Balanced Crystalloids versus SaLine in PrEdicted SeVERe Acute Pancreatitis Patients: a multicenter, stepped-wedge, cluster-randomized, controlled trial

The CLEVER-AP Trial

Protocol Ver.2.0 dated Mar. 16. 2021

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The Affiliated Hospital of Qingdao University

First People's Hospital of Yunnan Province

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1.Abrreviations

AP	Acute pancreatitis
SAP	Severe acute pancreatitis
AKI	Acute kidney injury
LR	Lactated ringers
SIRS	Systemic inflammatory response syndrome
PSAP	Predicted severe acute pancreatitis
IPN	Infected pancreatic necrosis
CRP	C-reaction protein
APACHE II	Acute physiology and chronic health evaluation II
RRT	Renal replacement therapy
CRRT	Continuous renal replacement therapy
CDMC	Coordinating and data management center
DSMB	Data and safety monitoring board
SAE	Serious adverse events
ICU	Intensive care unit
SOFA	Sequential organ failure assessment
ITT	Intention-to-treat
FAS	Full-analysis set
AEs	Adverse events
HREC	Hospital human research ethics committee
ICC	Intra-class correlation coefficient
CAC	Cluster auto-correlation
BUN	Blood urea nitrogen
MAKE	Major adverse kidney events
VAS	Visual analogue scale
GLMMs	Generalized linear mixed-model
NGAL	Neutrophil gelatinase-associated lipocalinz
IV	Intravenous

OF	Organ failure
OFFD	Organ failure free days

2.Study Administrative information

2.1 Study timelines

August 2019	CLEVER-AP protocol drafted
November 2019	The first National Expert Symposium
May 2020	CLEVER-AP protocol ver 1.0 finalized
June 2020	Hospital Human Research Ethics Committee (HREC) submissions
July 2020	Study material finalized HREC approvals obtained
Mar 2021	CLEVER-AP protocol ver 2.0 finalized
April 2021	Patients recruitment commences

2.2 Steering and management committee

Steering and management committee is responsible for approval of the full protocol, database, and its related methods. The members of the committee will also oversee the implementation of the study and play an advisory role.

Members of the steering committee are listed below

Prof. Weiqin Li (Primary investigator)

Prof. Zhihui Tong

Dr. Lu Ke

Dr. Bo Ye

Bin Wu

Prof. Mingzhi Chen,

Prof. Shumin Tu

Prof. Xiaomei Chen

Prof. Mei Yang

Prof. Guoxiu Zhang

Prof. Qiang Li

Prof. Xinting Pan

Prof. Lijuan Zhao

Prof. Honghai Xia

2.3 Coordinating and data management center

Coordinating and data management centers (CDMC) will be organized before the implementation of the current study. They are responsible for day to day management of the trial, assistance for ethics application at each center, protocol and case report form design, online database design and maintenance, protocol training for the participating centers, randomization, data entry and quality control, severe adverse event(SAE) monitor and notification and data analysis. The CDMC plans to meet before enrollment, three months after initial enrollment and six months after initial enrollment to ensure qualified data entry.

Members of CDMC are listed below

Dr. Lu Ke

Dr. Bo Ye

Ms. Yan Chen

Ms. Mingfeng Huang

Ms. Yuan Wang, and all the research nurses and coordinators from the participating centers. Meetings will be organized as required and no routine meeting is planned.

2.4 Writing and publication committee

The writing and publication committee is responsible for drafting the manuscript and submission of the manuscript to adequate journals. The Writing and publication committee will also decide on the authorship of this study. After the conclusion of

this study, all the participating centers are welcome to submit proposals for post-hoc analysis to the writing and publication committee is responsible for reviewing and rating all the proposals for further analysis.

