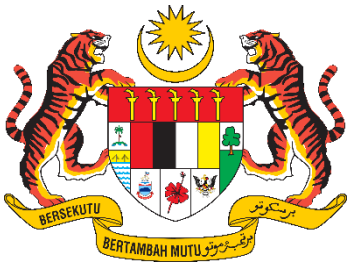
A Double-Blind, Randomized Control Trial of Rapidly Infused High Strong Ion Difference Fluid versus Hartmann's solution on Acid-Base Status in Sepsis and Septic Shock Patients in the Emergency Department Hospital Pulau Pinang

Protocol number: ED-HPP-1701 (15th Jan 2017)
NCT number: NCT03530046



Confidentiality Statement

May not be used, divulged, published or otherwise disclosed without the written consent of the Principal Investigator.

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Study Title: A Double-Blind, Randomized Control Trial of Rapidly Infused High Strong Ion Difference Fluid versus Hartmann's solution on Acid-Base Status in Sepsis and Septic Shock Patients in the Emergency Department Hospital Pulau Pinang

Clinical study protocol number/version: ED-HPP-1701

Development phase: Ethics approval

Study initiation date: 1st Feb 2017

Study completion date: 31st Jan 2018

Date of protocol: 24 Oct 2016

Amendment number(s) and date : Version 1.0 (15th Jan 2017)

Author(s) : Dr. Yeoh Chun Chiat

Author's and Reviewer's signature and date:

Protocol Author	Reviewed and approved by
Signature:	Signature:
Date:	Date:

This protocol incorporates the following amendment(s):

Amendment No.	Date of Amendment	Initials of Principal Investigator
1	15/1/2017	

1 SYNOPSIS

Title of study:
A Double-Blind, Randomized Control Trial of Rapidly Infused High Strong Ion Difference Fluid versus Hartmann's solution on Acid-Base Status in Sepsis and Septic Shock Patients in the Emergency Department Hospital Pulau Pinang

Sponsor: Self funding

Clinical Phase:
Non- applicable

Investigators:
Name and institution of Principal investigator:
Chun Chiat Yeoh, Emergency Physician Trainee, Emergency Department, Hospital Pulau Pinang.

Name and Institution of Co-Investigators:

1. Aik Howe Teo, Consultant Emergency Physician, Emergency Department, Hospital Pulau Pinang
2. Sasi Kumar A/L Sappanie, Senior Medical Officer, Emergency Department, Hospital Pulau Pinang.
3. Sherene Tan Su Ann, Pharmacist, Pharmacy Department, Hospital Pulau Pinang.
4. Abdul Muhaimin bin Noor Azhar, Emergency Physician and Lecturer, Emergency Department, University of Malaya

Study period: 1 year
Planned date of first subject enrolment: 1st Feb 2017
Planned date of last subject completed: 31st Jan 2018

Objectives:

Primary objective*:*
To determine the mean difference of blood pH and bicarbonate level at 2 hours or after 30ml/kg administration of high SID fluid or Hartmann's Solution (whichever occurs first).

Secondary objectives:
To determine:

- the mean difference in lactate level at 2 hours,
- all-cause mortality at 30 days,
- development of pulmonary edema,
- the mean length of stay in hospital,
- the incidence of acute kidney injury (AKI) as defined by the AKIN criteria

of high SID fluid and Hartmann's Solution

Methodology:

The study is a double-blind randomized controlled trial with parallel design and an allocation ration of one to one. Eligible subjects are assigned in a 1:1 ratio by means of randomization using online randomizer, http://www.randomiser.com. The code is saved in the randomization log which will only be secured by an assigned pharmacist. A trained nurse or pharmacist will prepare the study fluids (either half saline with addition of 75mEq/L sodium bicarbonate or Hartmann's solution) according to the randomization list right after a suitable patient is recruited.

Blinding will be achieved by using unlabeled 500cc saline bottle. The study fluids will be macroscopically indistinguishable.

