Effectiveness of anisodamine for the treatment of critically ill patients with septic shock (ACIdoSIS study): study protocol for randomized controlled trial

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Background: Septic shock is an important contributor of mortality in the intensive care unit (ICU). Although strenuous effort has been made to improve its outcome, the mortality rate is only marginally decreased. The present study aimed to investigate the effectiveness of anisodamine in the treatment of septic shock, in the hope that the drug will provide alternatives to the treatment of septic shock.

Methods: The study is a multi-center randomized controlled clinical trial. Study population will include critically ill patients with septic shock requiring vasopressor use. Blocked randomization was performed where anisodamine and control treatments were allocated at random in a ratio of 1:1 in blocks of sizes 2, 4, 6, 8, and 10 to 354 subjects. Interim analysis will be performed. The primary study end point is the hospital mortality, and other secondary study endpoints include ICU mortality, length of stay in ICU and hospital, organ failure free days. Adverse events including new onset psychosis, urinary retention, significant hypotension and tachycardia will be reported.

Discussion: The study will provide new insight into the treatment of septic shock and can help to reduce mortality rate of septic shock.

Trial registration: NCT02442440 (https://register.clinicaltrials.gov/).

Keywords: Anisodamine; septic shock; intensive care unit (ICU); mortality; randomized controlled trial

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Introduction

Septic shock is an important contributor of mortality in the intensive care unit (ICU). The crude mortality is reported to be from 30% to 65% (1-5). Although there are significant advances in the management of septic shock in recent decades, the mortality rate was only marginally reduced. For example, the CUB-Réa Network study reported that the mortality rate of septic shock declined from 62.1% in 1993 to 55.9% in 2000 (6). The well-known Surviving Sepsis Campaign has also made every effort to reduce mortality rate of severe sepsis and septic shock. The organization recommended bundled strategies including early goal directed therapy (EGDT) for the management of septic shock (7,8). Although EGDT was once the mainstay therapy of septic shock, its efficacy has been questioned by recent several large randomized controlled trials (9,10). Therefore, the treatment of septic shock is still a global challenge and there is no well-established intervention that can reduce its mortality.

Anisodamine is an active agent isolated from a Chinese herb medicine. Both experimental and clinical studies have shown some potential beneficial effects of anisodamine in improving outcomes of shock (11-13). It was reported that anisodamine could reduce the mortality rate of fulminant epidemic meningitis from 66.9% to 12.4% (14). The efficacy of anisodamine might be mediated via the inhibition of thromboxane synthesis, granulocyte and platelet aggregation (15). Although anisodamine has been widely used in the treatment of septic shock in mainland China, there is no solid evidence from well-designed clinical trials to support its efficacy. The aim of the study is to investigate the effectiveness of anisodamine in the treatment of critically ill patients with septic shock.

Methods

Study design and setting

The study was a prospective randomized controlled trial that will recruit a maximum of 346 patients over a 2-3 years period. Patients with septic shock will be enrolled at participating hospitals in mainland China. Investigators in each participating center will screen patients with septic shock for potential eligibility. The study was reviewed and approved by the institutional review board of Jinhua Municipal Central Hospital (approval No. 2015-13) and the ethics committee of each participating center. Informed consent will be obtained from participants or their next-of-kin. The study was registered in the website ClinicalTrials.gov (registration No.: NCT02442440).

Participants

Inclusion criteria included patients with sepsis plus use of vasopressors. Systemic inflammatory response syndrome (SIRS) is defined as meeting at least one of the following 3 criteria for a systemic inflammatory response. One of the SIRS criteria must be either the WBC criteria (I) or the body temperature criteria (II):

(I) White blood cell count >12,000 or <4,000 or >10% band forms;
(II) Body temperature >38 ℃ (any route) or <36 ℃ (accepting core temperatures only; indwelling catheter, esophageal, rectal);
(III) Heart rate (>90 beats/min) or receiving medications that slow heart rate or paced rhythm;
(IV) Tachypnea (>20 breaths per minute), or, an arterial partial pressure of carbon dioxide less than 4.3 kPa (32 mmHg).

Suspected or documented infection included the following sites: thorax, urinary tract, abdomen, skin, sinuses, central venous catheters, and bacterial meningitis.

