Acetate Ringer's solution versus 0.9% saline for septic patients: study protocol for a randomized controlled multi-center crossover trial

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Abstract

Background: The previous study demonstrated that there were no significant differences between saline and balanced crystalloid solution infused in critical illness. However, the sepsis subgroup analysis showed the statistical difference. Thus, we will specifically focus on septic patients in this study to compare the effects of saline and balanced solution. We hypothesize that effects of saline on acute kidney injury (AKI) are related to the underline AKI severity and total volumes of infusion.

Methods/design: The investigators designed a pragmatic, multi-center crossover trial recruiting 312 patients who are diagnosed as sepsis/septic shock in the intensive care unit (ICU) and will be assigned with either acetate Ringer's solution or saline in the corresponding month. Patients with an end-stage renal disease (ESRD) or who need renal replacement therapy (RRT) prior to or at the time of enrollment are excluded. Enrolled patients will be regarded as with mild, moderate or severe sepsis on the basis of the severity of their illness, and will be divided into subgroups according to their initial renal function and various intravenous infusion volumes when being analyzed. The primary outcome is major adverse kidney events (MAKE), including the composite of in-hospital death, receipt of new renal replacement therapy, or persistent renal dysfunction. Secondary outcomes include 28 days-mortality, internal environment disturbance, incidence and duration of vasoactive drug treatment, duration of mechanical ventilation, duration of RRT and ICU and hospital length of stay.

Results and conclusions: To our knowledge, this study will be the first to focus on septic patients and provide credible and evident data on the comparison of outcome between acetate Ringer's solution and saline for intravenous infusion in adult septic patients on the basis of baseline renal function and infusion volumes taken into consideration.

Trial registration: ClinicalTrials.gov, identifiers: NCT03685214. Registered on 15th August 2018. https://clinicaltrials.gov/ct2/show/NCT03685214

Keywords: sepsis; septic shock; acute kidney injury; saline; acetate Ringer's solution.

Background and rationale

Sepsis, a common problem in the intensive care unit (ICU) with high morbidity and mortality(1-4), is the main cause for acute kidney injury (AKI) in critically ill adults(5). Several studies have shown that septic AKI accounts for nearly half of all kinds of AKI(6), and increases mortality six to eight fold(6, 7). Fluid resuscitation plays a vital role in the treatment of sepsis and septic shock(8, 9), which attaches great significance to the type of solution infused during fluid management. Saline is not a "normal" fluid with high level of chloride which may be related to AKI and mortality(10, 11), but it is still commonly administered on a global basis so far(12)although a preference for balanced crystalloid solution on venous transfusion is emerging(13, 14).

Until now, no consensus has been reached on the choice of crystalloid for critically ill patients(15, 16), even for septic patients. The SPLIT (Saline v Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy) study conducted in four New Zealand ICUs(15)concluded with no difference neither in the primary outcome of the incidence of AKI nor in secondary outcomes of RRT use and mortality between the use of a buffered crystalloid and saline. However, this study was criticized for the relatively small volume of fluid as it may have been too low to cause detectable renal toxicity(16). Another trial comparing saline to buffered crystalloids solutions (lactated Ringer's solution and Plasma-Lyte A) in a single ICU, the SALT (Isotonic Solution Administration Logistical Testing) study, demonstrated no difference in the overall incidence of AKI or major adverse kidney events (MAKE) including death from any cause, new receipt of renal replacement therapy (RRT), or persistent renal dysfunction. However, there was a difference on MAKE in septic patients who received larger volume of crystalloids. Both of them indicate a necessity of further investigations infusing higher volume of fluids in higher-risk populations. A dose-response relationship existed(16).

A recent multiple-crossover trial in critically ill adults in five ICUs demonstrated that the use of balanced crystalloids resulted in a lower rate of MAKE than the use of saline(17)though it showed no significant difference in the incidence of AKI and mortality respectively. It also showed difference in sepsis subgroup, but the potential dose-response relationship related with infusion volumes in the subgroup was not clarified(18). Thus, it still remains uncertain whether balanced crystalloids still show superiority over saline in septic patients, whether it is related to their initial renal function, and whether there is a dose-response relationship between fluids and outcomes. Thus, we carry out this study for further investigations.

