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Review Article

Efficacy of esmolol for septic shock and sepsis: a meta-analysis of randomized controlled studies

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Abstract: Introduction: Esmolol treatment has emerged as an important adjunct for septic shock and sepsis. However, the use of esmolol to treat septic shock and sepsis has not been well established. We conduct a systematic review and meta-analysis to evaluate the efficacy of esmolol for septic shock and sepsis. Methods: PubMed, Embase, and the Cochrane Central Register of Controlled Trials are searched. Randomized controlled trials (RCTs) assessing the influence of esmolol treatment on septic shock and sepsis are included. Two investigators independently have searched articles, extracted data, and assessed the quality of included studies. Meta-analysis is performed using the random-effect model. Results: Six RCTs involving 363 patients are included in the meta-analysis. Compared with control intervention in septic patients, esmolol treatment is associated with significantly increased survival rate (RR = 1.71; 95% CI = 1.13 to 2.60; P = 0.01), decreased TnI (Std. MD = -1.91; 95% CI = -2.39 to -1.43; P < 0.00001) and CK-MB (Std. MD = -0.90; 95% CI = -1.37 to -0.43; P = 0.0002), and shows no important impact on MAP (Std. MD = 0.05; 95% CI = -0.22 to 0.32; P = 0.71) and CVP (Std. MD = -0.11; 95% CI = -0.50 to 0.28; P = 0.58). Conclusions: Esmolol treatment can significantly improve survival rate, and reduce TnI and CK-MB, with no remarkable influence on MAP and CVP in patients with septic shock and sepsis.

Keywords: Septic shock, sepsis, esmolol, randomized controlled trials, meta-analysis

Introduction

Severe sepsis and septic shock have achieved high prevalence in millions of people around the world and approximately 25% of these patients would be killed each year [1-3]. Severe sepsis and septic shock can result in excessive sympathetic outflow, high plasma catecholamine levels, myocardial depression, vascular hyporeactivity, and autonomic dysfunction [4, 5]. These patients always suffer from a low resistance, high cardiac output circulation with tachycardia and arterial hypotension [6-8]. Norepinephrine is the recommended mainstay of for sepsis-related hypotension, but excessive adrenergic stress can lead to multiple adverse effects such as direct myocardial damage, insulin resistance, thrombogenicity, immunosuppression, and enhanced bacterial growth [9, 10]. Poor outcomes in critically ill patients have some association with high plasma catecholamine levels, the extent and duration of catecholamine therapy, and tachycardia [11, 12].

Beta-adrenergic blockade fabricates the heart rate control and limits adverse events related to sympathetic overstimulation [10]. The pretreatment using beta-blockade also shows some benefits to sepsis [13, 14]. Heart rate control can improve cardiovascular performance, but may lead to cardiovascular decompensation in human septic shock [15]. Esmolol infusion for septic patients is reported to improve tissue metabolism and central venous oxygen saturation, and reduce hospital stay and mortality [16-18].

However, the use of esmolol for severe sepsis and septic shock has not been well established. Recently, several studies on the topic have been published, and the results have been conflicting [16, 17, 19, 20]. Considering these inconsistent effects, we therefore conducted a