Members are listed below

Prof. Weiqin Li

Dr. Lu Ke

Dr. Bo Ye

Dr. Tao Chen

Prof. John Windsor

Prof. Gordon Doig

Prof. Rinaldo Bellomo

Prof. Georgios Papachristou

Prof. James Buxbaum

Ms. Jiajia Lin

2.5 Data and safety monitoring board

Data and safety monitoring board (DSMB) is an independent group of experts that offers advise during the implementation of the study. The DSMB can recommend that a trial be stopped early because of concerns about participant safety.

Members of DSMB are listed below

Prof. Liang Xia (The First Affiliated Hospital of Nanchang University)

Prof. Man Liu (Nanjing University)

Prof. Wenkui Yu (The Drumtower Hospital)

2.6 Registration

The CLEVER-AP trial was registered with the CHiCTR registry

(ChiCTR2100044432).

2.7 Funding

The trial was funded partly by the Key Research and Development Program Foundation of Jiangsu Province of China (no. BE2015685), and partly by Jiangsu Nhwa Pharmaceutical Co., Ltd.

3. Background and rationale

The leading determinant responsible for high mortality in patients with severe acute pancreatitis (SAP) is organ failure(OF)[1]. The kidney tends to be involved in the early course of SAP due to both anatomical adjacency and early compromised renal perfusion caused by hypovolemia and persistent inflammation [2-3]. It has been reported that 25%-59.5% of patients developed acute kidney injury (AKI) during the course of SAP [4-5]. Previous guidelines for the management of AP suggested that timely and adequate fluid therapy in the acute phase is pivotal for maintaining sufficient intravascular volume and perfusion in remote organs such as the kidney [6-8]. Currently, saline (0.9% sodium chloride; “normal saline”) is the most commonly used isotonic crystalloid in fluid resuscitation for SAP patients all over the world [9]. However, the chloride concentration of saline (154 mmol per liter) is significantly higher than that of human plasma (94 to 111 mmol per liter), which means the infusion of saline could potentially cause hyperchloremic metabolic acidosis depending on the rate and volume of fluid infusion, which may increase inflammation and impair renal perfusion through multiple mechanisms[10]. Although the clinical significance of these physiological effects is not fully understood yet, accumulating evidence suggests that the supraphysiologic chloride concentration of saline may contribute to kidney injury in critically ill patients [11-12], but no solid evidence exists in SAP patients.

Most guidelines for AP currently recommend balanced crystalloid solutions like Lactated Ringers(LR) for early resuscitation, which are based on the studies showing that LR dampens the inflammatory response in acute pancreatitis as measured by systemic inflammatory response syndrome(SIRS) and C-reaction protein(CRP) at 24 hours[13-15]. However, studies focusing on the effect of different crystalloids on plasma chloride concentration and renal function in SAP patients are rare in the literature. In our previous study, we found that aggressive resuscitation and chloride exposure in the first 24 hours were risk factors for new-onset AKI in moderate-SAP and SAP patients [16]. Therefore, a well-designed, sufficiently-powered clinical study assessing the impact of balanced crystalloids versus saline on plasma chloride concentration and renal function in SAP patients is warranted. As SAP can not be defined early during the disease, we use predicted severe acute pancreatitis(PSAP) patients as our study population.

4. Study Design

4.1 Aims and hypothesis

We aimed to evaluate the effects of balanced crystalloids versus saline on plasma chloride concentration in PSAP patients. Renal function and clinical outcomes will also be compared between groups. The hypothesis is that balanced crystalloids can reduce the plasma chloride concentration on day3 compared to saline.

4.2 General study setting

The present clinical interventional study will be performed in 11 different hospitals across China. It is a multicenter, stepped-wedge, cluster-randomized study.

5. Study population

5.1 Patient recruitment

According to the previous study, the standard deviation of serum chlorine in patients with SAP is conservatively estimated at 6mmol/L [17]. Therefore, 240 patients will be recruited from eleven centers within twelve months (20 patients per month) and will provide 90% power to detect the serum chlorine difference of 1.5 mmol/L or more between the balanced crystalloid and the saline group on the basis of within period intra-class correlation coefficient (ICC) of 0.05, and cluster auto-correlation (CAC) of 0.5.