Objectives

This multi-centered crossover trial is the first study designed to focus on septic patients and verify if acetate Ringer's solution is superior to saline, especially in the patients with septic AKI. It is aimed to provide credible and evident data and clarify if (1) there is a significant difference in the overall outcome between acetate Ringer's

solution and saline in septic patients, (2) the effect is dependent on the baseline renal function, and (3) there is a dose-response effect by subgroup analysis.

Methods/Design

This protocol is designed in accordance with Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines(19). All the data will be collected at each time spot as shown in the Standard Protocol Items [Fig.1].

Design and setting

The study is a multi-center, interventional prospective, cluster-level, pragmatic, unblinded, crossover trial，which is planned to be conducted from March 1st 2019 to February 28th, 2022 in two ICUs at Zhongnan Hospital of Wuhan University and Wuhan Central Hospital of Tongji Medical College, Huazhong University of Science and Technology with a planned sample size of 312 participants.

The process of this trial is described in the following chart [Fig2]. Patients diagnosed as sepsis or septic shock will be recruited into this trial and receive either balanced crystalloids or saline when intravenous infusion is needed. To exclude the possible difference caused by various types of balanced crystalloids, we will choose acetate Ringer's solution as the only balanced crystalloid. The solution applying to septic patients will exchange in turn month by month, and participants will be assigned with the corresponding solution according to the month in which they are enrolled. To observe their renal function progress, participants will also be divided into subgroups of no AKI and AKI (AKI stage 1, AKI stage 2 and AKI stage 3) according to Kidney Disease Improving Global Outcomes (KIDIGO) criteria for their initial creatinine level or urine volume within the first 24 hours(20)once enrolled. Laboratory tests of renal function and blood gas analysis will be detected during the first five days after recruitment in order to investigate the relationship between the primary/secondary outcome and the fluids. All the patients will be monitored for 28 days-survivals. Conformed to the concept of a pragmatic clinical trial(21), the eligibility criteria are broad, the sample size is appropriate, and study procedures are embedded into routine care and carried out by clinical personnel.

Ethical considerations

This study follows the principles of the Helsinki Declaration 2013. The whole protocol has been reviewed and approved by the Ethics Committee of Zhongnan Hospital of Wuhan University (Clinical Ethical Approval No. 2018010) and the Ethics Committee of Wuhan Central Hospital of Tongji Medical College, Huazhong University of Science and Technology (Hospital Ethical Approval No. 201904).

Registration, monitoring and fund

The study was registered on ClinicalTrials.gov before the participants' enrollment started (identifiers: NCT03685214). An independent data and safety monitoring

board (DSMB) is monitoring the progress and safety of the trial. The DSMB is comprised of two academic intensivists outside the study who are experienced in the conduct of clinical trials in critical illness, being able to pause the trial to investigate or give suggestions on potential safety issues to improve our design and implement. The trial is initiated by investigators with funding provided by Wu Jieping Medical Foundation (Project identifier: HRJJ20171026).

Participant patients

Patients will be enrolled from the following hospitals: Zhongnan Hospital of Wuhan University, Wuhan Central Hospital of Tongji Medical College, Huazhong University of Science and Technology. The above two hospitals are both tertiary hospitals integrating clinical, scientific research and teaching. Participating ICUs began enrollment sequentially over the first year of the study. Each ICU will enroll participants for an equal number of acetate Ringer's solution and saline months for at least 12 months.

Participants' inclusion criteria are as follows:

1. At the age of 18 to 80;
2. Diagnosed as sepsis (a possible or specific proof for infection plus Sequential Organs Failure Assessment (SOFA) scores≥2)(22).

Participants' exclusion criteria are as follows:

1. Patients once having received RRT;
2. Patients requiring RRT prior to enrollment;
3. Patients possessed with only one kidney;
4. Patients with a medical history of renal transplant；
5. AKI caused by permanent kidney artery embolism or surgery injury to kidney artery;
6. AKI caused by glomerulonephritis, interstitial nephritis or vasculitis;
7. AKI caused by postrenal obstruction;
8. Hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura;
9. Patients having received fluid resuscitation over 1000ml within 6 hours prior to ICU;
10. Pregnant women;
11. Patients enrolled into another clinical trial at the same time.