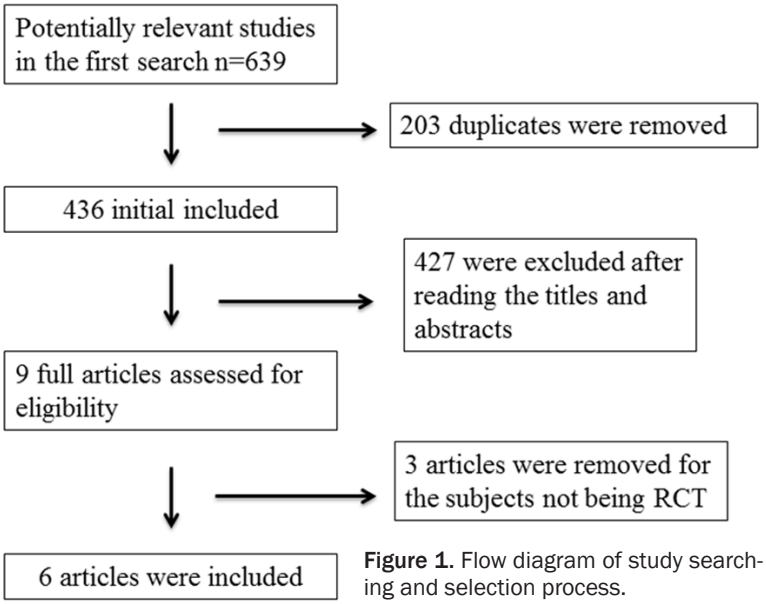

Figure 1. Flow diagram of study searching and selection process.

systematic review and meta-analysis of RCTs to evaluate the efficacy of esmolol treatment for septic shock and sepsis.

Materials and methods

Ethical approval and patient consent are not required since this is a systematic review and meta-analysis of previously published studies. The systematic review and meta-analysis are conducted and reported in adherence to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [21].

Search strategy and study selection

Two investigators have independently searched the following databases (inception to April 2018): PubMed, Embase, and the Cochrane Register of Controlled Trials. The electronic search strategy is performed using with the following keywords: “esmolol” and “septic shock” or “sepsis”. We also have checked the reference lists of the screened full-text studies to identify other potentially eligible trials.

The following inclusive selection criteria are applied: (i) patients are diagnosed with septic shock or sepsis; (ii) intervention treaments are esmolol treatment versus basic treatment; and (iii) study design is RCT.

Data extraction and outcome measures

We have used a piloted data-extraction sheet, which covers the following information: first author, number of patients, age, acute physiology and Chronic Health Evaluation II (APACHE II) scores, detail methods in two groups. Data are extracted independently by two investigators, and discrepancies are resolved by consensus. We have contacted the corresponding author to obtain the data when necessary. No simplifications and assumptions are made.

The primary outcome is survival rate. Secondary outcomes include troponin I (TnI), creatine kinase MB isoform (CK-MB), mean arterial pressure (MAP), central venous pressure (CVP).

Quality assessment in individual studies

The Jadad Scale is used to evaluate the methodological quality of each RCT included in this meta-analysis [22]. This scale consists of three evaluation elements: randomization (0-2 points), blinding (0-2 points), dropouts and withdrawals (0-1 points). One point would be allocated to each element if they have been mentioned in article, and another one point would be given if the methods of randomization and/or blinding had been appropriately described. If the methods of randomization and/or blinding were inappropriate, or dropouts and withdrawals had not been recorded, then one point was deducted. The score of Jadad Scale varies from 0 to 5 points. An article with Jadad score ≤ 2 is considered to be of low quality. If the Jadad score ≥ 3, the study is thought to be of high quality [23].

Statistical analysis

We have estimated Standard Mean differences (Std. MDs) with 95% confidence intervals (CIs) for continuous outcomes (TnI, CK-MB, MAP, CVP), and risk ratios (RRs) with 95% CIs for dichotomous outcomes (survival rate). A random-effects model is used regardless of heterogeneity. Heterogeneity is reported using the I^2 statistic, and $I^2 > 50\%$ indicates significant heterogeneity [24]. Whenever significant heterogeneity is present, we search for potential sources of heterogeneity. Sensitivity analysis is performed to detect the influence of a single

