Epinephrine versus Standard Treatment (Norepinephrine/Dopamine) as Vasopressor Therapy in Adults with Septic Shock: A Meta-Analysis

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ABSTRACT

Background. The Surviving Sepsis Campaign guideline recommends the use of norepinephrine or dopamine as vasopressor therapy in septic shock. Epinephrine is suggested as an alternative agent. However, mortality and morbidity data on the use of epinephrine versus other vasopressors remains controversial.

Objective. To evaluate the benefits of epinephrine versus standard treatment (norepinephrine/dopamine) in patients with septic shock using 28-day mortality as the primary outcome.

Methods. PUBMED, Cochrane Library, clinical trial registries and reference lists were searched for randomized controlled trials (RCTs) comparing epinephrine with standard treatment in adult septic shock patients. Trial authors were contacted for further information. Two reviewers independently evaluated methodological quality and extracted data. Conflicts were resolved by consensus. A random-effects model was used to estimate the relative risk (RR).

Results. No significant difference in 28-day mortality (RR = 0.99) and 90-day mortality (RR = 0.99) was found between patients that received epinephrine versus those that received standard treatment. Post-hoc analysis of overall mortality also showed no significant difference between groups. Noted adverse effects include tachycardia and lactic acidosis within the first 24 hours. Beyond that period, no difference was noted between epinephrine and standard treatment.

Conclusion. Epinephrine as vasopressor therapy in adult septic shock patients may be as effective as standard treatment in reducing 28-day mortality. However, lack of high quality studies precludes drawing of definite clinical guidelines. Further investigation is warranted.

Key Words: shock, sepsis, epinephrine

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Introduction

Sepsis is the systemic inflammatory response to infection.[1] A study exploring the epidemiology of sepsis in the United States over a 22-year period revealed an annualized increase in the incidence of sepsis of 8.7%.[2] Adding to the burden of the disease is the high fatality of patients who are severely affected, with mortality rates ranging from 20% to as high as 50%.[3] Studies exploring sepsis in developing countries show similar data. In 2000, Alejandria et al reported the prevalence of sepsis in a Philippine tertiary university hospital to be 24.8% with 19.3% developing severe sepsis and 8.6% developing septic shock.[4] In the same study, a mortality rate of 23.5% was observed. Epidemiologic data conducted in other developing countries parallel these results.[5,6]

Efforts directed towards decreasing the high burden of sepsis has been an area of interest in recent years. Criteria for the diagnosis of sepsis has been defined by the international sepsis definitions conference and recommended treatment strategies have been put forward by the surviving sepsis campaign.[7,8]

The surviving sepsis campaign guideline is a set of recommendations that gives a model for severe sepsis management. Part of the recommendation is to maintain a mean arterial pressure (MAP) of $\geq$ 65 mmHg.[8] Sepsis-induced hypotension, is initially managed with fluid resuscitation. However, if septic shock ensues, vasopressor therapy, either with norepinephrine or dopamine as first choice agent, is advised. Epinephrine, on the other hand, is suggested as an alternative agent to septic shock that is poorly responsive to norepinephrine or dopamine. However, at the time of writing of the surviving sepsis guidelines, the committee noted that no high-quality primary evidence existed for recommending one catecholamine over the other.[8]

Epinephrine, otherwise known as adrenaline, is one of the most potent vasoconstrictors in the human body. It induces a rise in systolic blood pressure by its positive inotropic and chronotropic actions on the heart, acting on the beta-1 receptors, and by influencing vasoconstriction in many vascular beds, acting on alpha receptors.[9] A fall in the diastolic pressure after epinephrine injection observed in some individuals may be due to its modest effects on the

beta-2 receptors of skeletal muscles. Under physiologic conditions, epinephrine acts mainly as a hormone, acting mostly on cells distant from the adrenal medulla.[9]