Study treatments

The intervention of treatment lies in fluid management. After grouping based on the month, participants will be assigned with acetate Ringer's solution or saline for intravenous infusion accordingly. The volume, infusion rate and additive content (e.g., potassium chloride) of the fluid will be determined by responsible clinicians. Other solutions are permitted to be used as carrier fluids for the infusion of any drug on the occasion when neither acetate Ringer's solution nor saline is considered compatible. Medication use except fluids will not be restricted in the study. Under some circumstances in which one particular crystalloid is inappropriate, such as hyperchloremia or hyperkalemia, physicians are allowed to make judgments and

choose the best solution for the care of a specific patient, and then the patient will be recruited into the other solution group regardless of what is supposed to be in that month.

The acetate Ringer's solution is manufactured by Heng Rui Pharmaceutical Company Limited of Jiangsu Province with trade name of Le Jia, which has volume sizes of 250ml and 500ml, while the saline is produced by Baxter Healthcare with different volume sizes of 100ml, 250ml, 500ml and 1000ml. Components of these two crystalloids are presented below [Fig.3]. The study is an open-label study, thus the exact solution used is known to investigators, clinicians and patients.

Crossover and allocation

Crystalloids for enrolled patients are assigned according to the number of the month. The solution applied in the beginning month in each ICU is determined randomly by Excel2016 of Microsoft Office to make sure that stratified patient groups will be randomized to receive either acetate ringers or saline solution, followed by a monthly rotation of fluids. According to the Excel2016-generated random numbers, Acetate Ringer's solution will be applied in the odd month and saline will be applied in the even month both in the two centers. The random number table is operated by the primary investigator alone and clinicians are not involved in the process.

Study fluid distribution and logistics

As it is mentioned above, the fluids applied in the beginning month in each ICU will be determined randomly by Excel2016 of Microsoft Office, and the fluids supposed to be assigned in the following months will be settled down. Since the study is non-blind and two fluids used in this study have already been widely applied in the daily care of patients in the above ICUs, there are not problems of logistics. Assigning participants to acetate Ringer's solution or saline is determined by the crossover design, executed by clinicians and monitored by the investigators.

Study outcomes

The primary outcome of this study is progress of kidney function, which is now named as MAKE (major adverse kidney events)(23)-a composite of in-hospital death, new renal-replacement therapy or persistent renal dysfunction (defined by an estimate glomerular filtration rate (eGFR) lower than 60 ml/min/1.73 m2 for at least 3 months(24, 25)).

Secondary outcomes will include:

1. 28 days-mortality;
2. Electrolytes disturbance, including hypernatremia, hyperchloremia and hyperkalemia as well as hyponatremia, hypochloremia and hypokalemia;
3. Changes of renal functions based on the biomarkers measured from the participants' plasma and urine samples collected in the first three days after enrollment.
4. Other clinical outcomes: ICU-stay days, ventilator days, vasopressor days, and

RRT days.

Pre-specified subgroups for primary and secondary outcome analyses will include:

1. With or without kidney injury (defined as baseline creatinine concentration at least 1.5 times above the upper limit of normal for the local laboratory);
2. With or without septic shock;
3. Low versus high severity of sepsis: mild, moderate and severe (defined by SOFA scores and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores)
4. Intravenous infused volumes of the assigned crystalloids.

Sample size and statistical power

The sample size was calculated based on the occurrence of AKI on patients with sepsis. There was no study regarding the incidence of septic AKI after the use of balanced crystalloids and saline; therefore, the incidence of MAKE on sepsis patients, which was around 35%(17), is taken into account. With a noninferiority limit of 1.5%, a total of 312 study participants (156 in each group) would result in a power of at least 80% with a one-sided type-1 error rate (α) of 2.5%, allowing a 20% withdrawal rate in each group.

Statistical analysis

Measurement data that conform to normal distribution will be described as mean ± SD, while ones that do not will be reported as the median and inter quartile range (IQR). Count data will be notified as frequencies and proportions. As for single factor analysis, the difference of measurement data will be compared with T-test between two groups or with one-way analysis of variance among three groups. Chi-square test and Fisher's exact test will be used for rate comparison. As for multi-factor analysis, variables which showed a significant difference in the univariate analysis will be processed by logistic multivariate regression analysis. Multiple linear regression analysis will be used to demonstrate the linear relationship between variables. P value <0.05 will be considered statistically significant. SPSS 22.0 will be used to complete data processing and statistical analysis.