Table 1. Characteristics of included studies

NO.	Author, study population and languages	Esmolol group					Control group					Jada scores
		Number	Age (years)	Male (n)	APACHE II score	Methods	Number	Age (years)	Male (n)	APACHE II score	Methods	
1	Wang 2017, China, Chinese	30	67.2 ± 12.5	18	-	Micro pump with dosage of esmolol 0.05-0.2 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$ in order to control heart rate less than 95 bpm	30	62.5 ± 14.5	21	-	Basic treatment	4
2	Liu 2015, China, Chinese	24	61.4 ± 6.9	14	20.75 ± 3.05	Micro pump with dosage of esmolol 0.05 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$	24	61.2 ± 6.4	13	21.21 ± 2.67	Basic treatment	4
3	Wang 2015, China, English	30	34 (21-60), median (range)	19	21.2 ± 5.7	Continuous intravenous infusion of esmolol, milrinone that commenced with a loading dosage of 30 ug/kg and was maintained at 0.375-0.5 ug/kg/min	30	38 (20-57), median (range)	19	20.8 ± 5.6	Continuous intravenous infusion of milrinone that commenced with a loading dosage of 30 ug/kg and was maintained at 0.375-0.5 ug/kg/min	4
4	Yang 2014, China, Chinese	21	51.0 ± 22.6	-	20.1 ± 9.2	Micro pump with dosage of esmolol 0.05 $mg{\cdot}kg^{-1}{\cdot}min^{-1}$	20	55.0 ± 25.4	-	21.3 ± 8.3	Basic treatment	3
5	Orbegozo Cortes 2014, Belgium, English	77	81.9 ± 7.2	26	-	esmolol infusion commenced at 25 mg × h^{-1} and progressively increased the rate at 20-minute intervals in increments of 50 mg × h^{-1}	77	76.6 ± 10.2	25	-	Basic treatment	3
6	Morelli 2013, Italy, English	77	66 (52-75), median (IQR)	54	-	Esmolol infusion commenced at 25 mg × h^{-1} and progressively increased the rate at 20-minute intervals in increments of 50 mg × h^{-1}	77	69 (58-78), median (IQR)	53	-	Basic treatment	5

APACHE II: Acute Physiology and Chronic Health Evaluation II.

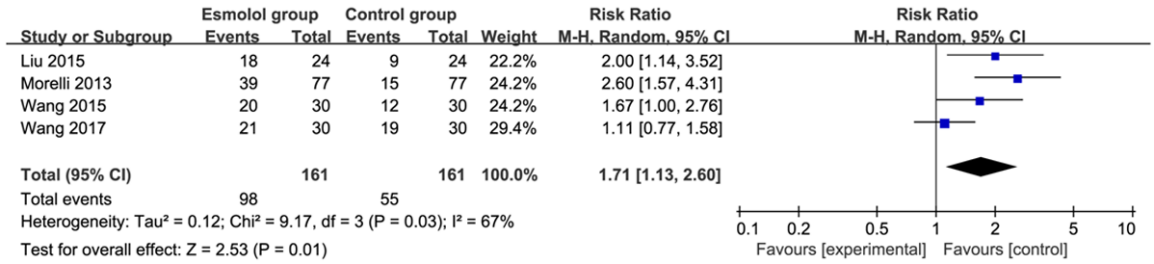

Figure 2. Forest plot for the meta-analysis of survival rate.

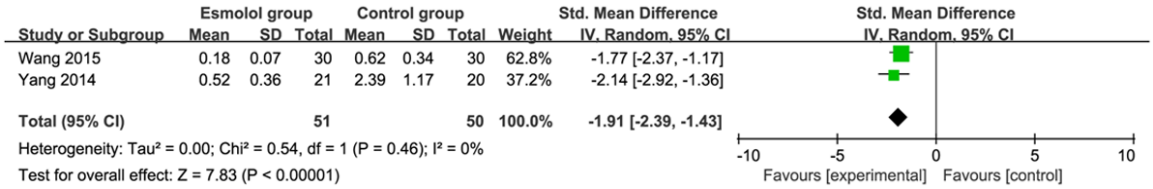

Figure 3. Forest plot for the meta-analysis of TnI (ng/mL).

study on the overall estimate via omitting one study in turn when necessary. Owing to the limited number (< 10) of included studies, publication bias is not assessed. Results are considered as statistically significant for $P < 0.05$. All statistical analyses are performed using Review Manager Version 5.3 (The Cochrane Collaboration, Software Update, Oxford, UK).

Results

Literature search, study characteristics and quality assessment

A detailed flowchart of the search and selection results is shown in **Figure 1**. 639 potentially relevant articles are identified initially. Finally, six RCTs that meet our inclusion criteria are included in the meta-analysis [16-20, 25].