Septic shock was defined as sustained arterial hypotension with systolic blood pressure (SBP) <90 mmHg, mean arterial pressure (MAP) <70 mmHg, or an SBP decrease >40 mmHg, despite adequate fluid resuscitation. To ease clinical screening process, we defined septic shock as the requirement of vasopressors despite adequate fluid resuscitation. Vasopressors include norepinephrine, epinephrine, phenylephrine and dopamine >5 mcg/kg/min.

Patients with following conditions will be excluded:

(I) Age <15 years old;
(II) Moribund (expected to die within 24 h);
(III) Stay in ICU for more than 24 h at enrollment;
(IV) Contraindications to anisodamine: elevated intracranial pressure, acute phase of intracranial hemorrhage, glaucoma, untreated bowel obstruction (surgically treated obstruction is not contraindicated), enlargement of prostate without urinary catheterization.

Randomization

Blocked randomization was performed where anisodamine and control treatments were allocated at random in a ratio of 1:1 in blocks of sizes 2, 4, 6, 8, and 10 to 346 subjects.

Table 1 Efficacy and futility stopping boundaries expressed in different scales

Analysis time	Sample size	Risk difference[¶]	Normalized Z	Fixed P[§]	Predictive power[$]
Efficacy					
1	59.0439	−0.4229	−3.3250	0.0004	0.0029
2	118.0879	−0.2791	−3.1032	0.0010	0.0081
3	177.1318	−0.2100	−2.8604	0.0021	0.0193
4	236.1757	−0.1655	−2.6030	0.0046	0.0433
5	295.2197	−0.1323	−2.3261	0.0100	0.1004
6	354.2636	−0.1026	−1.9760	0.0241	NA
Futility					
1	59.0439	0.1649	1.2963	0.9026	0.0106
2	118.0879	0.0407	0.4524	0.6745	0.0255
3	177.1318	−0.0178	−0.2418	0.4045	0.0511
4	236.1757	−0.0544	−0.8549	0.1963	0.0944
5	295.2197	−0.0807	−1.4184	0.0780	0.1725
6	354.2636	−0.1026	−1.9760	0.0241	NA

[¶], Risk difference was difference in mortality risk between treatment and control arm. A minus value indicates lower mortality rate in treatment arm. [§], The fixed sample P value that corresponds to the Z statistic (it should be noted that this is not a true P value for a sequential sampling plan). [$], The Bayesian predictive power based on a non-informative (improper) prior for the treatment effect (this estimates the probability of achieving a statistically significant result at the final analysis assuming that all possible alternative were equally likely a priori).

Block sizes are allocated unequally in the ratio 1:4:6:4:1 (Pascal's triangle).

Investigators at each participating center will screen all potentially eligible patients. If there are eligible patients they will inform randomization center via the software Wechat (Tencent, China). The center will allocate a number to that patient within 6 h and indicate which group the patient will be allocated to. The investigators know the allocation and this study is an open label trial.

Treatment

A bolus of 10 mg anisodamine was given intravenously as the loading dose, followed by micro-pump at the rate of 0.1 to 0.5 mg/kg/h. The maintenance dose will be titrated at the discretion of the treating physician according the microcirculation status, as well as the side effects. For example, infusion rate can be increased if the serum lactate continues to elevate. Conversely, if the use of anisodamine results in significant drop in blood pressure, the infusion rate can be reduced.

Anisodamine will be discontinued on the recovery of shock (vasopressor discontinuation and normalized serum lactate), significant adverse events, and death.

The control group received usual care without anisodamine.

Study endpoint

The primary study end point is the hospital mortality, defined as death status at hospital discharge.

Secondary study endpoints include ICU mortality, length of stay in ICU and hospital, organ failure free days. Organ failure will be assessed by using sequential organ failure assessment (SOFA) score. SOFA scores will be calculated daily for the first 7 days.

Adverse events

Adverse events including new onset psychosis, urinary retention, significant hypotension and tachycardia will be reported.

Data collection

Research coordinators will collect data and record it on paper data forms. The case report form (CRF) is written in Chinese to facilitate communication among investigators. Data will be checked and obvious outliers or impossible entries will be recorded and discussed with site research coordinators. The site research coordinator will check the value and correct it if necessary.