Epinephrine, similar to dopamine and norepinephrine, has a rapid onset and short duration of action.[10] Epinephrine and norepinephrine are both unstable in alkaline solution, readily oxidized when exposed to light and rapidly inactivated in the liver.[11,12] When used as an infusion, the diluent used for epinephrine is either 5% dextrose or normal saline.[10]

In 1993, Moran et al conducted a dose-profile analysis of epinephrine as an inotropic agent in septic shock. They concluded that epinephrine, at doses of 3-18 micrograms/min, increased cardiac index and oxygen delivery, without any effect on the systemic vascular resistance index or the pulmonary artery occlusion pressure.[13] The observed relationship between epinephrine dose and its effect on cardiac index and oxygen delivery was noted to be linear. In another study, Levy et al compared the effects of norepinephrine and dobutamine to epinephrine alone on hemodynamics in hyperdynamic dopamine-resistant septic shock. It was found that epinephrine is as effective as norepinephrine-dobutamine in its global hemodynamic effects.[14]

The reason for apprehension regarding the use of epinephrine as a first choice vasopressor in septic shock are its potential for tachycardia as well as its observed effect of decrease in global splanchnic flow and increase in lactate levels.[15] Catecholamines have also been found to have several effects on metabolism, causing hyperglycemia and increased VO2.[16] Several human and animal studies have demonstrated these effects.[14,16,17,18,19]

In a review by Levy in 2005, he reminded that these data regarding the splanchnic and lactate effects of epinephrine should be considered as pharmacological investigations of a vasoactive agent evaluated by particular monitoring devices.[15] Although equally important in the field of investigative research, these surrogate indices are of less significance to the practicing physician, more so to the patient. As such, studies on clinically significant outcomes such as mortality and morbidity are needed. To date, no evidence exists demonstrating that these surrogate markers translate clinically to a worse prognosis, specifically in terms of morbidity and mortality.

In 2004, a Cochrane review regarding vasopressor use in sepsis found that the available evidence was not suited to inform clinical practice. The authors were unable to determine whether a particular vasopressor is superior to other agents in the treatment of states of shock.[20] Several studies have been published since then. It is, therefore, the aim of this study to review the current available evidence for the risks and benefits of using epinephrine vs standard treatment as vasopressor therapy in septic shock.

Objectives

This study aimed to evaluate the benefits and risks of epinephrine vs standard treatment (norepinephrine/dopamine) as vasopressor therapy in adult patients with septic shock. Specifically, a comparison of the 28-day mortality was done through estimation of the relative risk. As secondary objectives, 90-day mortality and rates of serious adverse events were also examined.

Methods

Protocol and Registration

The study protocol for the meta-analysis underwent review and was approved by the technical review board of the Department of Internal Medicine. It was likewise reviewed and approved by the technical and ethics committees of the Research Implementation and Development Office of the University of the Philippines - Manila. [Study Code: GCS IM 2010-008 (R-020TE)]

Search Strategy

An electronic search in PUBMED, the Cochrane Library, and clinical trial registries was conducted with the use of "*epinephrine*", "*adrenaline*", "*shock*", *"septic shock"* and *"sepsis"* as keywords. The search strategy and study selection approach that were used are outlined in Appendix 1. The terms used in the PUBMED search as well as the results for each are shown in Appendix 2. Links to relevant articles were examined for possible inclusion. Reference lists of identified articles were searched for relevant studies. The search was limited to randomized controlled trials. No language restriction was imposed. Trial authors and experts in the field were contacted to further broaden the search.

Study Selection Criteria

One reviewer browsed through the titles and abstracts of studies identified in the electronic and hand search for possible inclusions. Full texts of studies judged to be relevant were retrieved and independently assessed for inclusion by two reviewers. A study was considered relevant if it met the following inclusion criteria:

1) it involved adult subjects ≥18 years in septic shock;
2) subjects were randomly assigned to their treatment groups;
3) epinephrine was used as a vasopressor therapy either alone or in combination with another drug;
4) norepinephrine or dopamine, alone or in combination with another drug, was used as an active comparator; and
5) mortality rates were reported.