The main characteristics of the six included RCTs are presented in **Table 1**. The six studies are published between 2013 and 2017, and sample sizes range from 41 to 154 with a total of 363. Two RCTs report the same disease sample, but with different follow-up time [18, 25]. Four RCTs are conducted in China [16, 17, 19, 20], and three of them are wrote in Chinese [16, 19, 20]. Four included RCTs involved septic shock [16, 18, 19, 25], and one included RCT involved sepsis [17].

Among the six RCTs, four studies have reported survival rate [16-18, 20], two studies have reported TnI [17, 19], two studies have reported CK-MB [17, 18], and four studies have reported MAP and CVP [16, 17, 19, 20]. Jadad scores of the six included studies vary from 3 to 5, and all six studies are considered to be high-quality ones according to quality assessment.

Primary outcome: survival rate

This outcome data is analyzed with the random-effects model, the pooled estimate of the four included RCTs suggested that compared to control group for septic shock and sepsis, esmolol intervention can substantially improve survival rate (RR = 1.71; 95% CI = 1.13 to 2.60; P = 0.01), with significant heterogeneity among the studies (I^2 = 67%, heterogeneity P = 0.03, **Figure 2**).

Sensitivity analysis

Significant heterogeneity is observed among the included studies for the survival rate (I^2 = 67%). As shown in **Figure 2**, the study [20] shows results that are completely out of range of the others and probably contributes to the heterogeneity. After excluding this study, the results suggest that esmolol intervention is associated with an improved survival rate (RR = 2.06; 95% CI = 1.52 to 2.79; P < 0.00001). No evidence of heterogeneity was observed among the remaining studies (I^2 = 0%).

Secondary outcomes

Compared to control group for septic shock and sepsis, Esmolol treatment is associated with significantly reduced TnI (Std. MD = -1.91; 95%

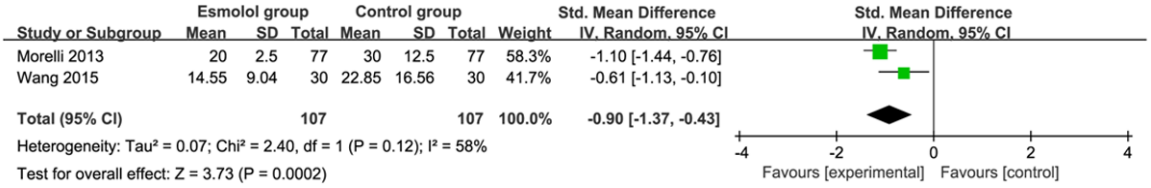

Figure 4. Forest plot for the meta-analysis of CK-MB (IU/L).

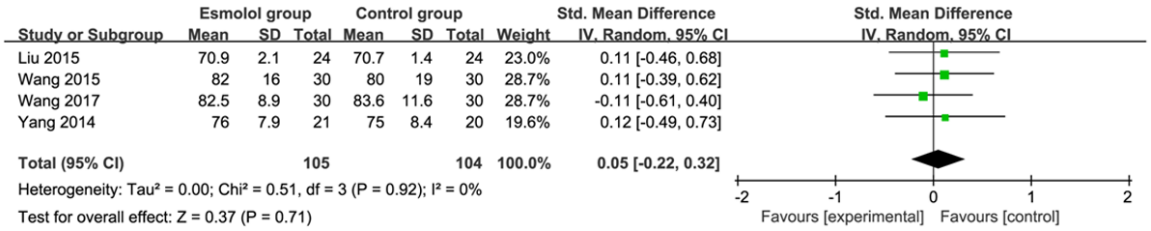

Figure 5. Forest plot for the meta-analysis of MAP (mmHg).