Group sequential analysis

Sequential trial analysis will be performed. We planned to perform 6 interim analyses at the accrual sample size of 59, 118, 177, 236, 295 and 354 (*Table 1*). The trial may be stopped at early for efficacy or futility at respect adjusted significance levels. Asymmetric two-sided group sequential design will be performed with binding futility bound, 6 analyses, a sample size of 354, 80% power and 2.5% (1-sided) type I error. The mortality rate in the control group was assumed to be 50%, and the new intervention could reduce the mortality rate by
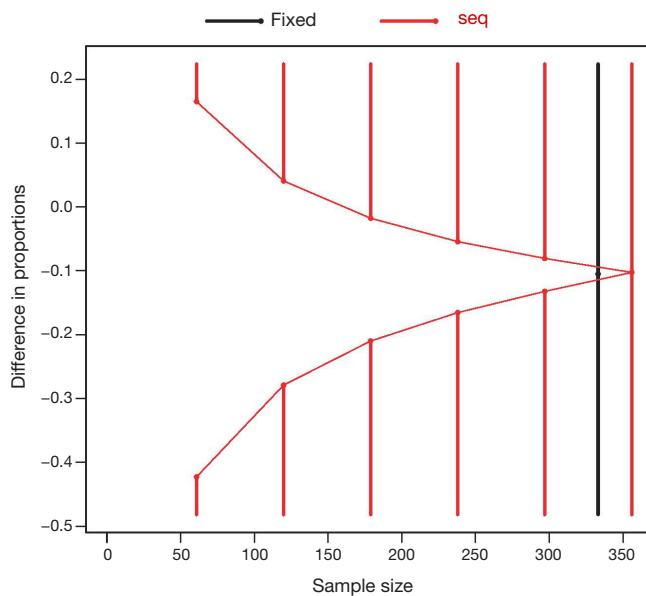
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Figure 1 Spending futility and efficacy boundaries for sequential trial analysis. Trial will stop at crossing either boundaries.
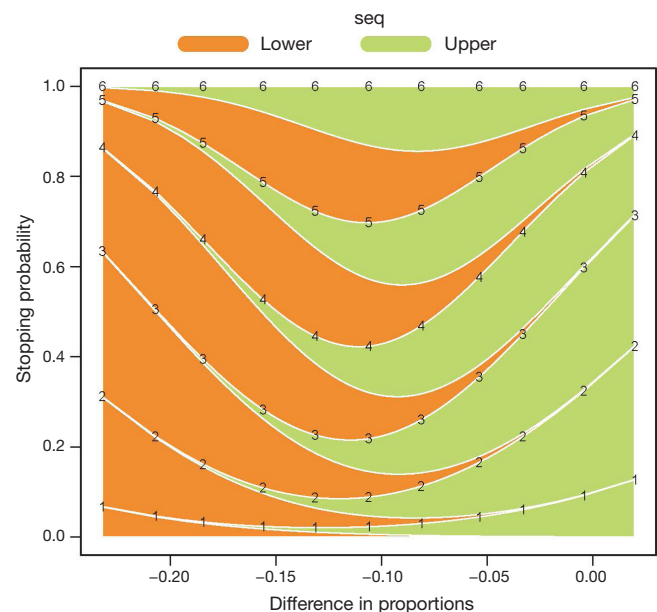

Figure 2 Cumulative probability of crossing boundary by different relative risks. Upper boundary indicates futility boundary and the lower boundary indicates efficacy boundary.

15%. Fixed sample size with the same operating characteristics is 339. Efficacy bounds were derived using a Hwang-Shih-DeCani spending function with gamma =–4. Futility bounds were derived using a Hwang-Shih-DeCani spending function with gamma =–2 (16). *Figure 1* shows the spending futility and efficacy boundaries where spending computations assume trial stops if a bound is crossed.