All clinicians, patients and investigators will be blinded for the coding of the study fluids used during resuscitation. Unblinding of the code will be only done after analysis of the primary outcome was completed except for rare emergency cases when treating physician believes that clinical management depends importantly upon knowledge of whether the patient received high SID fluid or Hartmann's solution.

Subjects receive study fluid and the rate of infusion depends on clinical judgment by the treating physician. Each subject is monitored every 30 minutes for blood pressure, pulse volume and capillary refill time. Blood samples are taken for electrolytes, urea and creatinine measurement, blood gas analysis with lactate at baseline before the initiation of study fluid. When 30ml/kg of study fluid is administered or at 2 hours (whichever occurs first), another blood gas with lactate will be taken. Study fluid may be discontinued depending on the clinician's judgement. If the study fluid needs to be discontinued, the total amount of test fluid will be recorded and the subject will be excluded from the analysis.

Subjects are subsequently followed up in the ward for BUSEC within 48 hours and for all-cause mortality in 30 days.

At least one trained staff member will be available throughout the intervention period.

Number of patients:

162 patients.

Number of centre(s):

1

Inclusion criteria:

- age≥18 years
- fulfills 2/3 qSOFA criteria
- presumed infection
- a blood pH at presentation ≤ 7.35
- hyperlactatemia (blood lactate level, >2mmol/L)

Exclusion criteria:

- existing cardiac failure, major cardiac arrhythmia, advanced chronic kidney disease or end stage failure
- known pregnancy
- suspected dengue
- primary diagnosis is related to burn, trauma, or drug overdose
- if more than 500cc of resuscitation fluid was administered before enrolment.

Test treatment, dose and mode of administration:
High SID fluid (half saline with addition of 75 mEq/L sodium bicarbonate), administered via intravenous infusion.

Dose: 30ml/kg or after 2 hours administration, whichever occurs first

Duration of treatment with study medication:
2 hours

Criteria for evaluation:

1. The primary clinical outcome was change of blood pH and bicarbonate level at 2 hours or after 30ml/kg of test fluid administered, whichever is earlier.
2. Secondary outcomes
   a. the change in lactate level at 2 hours or after 30ml/kg of test fluid administered, whichever is earlier,
   b. all-cause mortality at 30 days,
   c. development of pulmonary edema,
   d. length of stay in hospital,
   e. the incidence of acute kidney injury (AKI) as defined by the AKIN criteria

Statistical methods:

1. Sample size is calculated using PS software. The sample size calculation assumed the following: α value 0.05, power of 0.95 and standard deviation of 0.05 from previous study (26). It is powered to detect a 0.03 difference in pH between 2 study fluids. The calculated sample size was 73 patients each arm with total 146 patients. Considering drop-out rate of 10%, total sample size is 162 (81 patients each arm).
2. Data analysis will be performed using the SPSS program. Descriptive analysis will be used to describe demographic and disease characteristics of the patients. Percentages and frequencies will be used for categorical variables while means and standard deviations will be calculated for continuous variables. The significance level is set at p-value less than 0.05.
3. The mean difference of blood pH, bicarbonate level and lactate level between the two study fluids will be analyzed using Independent T-test (normally distributed) or Mann-Whitney Test (non-normally distributed).
4. The all-cause mortality at 30 days, development of pulmonary edema and incidence of acute kidney injury will between the two study fluids will be analyzed using binary logistic regression.
5. The length of stay in hospital between the two study fluids used will be analyzed using Independent T-test (normally distributed) or Mann-Whitney Test (non-normally distributed).