The starting date of patient recruitment was April 1st, 2021, and the planned finishing date is March 31st, 2022. The follow up will be finished after the discharge of the last recruited patient.

5.2 Eligibility Criteria

5.21 Inclusion Criteria

1. Symptoms and signs of AP based on abdominal pain suggestive of AP, serum amylase at least three times the upper limit of normal, and/or characteristic findings of AP on computed tomography;

2. Within 72 hours from the onset of the disease;

3. Age between 18 to 70 years old;

4. Acute physiology and chronic health evaluation II(APACHEII)≥8 and CRP>150mg/L.

5.22 Exclusion Criteria

1. Patients with chronic renal disease (All patients with an eGFR <60 ml/min/1.73 m^2 for three months are defined as having chronic kidney disease);

2. Patients who need emergent RRT at the time of admission. The indication for RRT will be according to the criteria described by Bellomo et al[18];

3. Patients who are pregnant or lactating at the time of enrollment;

4. Patients who undergo RRT before admission;

5. Patients receiving percutaneous or transmural drainage for pancreatic necrotic collections or surgery before admission or requiring emergency surgery due to abdominal compartment syndrome, bowel ischemia, etc., at admission;

6. Patients who present with fulminant multiple organ failure with predicted death within 24-48 hours (e.g., severe respiratory failure, severe systemic circulatory failure, coma, or other dangerous symptoms that are difficult to reverse);

7. Patients with a known history of severe cardiovascular, respiratory, renal, hepatic, hematologic, or immunologic disease defined as (1) greater than New York Heart Association class II heart failure, (2) active myocardial ischemia, or (3) cardiovascular intervention within previous 60 days, (4) history of cirrhosis or (5) severe chronic obstructive pulmonary disease requiring home oxygen.

6. Main methods and materials

6.1 Patients screening procedures

All patients presenting to the participating sites will be assessed by the treating physician and receive medical care immediately according to the current best clinical practice. The treating clinician team will be responsible for identifying potential participants and contacting the CLEVER-AP coordinator or a member of the CLEVER-AP study team who will assess the patients for eligibility. Screening tools will be provided, and a screening log will be kept.

Each participating site will be led by a CLEVER-AP project leader (site primary investigator), and a site coordinator will be appointed. The former will be responsible for implementing the protocol if assigned to the study group and

monitoring the CLEVER-AP trial, and the latter will be responsible for daily screening and data management.

6.2 Recruitment

This trial was approved by the ethics committee of Jinling Hospital, Nanjing University (N. 2020NZKY-015-01) with a waiver of informed consent. For the participating sites, all appropriate ethics committees approved the study, and consent-waived consent, or opt-out consent was obtained as required.

6.3 Randomization procedures

6.3.1 Sequence generation

The unit of randomization is the cluster (e.g., site) rather than the individual patient. We will recruit a convenience sample of practices from within our network of AP in China. Once eligible, each enrolled site will be randomly assigned to the sequences of treatments for the time of crossover from control using a computer-generated list of random numbers. During the first one month of data collection, all sites will start with normal saline. Every one month thereafter, one center will be randomized to balanced solution without a transition period.

The allocation sequence will only be made available to the trial statistician. Study investigators will be blinded to the allocation sequence, with only the next site randomized for rollout being revealed at each intervention implementation time point. Study participants will be blinded to the allocation sequence and those not yet receiving the intervention will not be aware of the time at which they will have the intervention implemented.

6.3.2 Blinding method

Due to the nature of the study, blinding investigators will not be applicable.

However, study participants, operators who performed the blood test, and data analysts will be masked to the allocation sequence.

6.4. Study procedures

6.4.1 Interventional arms

Arm#1 Balanced crystalloids group

Patients in a treatment block randomized to physiologically-balanced isotonic fluid will receive Sterofundin ISOTM(Table 1) whenever isotonic intravenous fluid administration is ordered by the treating provider before death, discharge or 7 days after enrollment (whichever happens first).