Studies that met the inclusion criteria were then evaluated for methodological quality using the Jadad[21] scale.

This was done independently by the two reviewers. Conflicts were resolved by consensus.

Data Collection and Analysis

Data were extracted independently by two reviewers. The following data were obtained from each study: Title, author and year of publication; total population for the study and the population for each treatment arm; 28-day mortality in the epinephrine group; 28-day mortality in the standard treatment group; and relative risk of 28-day mortality for epinephrine compared to standard treatment. Reports on the secondary outcome of relative risk of 90-day mortality and serious adverse events were also extracted where available. Any discrepancy between the reviewers was resolved by discussion and consensus.

The analytic approach and software provided by the Cochrane Collaboration was used for all analyses. (Review Manager (RevMan) [Computer program]. Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008. Cochrane Centre, Copenhagen, Denmark). Relative risks (RRs) for studies with at least 1 occurrence in either study group for the outcome were calculated. Trials with missing outcome data in both groups were excluded from the meta-analysis of that outcome. Pooled RR and 95% confidence interval (CI) for the 28-day and 90-day mortality using both fixed- and random-effects models are reported. Findings were considered to be statistically significant if the test for overall effect has a *P* value of less than .05. The risk estimates and confidence intervals were illustrated using forest plots. Heterogeneity was assessed through the $\chi 2$ test with the methods of Mantel and Haenszel and quantified using the I^2 test.[22] All possible sources of material were sought to ensure lack of publication bias.

The final report was written in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).[23]

Results

Study Selection

A total of 948 studies were considered for inclusion in the meta-analysis. 897 studies were excluded after the initial screening of the title and abstract due to irrelevance. 23 reviews were also excluded on the initial screening. 23 reports were further excluded after review of the full-texts as these were either duplicates or non-RCT studies. The five remaining studies were included in the meta-analysis.[14,24,25,26,27] Summarized in Figure 1 is the search and study selection process.

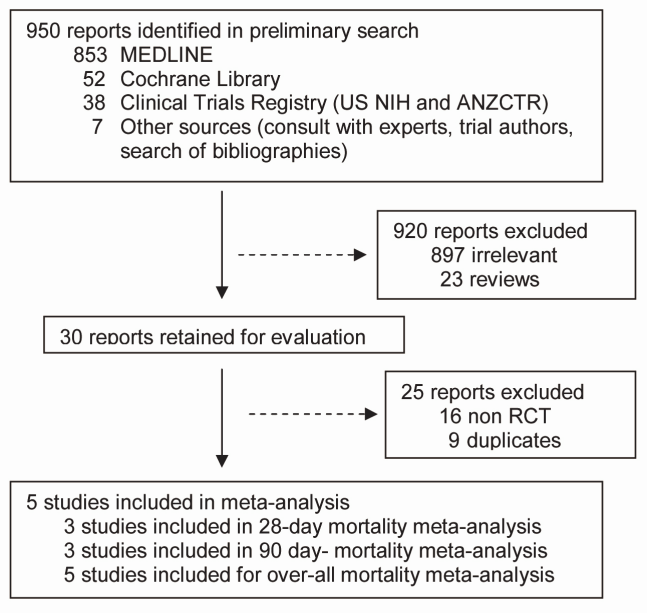

Figure 1. Literature Search and Study Selection

Study Characteristics

The characteristics of the studies included are summarized in Table 1. A total of 562 septic patients were represented. Mean age ranged from 54 to 70 years. Most of the patients were recruited from centers based in France. ACCP/SCCM's definition of sepsis was adapted by most of the studies. Most of the trials defined shock as a MAP < 70 mmHg. Most of the studies used norepinephrine plus dobutamine as the active comparator. One study used norepinephrine plus dopexamine while another used norepinephrine alone. Only the study by Djillali et al had 28-day mortality as a primary outcome.