-End-

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4 LIST OF ABBREVIATIONS

^{0}C	Degree Centigrade
AE	Adverse event
BP	Blood pressure
BUSEC	Blood for urea, serum electrolytes and creatinine level
CRF	Case report form
CV	Curriculum vitae
GCP	Good clinical practice
IEC	Independent Ethics Committee
ID	Identification
IRB	Independent Review Board
mmHg	Millimeter mercury
SAE	Serious adverse event
SID	Strong Ion Deficit

5 GLOSSARY OF TERMS

(Comprehensive list of commonly used terms is found in Malaysian Guidelines for GCP)

Eligible	Qualified for enrolment into the study based on strict adherence to inclusion and exclusion criteria.
Evaluable	Meeting all eligibility criteria, complying with the procedures defined in the protocol and therefore included in analysis.
Investigator	Treating physician
Protocol amendment	Any change in a study protocol which affects the safety of subjects, the scope, design, assessments or scientific validity of the clinical investigation.
Subject(s)	Individuals enrolled in the clinical study.

6 ETHICS & REGULATORY CONSIDERATIONS

6.1 Independent Ethics Committee

The study protocol and any other documents that the IEC may need to fulfil its responsibilities including the Patient Information Sheet, Consent Form, subject requirement procedures and advertisements to be used, and information on payments and compensation available to subjects, will be submitted to a properly constituted Independent Ethics Committee (IEC). Unconditional approval or a favourable opinion must be received from the IEC before commencement of this study. Approval from the committee must be documented in a letter to the investigator specifying the study title, protocol number, the documents reviewed, the date on which the committee met and granted the approval, the name, occupation and institutional affiliation of the chairman and members of the IEC, and provisions for periodic review if any. Any amendments to the protocol, other than administrative ones, must also be approved by this committee.

The principal investigator will inform the IEC of:

- Any amendment to the protocol, informed consent changes or revisions of other documents originally submitted for review.
- Any serious and/or unexpected events occurring during the study, where required.
- Any new information that may adversely affect the safety of the subjects or the conduct of the study.
- An annual update on the progress of the study and/or request for re-approval, where required.
- Final study report when the study has been completed, where required.

All correspondence with the IEC should be filed by the principal investigator in the Investigator's Study File.

6.2 Ethical conduct of the study

The study will be conducted in compliance with the protocol and CRC standard operating procedures. These are designed to ensure adherence to the ethical principles that have their origin in the "World Medical Association Declaration of Helsinki" (see Appendix), "Malaysian Guidelines for Good Clinical Practice" and applicable regulatory Requirements.

6.3 Informed consent and subject information

Freely given informed consent must be obtained from every subject prior to participation in this study. The investigator must inform every subject in detail about the nature of the study, its purpose, the treatments and the probability of random assignment to treatment groups, those aspects of the study that are experimental, the procedures involved including all invasive procedures and the discomfort they may entail, the reasonably expected benefits the expected duration and the approximate number of subjects involved and the subject's responsibilities.

Study subjects must also be informed that:

- Participation in this study is voluntary and that he/she may withdraw from this study at any time for any reason and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.
- They will be notified in a timely manner if information becomes available that may be relevant to their willingness to continue participation in the study.
- Alternative procedures or treatments that may be available and the important potential benefits and risks of these available alternative procedures or treatments.
- Any compensation for additional costs and/or injury caused to a subject attributable to participation in the study.
- Financial expenses, if any, to the subject for participating in the study as well as prorated payment, if any, to the subject for participating in the study.
- Any foreseeable circumstances and/or reasons under which the subject's participation in the study may be terminated.
- The person(s) to contact for further information regarding the study and whom to contact in the event of study related injury.

Written consent will be obtained from each subject involved in the study. If written consent from the subject is not possible, written consent can be obtained from the subject's representative who is subject's parent or guardian, stating why the patient was unable to sign the consent form. The informed consent form used to document written or oral consent in the study must be received prior to approval from the IEC. If the subject and his/her representative are unable to read, the investigator or designee must explain to the subject the content of the Patient Information Sheet and Consent Form point by point in the presence of an impartial witness. The witness should personally sign and date the consent form. The potential study subject and/or his/her parent/guardian should be given the opportunity to ask questions and time for consideration.

