trials met the inclusion and exclusion criteria; therefore, more clinical studies are required to confirm our results [19]. Second, because of the previous limitation, we cannot further implement a meta-regression analysis to perform an exploratory study [19]. Finally, the nature of the meta-analysis also limits the granularity of the data used in the primary analyses because data on the exact timing and adequacy of volume resuscitation and appropriate antibiotic therapy were missing from all RCTs.

Conclusions

This study evaluated the effectiveness of DAA in sepsis patients via a meta-analysis of the published studies. Our results indicated that DAA therapy had greater effectiveness and ability to increase the bleeding events in sepsis patients, compared to the control. Additionally, DAA showed no effect on the 28-day and 90-day all-cause mortality and intracranial hemorrhage in patients with severe sepsis and shock. Based on these findings, DAA should be used carefully in the treatment of severe sepsis and septic shock in adults.

Disclosure of conflict of interest

None.

Authors' contribution

WJZ had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. SZ and QQW designed the study. SZ, HYZ and QQW developed and tested the data collection forms. WJZ acquired the data. SZ, HYZ and WJZ conducted the analysis and interpreted the data. WJZ drafted the manuscript. All authors critically revised the manuscript. WJZ had guarantor.

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