Arm#2 Saline group

Patients in a treatment block randomized to saline fluid will receive 0.9% Saline(Table 1) whenever isotonic intravenous fluid administration is ordered by the treating provider before death, discharge or 7 days after enrollment (whichever happens first).

6.4.2 General management

First, all patients received initial standard treatment, including continuous vital signs recording, fluid resuscitation, early enteral nutrition, routine medical treatment (antibiotics and sedatives as needed), and mechanical ventilation if needed.

Initiation of RRT should be based on the criteria described by Bellomo et al [18]. Patients who have AKI (at least 1.5 times increase in creatinine from known baseline value) and meet predefined specific criteria of will be eligible for initiation of RRT:

1. Anuria (negligible urine output for 6 hours)
2. Severe oliguria (urine output < 200 mL over 12 hours)

3. Hyperkalemia (potassium concentrations > 6.5 mmol/L)

4. Severe metabolic acidosis (pH < 7.2 despite normal or low partial pressure of carbon dioxide in arterial blood)

5. Volume overload (especially pulmonary edema unresponsive to diuretics)

6. Pronounced azotemia (urea concentrations > 30 mmol/L or creatinine concentrations > 300 μmol/L)

7. Clinical complications of uremia (e.g., encephalopathy, pericarditis, neuropathy)

Patients will be cared for by the local treating team at each participating site. All clinical decisions will be left to the discretion of the treating clinical teams and recorded in the patient's medical record. When pancreatic infection occurs, percutaneous or transmural drainage will be the primary choice of treatment, followed by debridement based on the technical preference of the participating site according to a step-up approach. An independent DSMB will be organized to oversee all subjects' safety. The expert panel will offer suggestions for uniform treatment.

7. Outcome measures

7.1 Primary outcome measures

The primary outcome measure is plasma chloride concentration on day3 (the day of enrollment will be set as day 1).

7.2 Secondary outcome measures

7.2.1 Renal function outcomes

1. MAKE 30 (Major Adverse Kidney Events by hospital discharge or day 30).
2. 30-day mortality censored at hospital discharge or 30 days after enrollment;

3. New RRT censored at hospital discharge or 30 days after enrollment;

4. Persistent renal dysfunction censored at hospital discharge or 30 days after enrollment;

7.2.2 Clinical outcomes

1. Requirement of intensive care unit(ICU) admission during the index admission
2. ICU free and alive days to day 30
3. Ventilator-free and alive days to day 30
4. Vasopressor-free and alive days to day 30
5. RRT-free and alive days to day 30
6. New-onset organ dysfunction as judged by sequential organ failure assessment(SOFA) score [Time Frame: 30 days after enrollment]
7. Change of SOFA score from day1 to day7
8. Organ failure free days to day7
9. Change of SIRS score from day1 to day7
10. SIRS-free days to day7
11. Change of abdominal pain(visual analogue scale(VAS) score) from day1 to day7
12. Intravenous morphine equivalent dose from day1 to day7
13. Proporation of intolerance to solid diet from day1 to day7
14. Occurence of infected pancreatic necrosis(IPN) during the index admission.
15. Occurence of sepsis during the index admission.
16. Occurence of intra-abdominal bleeding during the index admission.
17. Occurence of gastrointestinal fistula during the index admission.
18. Occurence of all-cause mortality during the index admission.
19. Requirement of open surgery during the index admission.

7.2.3 Additional outcomes

1. Highest creatinine in the first 30 days
2. Highest serum chloride in the 30 days after enrollment
3. Change in serum chloride from day1 to day 7
4. Change in serum bicarbonate from day1 to day 7
5. Plasma neutrophil gelatinase-associated lipocalin(NGAL) concentration at day1, day2, day3, and day5

6. Length of stay in hospital during the index admission.
7. Healthcare resource use during the index admission.

7.3 Definition of outcomes

MAKE 30: The MAKE 30 endpoint will be considered present if at least one of the following occurs: (1) A patient dies prior to hospital discharge or day 30; (2) A patient receives new RRT between enrollment and hospital discharge or day 30, or (3) A patient has persistent renal dysfunction at the time of hospital discharge or day 30.