A copy of the Patient Information Sheet and signed Consent Form should be given to the subject or subject's parent/guardian if patient was unable to sign the consent form. The original must be filed by the principal investigator in the Investigator's Study File. A sample of the Patient Information Sheet and Consent Form can be found in the Appendix of this protocol.

6.4 Patient protection procedures

6.4.1 Procedures in the event of Emergency

The investigator is responsible for ensuring that procedures and expertise are available to cope with medical emergencies during the study. An emergency may constitute an SAE.

6.4.2 Procedures in the event of Pregnancy

The subject must be instructed to inform the investigator if she becomes pregnant during the study and seek advice regarding continuation of the study treatment. The investigator should follow up the pregnancy until the outcome is known.

6.4.3 Patient data protection

The investigator must assure that the subjects' anonymity will be maintained

and that the confidentiality of records and documents that could identify subjects will be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements.

- Subjects must be identified only by their assigned identification number and initial on all CRFs
- The investigator will keep a Patient Identification List with complete identification information (name, address, contact number, NRIC number) on each subject.
- Documents not for submission to CRC such as subject's written informed consent form, will be maintained by the investigator in strict confidence.

All the data will be stored in a password encrypted computer which only the principle and co-investigators has access to it. The data will be analyzed by SPSS software using the same computer. Once data analysis is completed, the data will be transferred to password encrypted CD and will be kept in the high security safe in the Emergency Department, Hospital Pulau Pinang.

7 INTRODUCTION AND BACKGROUND

Intravenous administration of saline has become a routine component in resuscitating critically ill adult patients in emergency department. Fluid resuscitation using saline was first described in 1831 during the Cholera endemic.(1) Since then, saline use for replacement or maintenance became the mainstay of critical care. In patients with sepsis and septic shock especially, large volume resuscitation in early stage up to 30ml/kg is crucial in maintaining the hemodynamical stability and to improve survival. (2) Therefore, the selection and administration of resuscitation fluids in septic patients is crucial and must be tailored according to patients' situation (3).

Stewart pointed out that whole body acid–base balance is mainly regulated by strong ion movements through membranes (4). The crystalloid strong ion difference (SID) is the net electrical charge difference of the infusate strong cations minus the anions. The traditional saline-based fluid resuscitation strategy, however, fails to link the physicochemical properties of the crystalloid solution or crystalloid strong ion difference (SID).(5,6,7)

Large volume saline-based resuscitation was found to cause hyperchloreamic acidosis in both abdominal and gynecological surgery patients. (8,9) High chloride content, the dilution effect due to extravascular bicarbonate, and a strong ion difference (SID) per Stewart's formula have been implicated as the causes of acidosis.(10) Hyperchloraemia will alter tubuloglomerular feedback by causing renal vasoconstriction,(11) decreased renal artery flow velocity, blood flow, and cortical tissue perfusion,(12) and ultimately reduced glomerular filtration rate,(13) leading to salt and water retention.

Several studies evaluating the relationship between choices of fluid in resuscitation and metabolic acidosis have been conducted. When compared with crystalloids, colloids have not been shown to improve patient-centred outcomes. (14) On the other hand, recent literatures showed that among all the choices of crystalloids, balanced saline for example hartmanns' solution, is superior in terms of higher survival rate and lower incidence of kidney injury(15-20), due to its similarity to human plasma in their composition and higher strong ion difference, Up to date, there are 2 recognised high SID fluids available in the market, namely Normosol and Plasmalyte. Shin et al(21) had showed that intraoperative fluid resuscitation wih high SID fluid is associated with lower lactate level post-surgery which is vital to improve the survival outcomes. High SID fluids also were proven to better choice in term of reducing the rate of acute kidney injury as they do not produce hyperchloraemia and acidosis.(12, 22)

Study by Omron and colleagues (23) showed that solutions whose SID was greater than 24.5 mEq/L such as one-half normal saline with addition of 75mEq/L sodium bicarbonate (SID= 75mEq/L) demonstrated a progressive metabolic alkalosis and less progressive metabolic acidosis. Kiran et al (24) demonstrated metabolic acidosis in critically ill patients especially with sepsis with septic shock was associated with statistically significant mortality up to 70% which is also consistent with the previous study by Jung et al. (25)

The aim of the study was to determine whether, among patients with severe sepsis and septic shock who needs initial high volume resuscitation, the use of high SID intravenous solution i.e. one-half normal saline with addition of 75mEq/L sodium bicarbonate (SID = 75 mEq/L) as an early fluid choice, when compared with Hartmann solution (SID = 28 mEq/L) is associated with greater change in body pH and bicarbonate level as well other adverse outcomes.