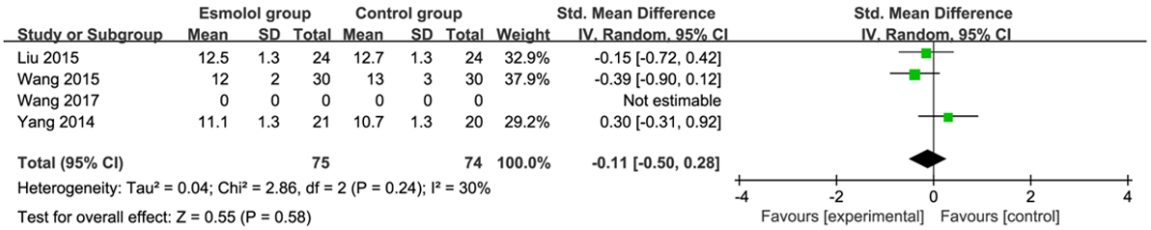

Figure 6. Forest plot for the meta-analysis of CVP (mmHg).

CI = -2.39 to -1.43; P < 0.00001; **Figure 3**) and CK-MB (Std. MD = -0.90; 95% CI = -1.37 to -0.43; P = 0.0002; **Figure 4**), with no substantial impact on MAP (Std. MD = 0.05; 95% CI = -0.22 to 0.32; P = 0.71; **Figure 5**) and CVP (Std. MD = -0.11; 95% CI = -0.50 to 0.28; P = 0.58; **Figure 6**).

Discussion

Tachycardia increases cardiac workload and myocardial oxygen consumption, and reduces diastolic relaxation time and impairment of diastolic function which further affect coronary perfusion and lead to a lower ischemic threshold [26, 27]. In patients with septic shock or sepsis, excessive sympathetic activation can produce catecholamine-induced cardiomyocyte toxic effects including inflammation, oxidative stress, and abnormal calcium handling [28, 29]. These mechanisms contribute to worsening of septic myocardial dysfunction and increased mortality [11, 12]. It is well known that beta-adrenergic blockade esmolol is effective to control heart rate. Our meta-analysis suggests that compared to control intervention, esmolol treatment is associated with significantly improved survival rate, reduced TnI and CK-MB, without remarkable influence on the hemodynamic variables including MAP and CVP in septic shock and sepsis.

Treating tachycardia in septic shock and sepsis remains controversial. In the early unresuscitated phase of septic shock, tachycardia serves as an important approach to compensate for any decrease in cardiac output [26]. Heart rate reduction may inhibit this adaptive physiologic response, and reduce oxygen delivery for organ perfusion and function. In some cases, tachycardia persists represent an expression of sympathetic overstimulation partly due to activation of peripheral afferent fibers by ischemia and inflammation in peripheral tissues [30]. Heart rate reduction will decrease myocardial oxygen consumption and improve diastolic function and coronary perfusion in sepsis, but an inadequate chronotropic response may neg-

atively affect cardiac output and tissue perfusion. The right timeframe for intervention and the optimal heart rate threshold are elusive and it is difficult to predefine a threshold value for heart rate in adherence to the patient's overall hemodynamic status and any preexisting comorbidities [26].

Esmolol has the advantage of being ultrashort-acting with a half life of approximately 2 minutes which allows for rapid achievement of a predefined heart rate target and enables rapid resolution of any potential adverse effect after drug discontinuation [31]. Targeted heart rates between 80/min to 94/min are reported to be achieved safely within the first 24 hours of esmolol treatment for septic shock. Lowering of heart rate by esmolol benefits to the improvement in ventricular filling during diastole, stroke volume and the efficiency of myocardial work [18]. These findings are consistent with the results of our meta-analysis.

This meta-analysis has several potential limitations that should be taken into account. First, our analysis is based on only six RCTs and four of them have a modest sample size ($n < 100$). Overestimation of the treatment effect is more likely in smaller trials compared with larger samples. Next, there is significant heterogeneity among the reviewed studies, and different doses and methods of esmolol infusion in included RCTs may account for this heterogeneity. Finally, the right timeframe for intervention and the optimal heart rate threshold remain undefined and future studies should focus on these issues.

Conclusion

Esmolol treatment can provide important benefits to patients with septic shock and sepsis.

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Disclosure of conflict of interest

None.

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