Analytic rationale

This study will recruit a meaningful sample sized participants with a wide range of baseline risk factors of the primary outcome who are exposed to the study intervention and can be divided into subgroups of distinct renal function. The baseline and secondary analysis will figure out whether the intervention makes a difference to patients' prognosis through these three aspects above.

Primary analysis

To describe the patients' distribution of this cluster-level trial, the primary analysis will be an intention-to-treat comparison of the primary outcome of changes of kidney function between the saline and acetate Ringer's solution. A generalized linear mixed-effects model will be used including fixed effects (sex, age, race, group

assignment, principal diagnosis, mechanical ventilation days, vasopressor days, ICU stay days) and random effects.

Main secondary analysis

We presume that participants will receive a wide range of total crystalloid volumes and that the more fluid patients receive, the more significant difference will be performed between the two groups. Also, we presume that the outcome may be related with participants' initial renal function. Based on these anticipations, in the main secondary analysis, patients will be divided into several groups according to different crystalloid infusion volumes and distinct initial renal function respectively. The proportion of patients experiencing the primary outcome will be compared between the same volume groups of saline and acetate Ring's solution respectively and between the same initial renal function groups, namely no AKI, AKI stage 1, AKI stage 2 and AKI stage 3, respectively. In this section, a logistic regression model with the primary outcome will be conducted to detect whether it differs significantly between saline and acetate Ringer's solution infusion on renal outcome in the same volume group or initial renal function group and whether the infused volume makes a difference.

Additional secondary analysis

1. Compare the secondary outcome between two groups;
2. Generalized linear mixed-effects modeling will be used to examine the interaction between crystalloid assignment and the following baseline variables with respect to the primary outcome in the intention-to-treat population:

a. Septic shock (yes/no)
b. The APACHE II scores and SOFA scores at the day of enrollment
c. Receipt of mechanical ventilation (yes/no) and ventilation days
d. Receipt of vasopressor (yes/no), vasopressor category and max dose
e. Receipt of RRT (yes/no) and RRT days
f. Stage of AKI on the enrollment day (no AKI, AKI, chronic kidney disease without receiving RRT regularly)
g. Main diagnosis at the time of admission to hospital (nervous system disease, respiratory system disease, cardiovascular system disease, digestive system disease, urinary system disease, hematologic system disease, endocrine system disease)
h. Complications (Hypertension, diabetes, coronary heart disease, etc.)

Handing of missing data

Of the primary outcome, data of the rate of AKI and the percentage of new receipt of RRT are not supposed to be missing for any patients. Nevertheless, some data of renal function may be missing during the five days of the trial and the period before hospital discharge. If the values of the two days before and after the missing value are normal or have the same escalating/descending trend, the missing data will be averaged. Patients without a serum creatinine measurement between enrollment and

hospital discharge who survive and do not receive new RRT will be considered as not having experienced the primary outcome of MAKE. In addition, in-hospital mortality may be missing due to patients or authorized agents giving up treatment or other unpredictable accidents. If the patients or authorized agents give up treatment for the severity of illness and the patient is predicted little chance to survive by clinicians, their outcome is considered to be death.

Data collection and management

Patients' information and clinical data will be collected from the Hospital Information System (HIS) of the hospitals involved in this study, and recorded in the Case Report Format (CRF) by the trial manager or trained personnel. The information to be collected includes patients' demographic data, main diagnosis, assigned crystalloids, the clinical information (SOFA scores, APACHE II scores, renal function, etc.) at the time of enrollment (baseline data), clinical information including infused volume of the assigned fluids each day and renal function indexes during the first five days in ICU and survival at the 28th day. These data will be collected to assess and analyze primary and secondary outcomes. An electronic password-protected excel, which will be applied for statistical analysis, will be created to summarize the data of all participants. All the data will be accessed by only investigators and authorized personnel to monitor the completeness and authenticity of the table. The confidentiality is secured and all the data will be preserved for ten years for the purpose of a secondary analysis or investigations by the investigators. To protect patients' privacy, their names will not appear on the CRF table. Every participant will only be recognized by their study ID.