7.1 Potential Risks

Patient might sustain superficial hematoma after venipuncture for blood sampling. Extravasation of study fluid might occur during infusion. Supportive management will be given to minimize the damage should the risks occur.

7.2 Potential Benefits

From the previous literatures, both study fluids are proven to be safe and beneficial to patients.
High SID fluid is hypothesized to normalise the metabolic acidosis faster and to the greater extend as compared to Hartmann's Solution.

8 OBJECTIVES

8.1 Primary objective:

To determine the mean difference of blood pH and bicarbonate level at 2 hours or after 30ml/kg administration of high SID fluid or Hartmann's Solution (whichever occurs first).

8.2 Secondary objective(s):

To determine:

- the mean difference in lactate level at 2 hours,
- all-cause mortality at 30 days,
- development of pulmonary edema,
- the mean length of stay in hospital,
- the incidence of acute kidney injury (AKI) as defined by the AKIN criteria

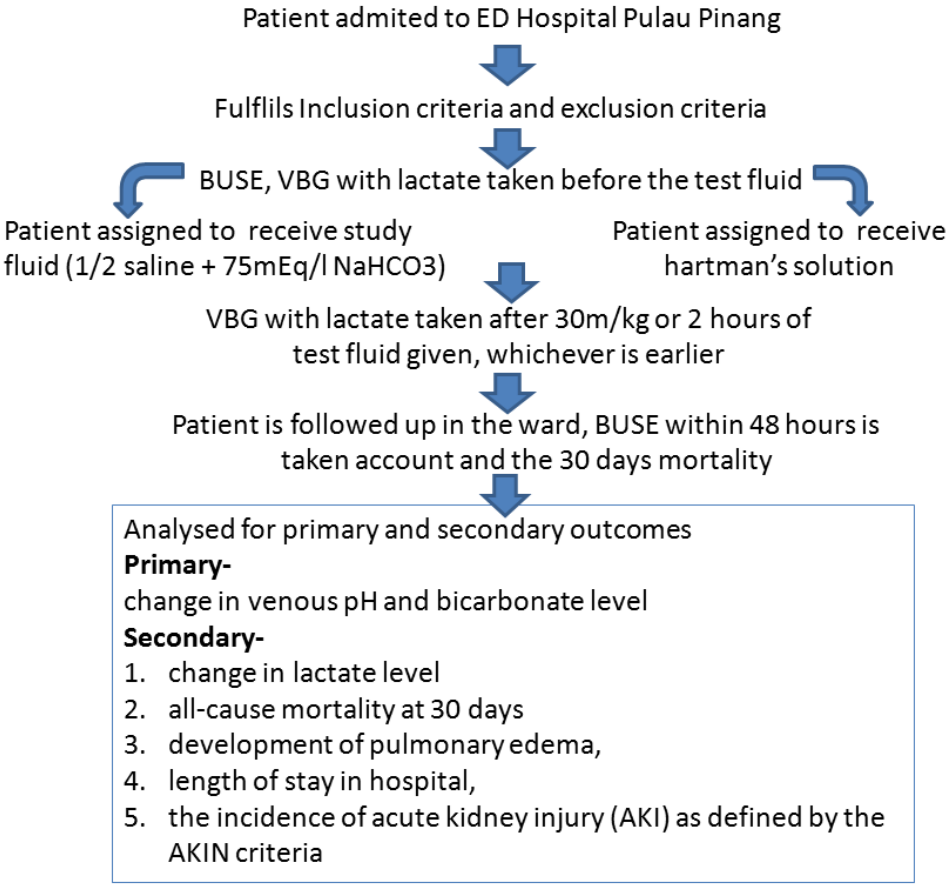
of high SID fluid and Hartmann's Solution