Assessment of bias

The five studies included in the meta-analysis were assessed for quality of methodological reporting. Studies were rated independently by the two reviewers with one of the reviewers blind to the study title, name and publication details. The detailed methodological quality of individual studies is shown in Table 2. Two of the studies were judged to be of high methodological reporting quality via the Jadad quality assessment tool. The rest of the studies received low scores in the Jadad rating scheme due to lack of blinding.

28-Day Mortality Results

Three studies were included in the meta-analysis for the risk of 28-day mortality among patients in septic shock treated with epinephrine versus standard treatment. A pooled RR of 0.95 (0.71 – 1.26) was found. Figure 2 shows the forest plot for the meta-analysis. The studies were homogenous, with an $I^2 = 10\%$.

Table 1. Characteristics of Randomized Controlled Trials Comparing Epinephrine vs Standard Treatment as Vasopressor Therapy in Septic Shock

Study	Population	N	Intervention in Epinephrine Group	Interventions in Standard Treatment Group	Primary Outcome
Levy et al, 1997	Hyperdynamic septic shock	30	Epinephrine infusion started at 0.3 microgram/kg per min titrated on MAP at 5 – min intervals to obtain a MAP >80 mmHg with a stable or increased cardiac index	Norpinephrine infusion started at 0.3 microgram/kg per min titrated on MAP at 5 – min intervals to obtain a MAP >80 mmHg with a stable or increased cardiac index; Dobutamine infusion at 5 microgram/kg per min	Hemodynamic parameters
Seguin et al, 2002	Septic shock	22	Epinephrine infusion started at 0.1 microgram/kg per min increased by 0.2 microgram/kg per min at 5 – min intervals to obtain a MAP 70 - 80 mmHg	Norpinephrine infusion started at 0.1 microgram/kg per min increased by 0.2 microgram/kg per min at 5 – min intervals to obtain a MAP 70 - 80 mmHg; Dobutamine infusion at 5 microgram/kg per min	Gastric perfusion
Seguin et al, 2006	Septic shock	22	Epinephrine infusion started at 0.2 microgram/kg per min titrated by 0.2 microgram/kg per min at 3 – min intervals to obtain a MAP 70 - 80 mmHg	Norepinephrine infusion started at 0.2 microgram/kg per min titrated by 0.2 microgram/kg per min at 3 – min intervals; Dopexamine infusion started at 0.5 microgram/kg per min titrated by 0.5 microgram/kg per min every three minutes to obtain a MAP 70 – 80 mmHg. Selection of agent to titrate was based on cardiac index	Gastric perfusion
Djillali et al, 2007	Septic shock	330	Epinephrine infusion started at 0.2 microgram/kg per min increased by 0.2 microgram/kg per min at 5 – min intervals to obtain a MAP 70 - 80 mmHg*	Norpinephrine infusion started at 0.2 microgram/kg per min increased by 0.2 microgram/kg per min at 5 – min intervals to obtain a MAP 70 - 80 mmHg; Dobutamine infusion at 5 microgram/kg per min*	28-Day Mortality
Myburgh et al, 2008	ICU patients judged to require an infusion of either epinephrine or norepinephrine for any cause	277 (158 had sepsis)	Epinephrine infusion, dose and target MAP were prescribed by the treating physician, 70 mmHg was used if no target MAP was specified	Norepinephrine infusion, dose and target MAP were prescribed by the treating physician, 70 mmHg was used if no target MAP was specified	Time to achieve a clinician-prescribed MAP

*MAP- mean arterial blood pressure, ICU- intensive care unit, *titration followed a pre-specified treatment algorithm*

Table 2. Risk of Bias in Studies

Study	Sequence Generation	Allocation Concealment	Blinding	Incomplete Outcome Data Addressed	Jadad
Levy et al, 1997	Unclear method (not stated) but randomization done	Unclear (not stated)	No	No loss to follow up	2
Seguin et al, 2002	Unclear method (not stated) but randomization done	Unclear (not stated)	No	No loss to follow up	2
Seguin et al, 2006	Computer-generated random list	Randomization done by an independent pharmacist	No	2 were excluded from the main endpoint due to technical difficulties but all were followed up for the 28 day and 90 day mortality	3
Djillali et al, 2007	Computer-generated random list	Randomization done centrally by an independent statistician	Yes	No loss to follow up	5
Myburgh et al, 2008	Computer-generated random list	Randomization code provided to designated staff not involved in the study	Yes	22 patients withdrawn from treatment group by treating clinician, Intention-to-treat analysis done	5