Risk evaluation and adverse events

The trial is considered to pose a low risk. Firstly, saline and acetate Ringer's solution have already been widely used in the clinical practice of ICUs of the above hospitals. Secondly, it still remains controversial which fluid (saline or balanced crystalloid solution) is better for septic patients. Thirdly, clinicians are allowed to make clinical judgments and choose the other crystalloid for a specific patient if they think the assigned one may increase the risk of poor prognosis. For instance, clinicians are authorized to give acetate Ringer's solution to patients with severe hyperchloremia for resuscitation in the month when saline is supposed to be used for the safety of participants. Therefore, the adverse events (AE) of this trial may be minimal.
Still, during the entire observational 28 days from the beginning of the trial, possible adverse events (AE) will be assessed and recorded in the CRF table. Investigators will evaluate the relationship between the events and our intervention by clinical judgment, and the events will be graded as mild, moderate and severe. Severe adverse events (SAE) should be considered if unexpected clinically significant critically ill diseases which may be resulted from fluid intervention happen. AEs, especially SAEs, must be reported to DSMB and followed until they are solved. At the end of the trial, AEs and their relationship to the study will be documented in a table and submitted.

Summary/Discussion

Fluid resuscitation is the mainstream for the treatment of patients with sepsis/septic shock, and all the guidelines recommend crystalloids as the first choice. Normal saline, a very common crystalloid, poses hyperchloremia and probably worsens AKI which is always complicated by sepsis(26). However, it is unknown if saline can be safely used in septic patients. Recent studies demonstrated no difference in kidney outcomes between saline and balanced solutions in overall critically ill patients(15-17), but difference in septic patients by subgroup analysis. This enlightens us to study on a possible dose-response relationship in a high-risk population. Thus, we hypothesize that the harmful effects of saline are associated with the initial kidney function and infused volume of fluids. To confirm this hypothesis, we will carry out this study. As sepsis or septic shock is one of the most typical problems requiring large volume of fluids, this also makes it clinically practical significant to investigate. To our knowledge, this study will be the first to focus on septic patients and compare the effects on outcome between balanced crystalloid solution and 0.9% sodium saline. In light of this study, a particular comparison will be conducted between acetate Ringer's solution and saline. Firstly, the patients recruited will be confined to septic/septic shock. Therefore, the conclusions will be applied specifically in septic population. Secondly, the analysis of the association between the due solution and outcome, especially the development of AKI, will be more in details. The infused volume and the baseline renal function will both be taken into consideration. If this trial demonstrates that balanced crystalloid solution or saline shows a priority over the other, it can revise the guideline on fluid resuscitation for septic/septic shock. Therefore, the results of this study may be instructive and meaningful.

Trial status

This is the second version of the protocol which was reviewed and approved on April 20th, 2018. Patient recruitment has started on March 1st, 2019 and will be completed on February 28th, 2022.

Abbreviations

AKI: acute kidney injury; ICU: intensive care unit; ESRD: end-stage renal disease; RRT: renal replacement therapy; SPLIT: Saline v Plasma-Lyte 148 for Intensive Care Unit Fluid Therapy; SALT: Isotonic Solution Administration Logistical Testing; MAKE: major adverse kidney events; SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials; KIDIGO: Kidney Disease Improving Global Outcomes; DSMB: data and safety monitoring board; HUS: Hemolytic uremic syndrome; SOFA: Sequential Organs Failure Assessment; eGFR: estimate glomerular filtration rate; APACHE II: Acute Physiology and Chronic Health Evaluation II; IQR: inter quartile range; CRF: Case Report Format; AE: adverse events; SAE: severe adverse events.

Declarations

Ethics approval and consent to participate

This study follows the principles of the Helsinki Declaration 2013. The whole protocol has been reviewed and approved by the Ethics Committee of Zhongnan Hospital of Wuhan University (Clinical Ethical Approval No. 2018010) and of Wuhan Central Hospital of Tongji Medical College, Huazhong University of Science and Technology (Hospital Ethical Approval No. 201904) respectively. Written informed consent will be obtained from all participants who will be informed about the purpose, intervention and possible risks/benefits of the study.

Consent for publication

Not applicable.

Availability of data and materials

The CRFs and final dataset will only be accessible to the study investigators.

Competing interests

None declared.

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Authors' contributions

FL, JZ, YZ, LS, YL, LH, LY, ZP designed this study; FL, JZ designed the statistical analysis plan; LS and LH wrote the bid for the research project and obtained permission from every ethics committee; FL, JZ, YZ, LY carried out this trial and draft this manuscript; ZP, LS, YL carefully reviewed the manuscript; All authors read and approved the final manuscript.