30-day In-hospital mortality: Death before hospital discharge, censored at 30 days after enrollment.

New RRT by day 30: The initiation of any renal replacement therapy between enrollment and 30 days censored at hospital discharge or 30 days after enrollment in a patient not known to have previously received RRT.

persistent renal dysfunction: persistent renal dysfunction is defined as ≥ 200% of creatinine from baseline. The value for baseline serum creatinine was determined in a hierarchical approach. The lowest serum creatinine between 12 months and 24 h prior to hospital admission was used when available. If no such creatinine value was available, the lowest creatinine value between 24 h prior to hospital admission and the time of ICU admission was used. If no creatinine value was available between 12 months prior to hospital admission and the time of ICU admission, a baseline creatinine value was estimated using a previously-described three-variable formula [creatinine = 0.74 − 0.2 (if female) + 0.003 × age (in years)].

ICU-free days to day 30: ICU-free days to 30 days after enrollment will be defined as the number of days alive and not admitted to an ICU after the patient's final discharge from the ICU before 30 days. If the patient is admitted to an ICU at day 30 or dies prior to day 30, ICU-free days will be 0.

Ventilator-free days to day 30: Ventilator-free days to day 30 will be defined as the number of days alive and with unassisted breathing to day 30 after enrollment, assuming a patient survives for at least two consecutive calendar days after initiating unassisted breathing and remains free of assisted breathing. If a patient

returns to assisted breathing and subsequently achieves unassisted breathing prior to day 30, ventilator-free days will be counted from the end of the last period of assisted breathing to day 30. If the patient is receiving assisted ventilation at day 30 or dies prior to day 30, ventilator-free days will be 0. Non-invasive mechanical ventilation or high flow oxygen therapy will not be counted as assisted breathing.

Vasopressor-free days to day 30: Vasopressor-free days to 30 days after enrollment will be defined as the number of days alive and not on vasopressors before 30 days. If the patient is on vasopressors at day 30 or dies prior to day 30, vasopressor-free days will be 0. Vasopressors are medicines that constrict (narrow) blood vessels, increasing blood pressure. They are used in the treatment of extremely low blood pressure, especially in critically ill patients which including norepinephrine, epinephrine, vasopressin, dopamine, phenylephrine, dobutamine and etc.

RRT-free survival to day 30: RRT-free days to 30 days after enrollment will be defined as the number of days alive and not receiving RRT after the final episode of RRT during the hospitalization. If the patient dies or continues to receive RRT at the time of discharge, the value will be 0.

Change of SOFA score from day1 to day7: To clearly reflect the change of OF (SOFA score) from day1 to day7, organ failure free days (OFFD) to day7 from enrollment was added, which was defined as the number of days alive without OF for respiration, renal and cardiovascular systems (defined by the SOFA score). An individual SOFA score of 2 or more was defined as OF . Only the final period of OFFD was included. Patients discharged from the hospital before 7 days were considered alive and free from OF since the day of discharge. Patients who died prior to day7 were assigned zero OFFD.

Change of SIRS score from day1 to day7: SIRS was defined by the presence of 2 or more criteria: (a) heart rate >90 beats/min, (b) core temperature <36°C or >38°C, (c) white blood count <4000 or >12,000/mm^3, and/or (d) respirations >20 breaths/min or PCO_2 <32mmHg. To clearly reflect the change of SIRS score from day1 to day7, SIRS free days to day7 from enrollment was added, which was defined as the number of days alive without SIRS. Only the final period of SIRS-free days was included. Patients discharged from the hospital before 7 days were considered alive and free from SIRS since the day of discharge. Patients who died

prior to day7 were assigned zero SIRS-free days.