90-Day Mortality Results

The same three studies were included in the meta-analysis for the risk of 90-Day mortality among patients in septic shock treated with epinephrine versus standard treatment. A pooled RR of 0.99 (0.82 - 1.19) was found. Figure 3 shows the forest plot for the meta-analysis. The studies were homogenous, with an $I^2 = 0\%$.

Post hoc analysis: Overall Mortality Results

All five studies reported mortality rates, albeit 2 of these did not specify if the reported rates were 28-day or 90-day mortality. As such, for an "over-all" mortality rate, a post hoc analysis was done wherein the mortality rates of the two studies which did not specify duration were pooled with the 28-day as well as the 90-day mortality reported in the other

three studies. The results of these meta-analyses are summarized in Figures 4 and 5, respectively.

Summary of Results

A meta-analysis comparing the mortality in adult septic shock patients who received epinephrine vs standard treatment (norepinephrine/dopamine) as vasopressor therapy was conducted. No significant difference in the 28-day mortality and 90-day mortality of patients receiving epinephrine versus those that received standard treatment was found. A post-hoc analysis of overall mortality also showed no significant difference between the two groups.

Epinephrine was reported to cause metabolic as well as cardiac effects. In one study, epinephrine was associated with the development of significant tachycardia and lactic acidosis that developed within the initial four hours and sustained for the first 24 hours of treatment. However, beyond that period, there was no difference between the two groups.[26] Other reported adverse effects included severe arrhythmias, cerebrovascular or myocardial events, limb ischemia and other side-effect that was possibly related to the use of catecholamines. There was no significant difference noted between epinephrine and norepinehrine groups in these adverse effects.[25]

Discussion

This study found no significant difference in the 28-day, 90-day and overall mortality rates among adult patients with septic shock treated with epinephrine vs standard treatment of norepinephrine/dopamine. These results accord those of a systematic review done in 2004 by the Cochrane group.[20] There is no prospective randomized controlled study that indicates the superiority of one vasopressor over the other in adults with septic shock. What recent data suggest is that there are true differences between vasopressors in local tissue perfusion. Epinephrine, specifically, has been shown to decrease splanchnic blood flow, resulting in transient increases in arterial, splanchnic and hepatic venous lactate concentrations. However, the deleterious effects of such observed phenomena remain to be determined. Reviewing the literature on the matter, Levy suggests that it is likely that despite a relative decrease in splachnic blood flow, the gut mucosa receives sufficient blood for its metabolic needs. This is thought to occur as a result of epinephrine's beta-2 properties, which redistributes splanchnic blood flow to the mucosa.[15] Again, the interpretation of such data is left undetermined due to the lack of clinical trials investigating the clinical implication of these laboratory values.

With these differences, it may be prudent to say that while no vasopressor is superior to the other, each