Figure 2 shows the cumulative probability of crossing boundary by different risk difference (effect size). *Table 2* shows the average sample size and cumulative stopping probability at each analysis under alternatives detected with specified power. When the true effect is larger, it is more probable that the final required sample size will be smaller and the trial is more likely to stop early. *Table 3* shows the inference at the stopping boundaries. The adjusted and unadjusted risk difference at each interim boundary is shown in *Figure 3*. Expected sample size varies by underlying different risk difference. It is shown that if the risk difference is extremely large or small the sample size required can be small. At the assumed risk difference of 0.15, the expected sample size is 260, which is smaller than the fixed sample size of 339 (*Figure 4*).

Statistical analysis

Baseline variables were expressed as mean (SD) or number

(percent) as appropriate. Skewed data were expressed as median and interquartile range. Comparisons between treatment and control arms will be performed by using student t test for variables of normal distribution, Mann-Whitney U test for skewed variables. Categorical data were compared by using Chi-square test. Mortality is a binary variable and the comparison will be made by using Chi-square test. Post hoc analysis will be performed if there are differences on baseline variable between treatment and control arms. Furthermore, multivariable regression model will be used to control for potential confounders.

All statistical analyses will be performed by using the R software (version 3.1.1). Sequential trial analysis is performed by using the gsDesign and RCTdesign packages (17). Statistical significance will be considered at a P value of less than 0.05.

Discussion

The hallmark pathophysiology underlying septic shock is the dysfunction of microcirculation, following by tissue hypoperfusion, cell death and organ dysfunction (18,19). Up to now, varieties of strategies have been investigated for their potential effects on improving microcirculation. These strategies include but not limited to early fluid

Table 2 Average sample size and cumulative stopping probability at each analysis under alternatives detected with specified power

Power	TrueEff	ASN	CumStpPrb 1	CumStpPrb 2	CumStpPrb 3	CumStpPrb 4	CumStpPrb 5	CumStpPrb 6
0.975	−0.2113	204.3989	0.0497	0.2376	0.5275	0.7857	0.9377	1
0.950	−0.1938	220.4296	0.0382	0.1853	0.4390	0.7055	0.8986	1
0.900	−0.1739	238.1963	0.0290	0.1386	0.3481	0.6081	0.8419	1
0.800	−0.1500	256.2138	0.0226	0.1017	0.2649	0.5028	0.7687	1

TrueEff, true underlying effect size; ASN, average sample size number; CumStpPrb, cumulative stopping probability.

Table 3 Inference at the stopping boundaries

Analysis	Sample size	BAM	CIlo.m	CIhi.m	Pval.m
Efficacy					
1	59.0439	−0.3926	−0.5816	−0.1714	0.0004
2	118.0879	−0.2495	−0.4097	−0.0952	0.0013
3	177.1318	−0.1875	−0.3234	−0.0575	0.0031
4	236.1757	−0.1522	−0.2675	−0.0325	0.0068
5	295.2197	−0.1278	−0.2287	−0.0137	0.0139
6	354.2636	−0.1066	−0.2113	0.0000	0.0250
Futility					
1	59.0439	0.1325	−0.0866	0.3234	0.8906
2	118.0879	0.0077	−0.1458	0.1702	0.5907
3	177.1318	−0.0434	−0.1737	0.0941	0.2960
4	236.1757	−0.0718	−0.1911	0.0457	0.1190
5	295.2197	−0.0910	−0.2034	0.0137	0.0440
6	354.2636	−0.1066	−0.2113	0.0000	0.0250

BAM, bias adjusted mean is the point estimate that would be reported for stopping exactly at the boundary; CIlo.m and CIhi.m, the confidence interval bounds for the true treatment effect, where the bounds are calculated using the MLE ordering; Pval.m, the true P value adjusted for the sequential sampling plan as calculated under the MLE (or mean) ordering.

Figure 3 Risk difference at bounds. It is shown that if the first analysis performed at accrual of 61 subjects shows a risk difference of more than 0.42, the study can be stopped for superiority of anisodamine.

resuscitation to restore circulatory volume, use of vasopressors to maintain macrocirculation and use of some immunomodulatory agents (20,21). Although some treatments have once shown promising results, consequent large trials tempered such enthusiasm. As a result, treatment of septic shock remains a great challenge for clinicians.