Infected pancreatic necrosis: positive culture of (extra)pancreatic necrosis obtained by means of FNA, or from the first drainage procedure or necrosectomy, or the presence of gas in the (extra)pancreatic collection on CECT.

Intra-abdominal bleeding: Bleeding requiring surgical, radiologic, or endoscopic intervention.

Gastrointestinal fistula: secretion of fecal material from a percutaneous drain or drainage canal after drain removal or from a surgical wound, either from small or large bowel; confirmed by imaging or during surgery.

Healthcare resource use

We will determine the intervention's impact on total hospitalization costs.

8. Ethics considerations

8.1 Ethical issues of this study

The major ethical considerations include:

Some components of the balanced solution(Sterofundin) can be harmful to specific patients. The actual fluid prescription will be at the discretion of the treating physician to ensure patients' safety.

8.2 Potential risks and benefits

No specific monetary compensation is available for each participant in this study.

8.3 Consent and confidentiality

Saline, Ringer's solution, and Sterofundin ISOTM are all intravenous(IV) crystalloids currently commonly used in the routine care of patients. Currently, no high-quality data suggest that the choice of crystalloid affects key patient-centered outcomes among AP patients. During the CLEVER-AP trial, each time a study crystalloid is ordered, the study confirms that the treating clinician does not feel

that a specific study crystalloid is required for the safe treatment of that specific patient at that specific point in time (see Study interventions section below). The trial is felt to pose a minimal risk because (1) exposure to the study crystalloids occurs only for patients whose treating clinician has already decided to administer an IV crystalloid, (2) all of the crystalloid solutions examined are already used in routine practice in the study environment, (3) no definitive prior data suggest that clinical outcomes are better with one crystalloid in comparison to the others. Given the minimal risk, the focus of the study on crystalloid use at a clinical level, as well as the impracticability of consenting each patient admitted to each site prior to the first administration of crystalloid, a waiver of informed consent was granted by the IRB of Jinling hospital (2020NZKY-015-01), The Third Hospital of Xiamen City (202009003), Jinjiang Hospital of Traditional Chinese Medicine (2020008), The First Hospital of Shangqiu city (2020-021), Qilu Hospital of Shandong University KYLL-202011-005), The First Hospital of Qujing city (20201209), The First Affiliated Hospital of Henan University of Science and Technology (2020-0124), The First Affiliated Hospital of Nanjing Medical University (2020-SR-501), The Affiliated Hospital of Qingdao University (QYFYKYLL 933311920), First People's Hospital of Yunnan Province (KHLL2020-KY062), and the Fist Affiliated Hospital of the University of Science and Technology of China (2021-KY-023).

8.4 Dissemination policy

All the primary investigators of the participating sites and the sponsor will have full access to the data after the conclusion of the study. Anyone who wants to do a post-hoc analysis needs to submit a formal writing proposal to the *writing and publication committee*. Only approved authors can have access to the database.

9. Data management, analysis, and statistics

9.1 Data collection

All the data that is necessary to define baseline patient characteristics, the implementation of fluid therapy, potential confounding co-interventions, and outcomes will be collected (Fig. 2).

The primary investigator of each center will be responsible for patients enrollment and data integrity. A group of statisticians will be accountable for pre-definition of statistical analysis and subgroup analysis.

A web-based electrical database will be used for data collection and storage (Unimed Scientific Inc., Wuxi, China). All data will be input by the primary investigator or nominated investigators (less than two for each participating center) approved by the primary investigator. Training for data entry will be performed by the provider of the electrical database and the sponsor of the CLEVER-AP trial.

9.2 Participant timeline

All patients who are enrolled will be followed until hospital discharge. Follow-up will be restricted to information regarding the vital status and other related study clinical outcomes. Follow-up will be conducted by study staff through either direct contact with the patient or their next of kin. Patients who withdraw from the study for any reason but do not withdraw for data use will also be followed up according to the study follow-up schedule and analyzed on an intention-to-treat(ITT) principle.