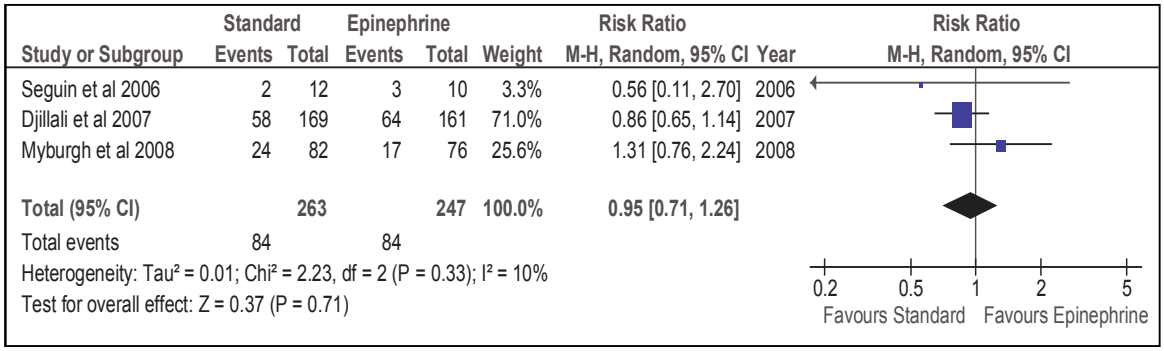

Figure 2. Forest plot of 28-day mortality among patients in septic shock treated with epinephrine versus standard treatment.

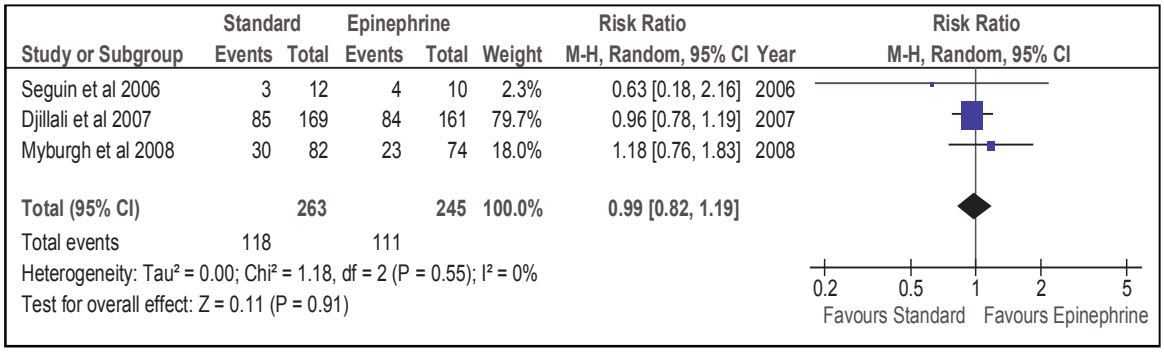

Figure 3. Forest plot of 90-day mortality among patients in septic shock treated with epinephrine versus standard treatment.

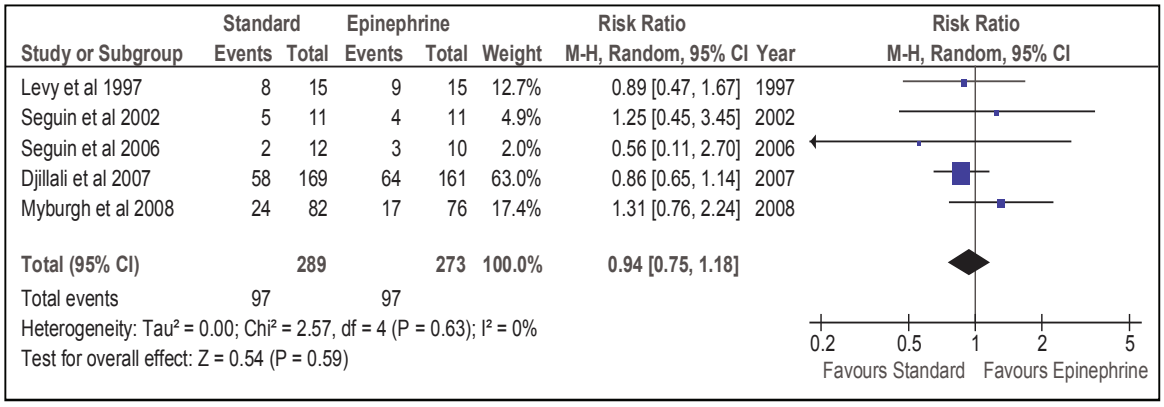

Figure 4. Forest plot of overall mortality among patients in septic shock treated with epinephrine versus standard treatment. (28-day mortality data used)