Anisodamine is a muscarinic antagonist with pharmacological effects similar to atropine. It was first isolated from a traditional medicinal herb *Scopolia tangutica Maxim* in the middle of 1970s. This Chinese herbal medicine has long been used as an analgesic by local people in the regions of
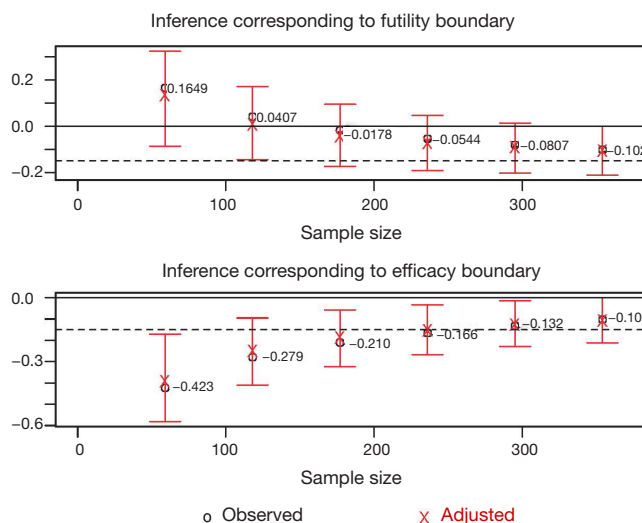
Qinghai and Xizang. Some animal studies have confirmed the role of anisodamine in improving microcirculation in septic shock, and other potential therapeutic effects include the inhibition of thromboxane synthesis, granulocyte and platelet aggregation (11,15). Although this drug is widely used in clinical practice in China, there is little clinical evidence from well-designed clinical trial that demonstrates its effectiveness in patients with septic shock. The present study was designed to bridge this gap.

One limitation of the study design is that the study is an open-labeled trial. However, we feel that this will not affect the primary outcome very much. The primary outcome used in the study is mortality that is solid and not prone to reporting bias. Other outcome assessors were blind to the allocation. Another limitation is that the titration of anisodamine infusion rate is largely determined by treating physicians. As a matter of fact, the therapeutic dose varied

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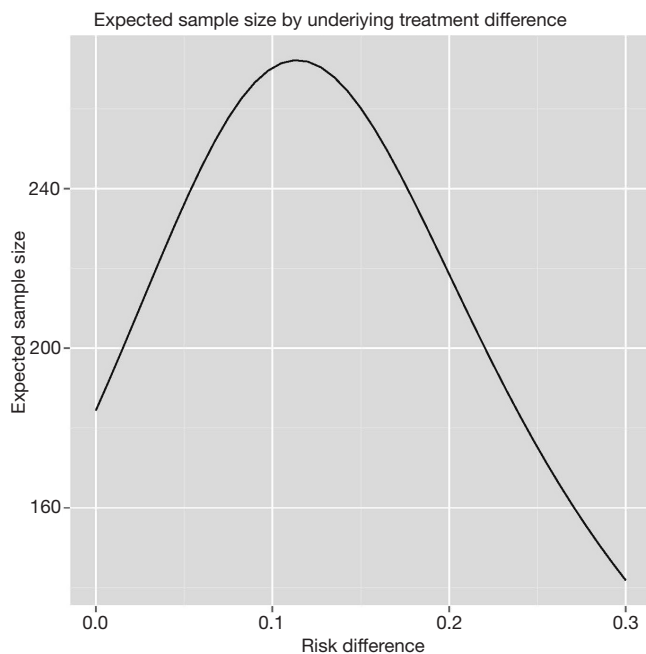
Expected sample size by underlying treatment difference

Figure 4 Expected sample size by underlying different risk difference. It is shown that if the risk difference is extremely large or small the sample size required can be small. At the assumed risk difference of 0.15, the expected sample size is 260, which is smaller than the fixed sample size of 339.

substantially among individuals and there is no rule-of-thumb for this titration. This is just like the titration of vasopressors. For example, the therapeutic dosage of norepinephrine ranges from 0.04 to 1 mcg/kg/min (22). Some patients may respond well to minimum doses, while others require large dose to maintain optimal MAP.

In conclusion, we believe that the study will provide new insight into the treatment of septic shock and can help to reduce mortality rate of septic shock.

Acknowledgements

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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