9.3 Sample size

According to the previous study, the standard deviation of serum chlorine in patients with SAP is conservatively estimated at 6mmol/L. Therefore, 240 patients will be recruited from eleven centers within twelve months (20 patients per month)

and will provide 90% power to detect the serum chlorine difference of 1.5 mmol/L or more between the balanced crystalloid and the saline group on the basis of within period ICC of 0.05, and CAC of 0.5. the standard deviation of serum chlorine in patients with SAP is conservatively estimated at 6mmol / L.

9.4 The flow of sites and patients

The flow of hospitals and patients through the trial will be reported in accordance with the CONSORT extension statement for cluster trials (Fig. 1). The flow diagram will include the number of eligible and recruited hospitals, the number of eligible and recruited patients and then, by allocated group, the number of patients who continued through the trial, the number of withdrawing, the number of data missing and the numbers included in the analysis.

9.5 Basic principle of analysis

The reporting and presentation of this trial will be following the CONSORT guidelines for stepped-wedge cluster-randomized trials [19], with the primary comparative analysis being conducted on an intention-to-treat basis.

Descriptive statistics will be used to assess any marked baseline differences in demographics or outcome measures between the two groups, taking clustering into account. Comparisons of binary outcomes will be expressed as relative risk with 95% confidence intervals and comparisons of continuous outcomes as mean differences together with 95% confidence intervals. Between-group comparisons will be made using generalized linear mixed-model(GLMMs) with an ICU-level random effect to address clustering by ICU and random slopes of time to account for temporal effects, as delineated by Hussey and Hughes.

In addition, a sensitive analysis will be undertaken without considering effects of clustering to ascertain whether the submodels significantly influenced the results of the primary effectiveness analysis, exploring the robustness and accuracy of the

primary conclusions.

Based on the principle of ITT, full-analysis set (FAS) will be performed on the population with outcome reporting (the follow-up visit for 30-day mortality). FAS will be used for the analysis of baseline characteristics and main therapeutic interventions

Two-sided 5% significance levels will be used to identify statistically significant results. All confidence intervals reported will be 95% confidence intervals. All p-values and estimates of change will be calculated at the individual level.

9.6 Interim analysis and safety monitoring.

An independent data safety and monitoring board (DSMB) (consisting of a surgeon, an intensivist, and a statistician) will oversee all aspects of patient safety. The DSMB will review all the safety profiles regularly (every 2 months) during the study. No formal interim meeting is planned.

9.7 Presentation of comparative analyses

The comparability analysis of baseline indicators will be based on the FAS of ITT. The main efficacy parameters will be analyzed by using FAS. The safety profile of the intervention will be analyzed based on SAS 9.4 will be used to perform all statistical analysis. Generalized linear mixed-model(GLMMs) will be employed with an ICU-level random effect to address clustering by ICU and random slopes of time to account for temporal effects, as delineated by Hussey and Hughes.

For each of the continuous outcomes, the mean and standard deviation for each allocated group will be presented, together with the mean between-group difference, 95% confidence interval for the difference and p value. For binary outcomes, the percentage and frequency of patients in the outcome category of interest (e.g., percentage of secondary infection) will be presented for each allocated group, along

with the relative risk for the intervention effect, and its 95% confidence interval and p value. Besides, the intracluster correlation coefficient will be reported for each outcome, based on the adjusted analyses, together with a 95% confidence interval. Detailed analysis stragetry will be found in the statistical analysis plan.

10. Safety issues

10.1 Data and safety monitoring board

DSMB is an independent group of experts that offers advise during the implementation of the study. The DSMB can recommend that a trial be stopped early because of concerns about participant safety.

10.2 Adverse events

Adverse events (AEs) are defined in accordance with the National Cancer Institute-Common Terminology Criteria for Adverse Events as any untoward medical occurrence in a patient, or clinical investigation subject administered an investigational intervention and which does not necessarily have to have a causal relationship with this treatment.