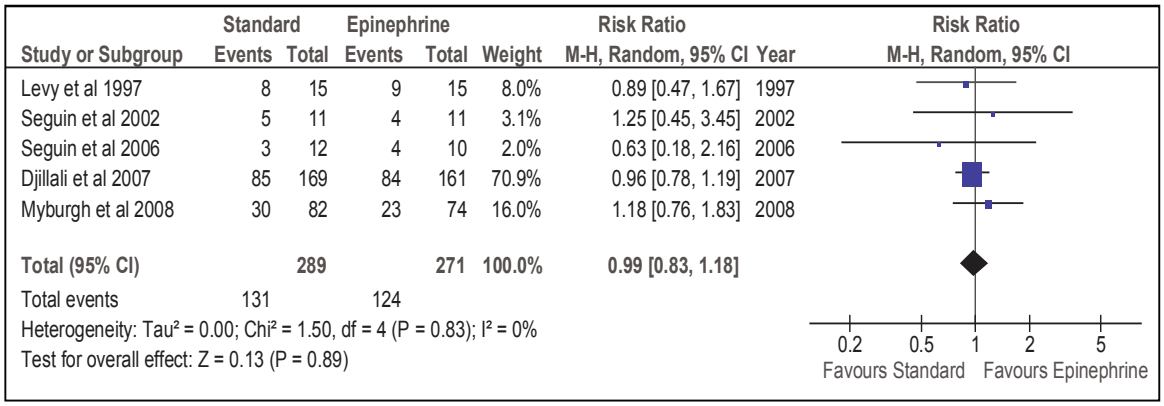

Figure 5. Forest plot of overall mortality among patients in septic shock treated with epinephrine versus standard treatment. (90-day mortality data used)

vasopressor may find a use in specific clinical settings involving septic shock. Rudis and Chant suggested that epinephrine may be particularly useful if used earlier in the course of septic shock in young patients and those who do not have any known cardiac abnormality.[28] This recommendation seems logical as this set of patients may be better able to tolerate the transient metabolic and hemodynamic effects of epinephrine. They may also gain benefit from the greater increase in cardiac index and oxygen delivery induced by epinephrine. Ultimately, however, the choice of vasopressor therapy in septic shock will depend on the clinician's experience and the patient's response to therapy.[26]

Limitations

Several limitations exist for this meta-analysis. Save for the study by Djillali et al, the studies were not designed to investigate the primary outcome of interest, i.e. 28-day mortality. Accordingly, the sample size recruited for the different trials are small rendering the studies underpowered. The reported 28-day mortality rates in the studies by Djillali et al and Myburgh et al suggest that a study population of more than 4000 patients is needed to determine a 5% absolute reduction in mortality. Performing a study of this magnitude may be unfeasible as of present.

Conclusions

No significant difference was detected in the 28-day and 90-day mortality rates of the two groups. In this regard, epinephrine as vasopressor therapy in adult septic shock patients may be as effective as the standard treatment (norepinephrine). Adverse effects included significant tachycardia and lactic acidosis, which were observed to be transient, with the difference between groups lasting only 24 hours. However, several limitations, such as the lack of high quality studies, preclude drawing definite clinical guidelines from this meta-analysis. As such, further investigation is warranted.