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Figure legends:

Fig.1 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist.

Baseline variables include: baseline renal function; main diagnosis and complications; severity of illness at enrollment; demographic characters; admission location. Intravenous fluid includes: saline; acetate Ringer's solution; other fluids. Receipt of invasive support includes: mechanical ventilation; receipt of RRT; vasopressors. Clinical outcomes include: vital status; vasopressor days, mechanical ventilation days, RRT days and serum creatinine at hospital discharge.

Fig.2 Study Flow

Abbreviations: RRT, renal replacement therapy; AKI, acute kidney injury; HUS, hemolytic uremic syndrome; ICU, intensive care unit

Fig.3 Components of two crystalloids used in the trial.

Fig.1

	STUDY PERIOD					
	Enrollment & Allocation	On-study				Termination
TIMEPOINT	ICU admission (Day 0)	ICU Day 1	ICU Day 2	ICU Day 3	ICU Day 4	28 days after enrollment
Enrollment	×					
Eligibility screen	×					
Allocation	×					
Interventions						
Acetate Ringer's solution	◆	———	———	———	◆	
Screening for contraindications	×	×	×	×	×	
0.9% saline	◆	———	———	———	◆	
Screening for contraindications	×	×	×	×	×	
Assessments						
Baseline variables	×					
Intravenous fluid receipt	×	×	×	×	×	
Serum creatinine and blood gas analysis	×	×	×	×	×	
Receipt of invasive support	×	×	×	×	×	
Clinical outcomes						×

Fig. 2

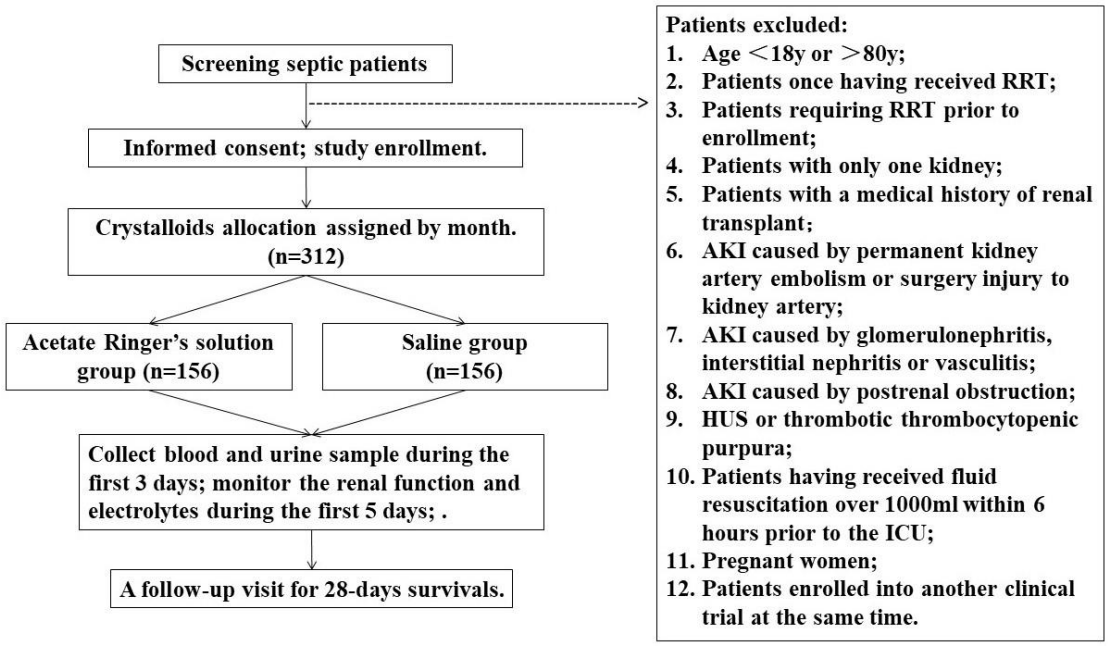

Fig. 3

Components	Acetate Ringer's solution (mmol/L)	0.9% Saline (mmol/L)
Na	140	154
K	4	-
Mg	1	-
Ca	1.5	-
Cl	115	154
Glucose	1%	-
Buffer system	Acetate 25	-
Osmotic concentration	304	286