It is recognized that the patient population(PSAP patients) will experience a number of common aberrations in laboratory values, signs, and symptoms due to the severity of the underlying disease and the impact of standard therapies. These will not necessarily constitute an AE unless they require significant intervention or are considered to be of concern in the investigator's clinical judgment.

In all cases, the condition or disease underlying the symptom, sign, or laboratory value should be reported, e.g., renal failure rather than hyperkalemia, and agitation rather than self-extubation.

10.3 Serious adverse events

SAEs are defined when any untoward medical occurrence that:

1.Results in death

2.Is life-threatening

3.Requires inpatient hospitalization or prolongation of existing hospitalisation

4. Results in persistent or significant disability/incapacity

5. Is a congenital anomaly/birth defect

6. Is an important medical event which may require intervention to prevent one of the previously listed outcomes.

In this study, all SAEs will be reported regardless of suspected causality.

10.4 Monitoring of potential adverse events

The DSMB will be responsible for overseeing all subjects' safety and monitoring total mortality and serious adverse events. All serious adverse events occurring during the trial will be reported to the CDMC within 48 hours. Minimum information to report will include:

1. Initials of the patient and study number

2. Course and nature of the event

3. An investigator's opinion of the relationship between study involvement and the event (unrelated, possibly, probably or definitely related)

4. Whether treatment is required and what treatment was applied

The contact information for CDMC

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Mobile number of the primary investigator:

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11. References

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Table 1: The compositions of each crystalloid solution.

Compositions	Sterofundin ISOTM	Normal saline
Na+	145.0mmol/L	154.0mmol/L
K+	4.0mmol/L	-
Ca2+	2.5mmol/L	-
Mg2+	1.0 mmol/L	-
Cl-	127.0 mmol/L	154.0 mmol/L
Acetate	24.0 mmol/L	-
Malate	5.0 mmol/L	-

Figure 1: Flow of Centers and patients through the CLEVER-AP trial

	2021									2022		
Center	April	May	June	July	August	September	October	November	December	January	February	March
1	S	B	B	B	B	B	B	B	B	B	B	B
2	S	S	B	B	B	B	B	B	B	B	B	B
3	S	S	S	B	B	B	B	B	B	B	B	B
4	S	S	S	S	B	B	B	B	B	B	B	B
5	S	S	S	S	S	B	B	B	B	B	B	B
6	S	S	S	S	S	S	B	B	B	B	B	B
7	S	S	S	S	S	S	S	B	B	B	B	B
8	S	S	S	S	S	S	S	S	B	B	B	B
9	S	S	S	S	S	S	S	S	S	B	B	B
10	S	S	S	S	S	S	S	S	S	S	B	B
11	S	S	S	S	S	S	S	S	S	S	S	B

Figure 2: Schedule of enrolment, interventions, and assessments

	STUDY PERIOD							
	Enrollment and Allocation	On study					Termination	
TIMEPOINT	Onset-72hours	Day 1	Day 2	Day 3	Day 4-7	Discharge before day 30	30 days after enrollment	Discharge after day 30
ENROLLMENT	X							
Eligibility screen	X							
Allocation	X							
INTERVENTIONS:	←	—	—	—	→			
Balanced crystalloids	←	—	—	—	→			
Screening for contradictions	X							
0.9% saline	←	—	—	—	→			
Screening for contradictions	X							
ASSESSMENTS	←	—	—	—	—	—	—	→
Baseline variables:	X							
Intravenous fluid receipt		X	X	X	X			
Plasma chloride concentration		X	X	X	X			
Serum electrolytes and others		X	X	X	X	X	X	
MAKE 30		X	X	X	X	X	X	
PASS score		X	X	X	X			
Organ function		X	X	X	X	X	X	
Receipt of invasive support		X	X	X	X	X	X	
Clinical outcomes						X	X	X