Acknowledgments

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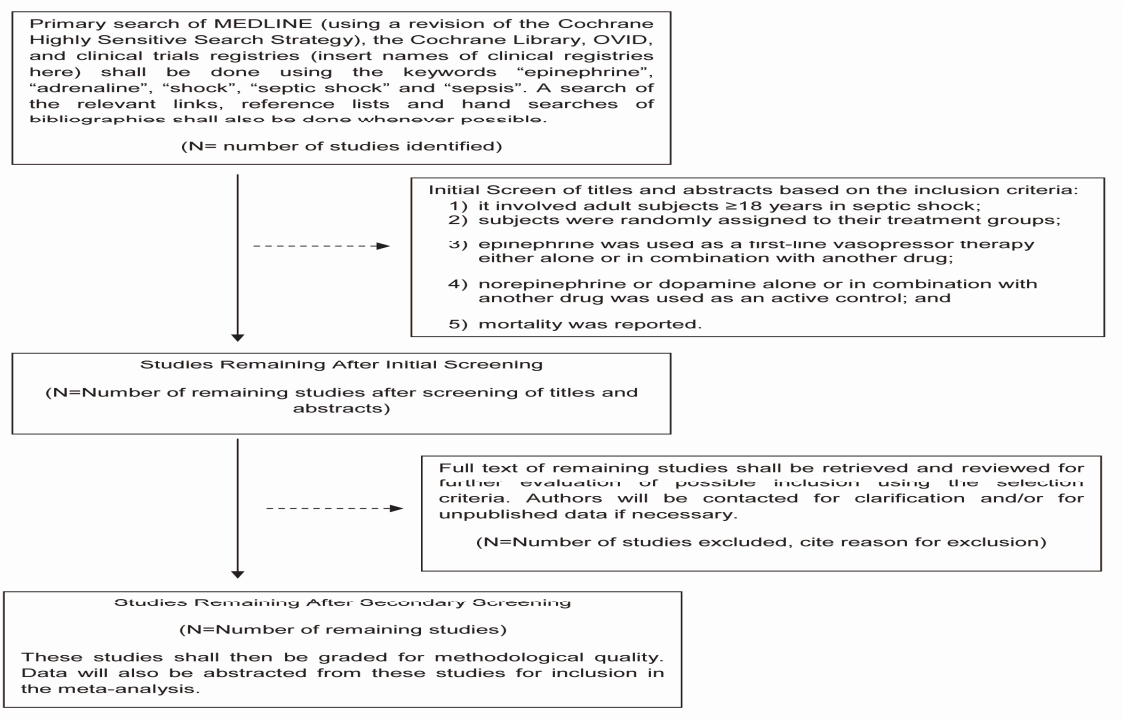
Appendix

Appendix 1. Search Strategy and Study Selection



Appendix 2. Search strategy used in PUBMED (Search done: March 9, 2010)

Search Number	Search term	Result
#1	randomized controlled trial [pt]	281637
#2	controlled clinical trial [pt]	80105
#3	randomized [tiab]	215543
#4	placebo [tiab]	123494
#5	drug therapy [sh]	1351563
#6	randomly [tiab]	149897
#7	trial [tiab]	252394
#8	groups [tiab]	1020851
#9	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8	2595009
#10	animals [mh] NOT humans [mh]	3436027
#11	#9 NOT #10	2213447
#12	epinephrine	118574
#13	("Epinephrine"[MeSH] OR "epinephrine sulfate " [Substance Name] OR "epinephrine transporter, Rana catesbeiana "[Substance Name] OR "Receptors, Adrenergic"[MeSH] OR "epinephrine glucuronide "[Substance Name] OR "epinephrine derived ATPase inhibitor "[Substance Name] OR "epinephrine cyclase " [Substance Name] OR "dipivefrin " [Substance Name])	135081
#14	#12 OR #13	145602
#15	shock	149572
#16	("Shock"[MeSH] OR "Shock, Septic"[MeSH])	51624
#17	#15 OR #16	149572
#18	sepsis	103995
#19	("Sepsis"[MeSH])	73684
#20	#18 OR #19	103995
#21	septic shock	21592
#22	#17 OR #20 OR #21	230113
#23	adrenaline	123816
#24	("Epinephrine"[Mesh] OR "3-(3,4-dihydroxyphenyl)-N-methylserine "[Substance Name] OR "NAD(P)H-adrenaline oxidase "[Substance Name] OR "3,4-diisovaleryl adrenaline "[Substance Name] OR "adrenaline-N-methyltransferase "[Substance Name] OR "adrenaline sulfate "[Substance Name] OR "dipivefrin "[Substance Name])	107284
#25	#23 OR #24	123816
#26	#14 OR #25	150364
#27	#11 AND #22 AND #26	853