9 STUDY DESIGN

9.1 Overall study design

A Double-blind, Randomized Control Trial

9.2 Schematic diagram of study design:



9.3 Discussion of study design

The study is a double-blind randomized controlled trial with parallel design and an allocation ration of one to one. Eligible subjects are assigned in a 1:1 ratio by means of randomization using online randomizer, http://www.randomiser.com. The code is saved in the randomization log which will only be secured by an assigned pharmacist. A trained nurse or pharmacist will prepare the study fluids (either half saline with addition of 75mEq/L sodium bicarbonate or Hartmann's solution) according to the randomisation list right after a suitable patient is recruited.

Standard 500cc half saline bottle and hartmann's solution will be used during the study. The trained nurse or pharmacist will completely tear off the labels on the bottle replace it with a label with only randomisation number and patient's ID. As for the investigational fluid regime, the trained nurse or pharmacist will initially draw out 37.5mls of half saline and then replace it with 37.5mls of sodium bicarbonate 8.4%. At the end of preparation, the study fluids will be macroscopically indistinguishable.

All clinicians, patients and investigators will be blinded for the coding of the study fluids used during resuscitation. Unblinding of the code will be only done after analysis of the primary outcome was completed except for rare emergency cases when treating physician believes that clinical management depends importantly upon knowledge of whether the patient received high SID fluid or Hartmann's solution.

Subjects receive study fluid and the rate of infusion depends on clinical judgment by the treating physician. Each subject is monitored every 30 minutes for blood pressure, pulse volume and capillary refill time. Blood samples are taken for electrolytes, urea and creatinine measurement, blood gas with lactate at baseline before the initiation of study fluid. When 30ml/kg of study fluid is administered or at 2 hours (whichever occurs first), another blood gas with lactate will be taken. Study fluid may be discontinued depending on the clinician's judgement. If the study fluid needs to be discontinued, the total amount of test fluid will be recorded and the subject will be excluded from the analysis. At the end of 2 hours of resuscitation or after 30ml/kg of study fluid is administered, subjects will be given the usual resuscitation fluid according to the treating physician's judgement.

Subjects are subsequently followed up in the ward for BUSEC within 48 hours and for all-cause mortality in 30 days.

At least one trained staff member will be available throughout the intervention period.

9.4 Study population

All eligible patients including ventilated patients admitted to Emergency Department with severe sepsis or septic shock within the study period.

9.4.1 Inclusion criteria

- age≥18 years
- fulfills 2/3 qSOFA criteria
- presumed infection
- a blood pH at presentation ≤ 7.35
- hyperlactatemia (blood lactate level, >2mmol/L)

*according to Third International Consensus Definitions for sepsis and septic shock 2016 (Sepsis 3), qSOFA criteria are Respiratory rate more than 22 breath per minute, systolic blood pressure less than 100mmHg and altered GCS. Score of 2 or more is associated with mortality rate more than 10%.

9.4.2 Exclusion criteria

- existing cardiac failure, major cardiac arrhythmia, advanced chronic kidney disease or end stage failure
- known pregnancy
- suspected dengue (patient who fulfilled the criteria of probable dengue at presentation)
- primary diagnosis is related to burn, trauma, or drug overdose
- if more than 500cc of resuscitation fluid was administered before enrolment.

9.4.3 Subject withdrawal & drop-out

All subjects can choose to withdraw at any time.

Study fluid may be discontinued depending on the clinician's judgement. If the study fluid needs to be discontinued, the total amount of test fluid will be recorded and patient will be excluded from the analysis.

9.4.4 Procedures for handling withdrawal

Subjects who withdraw or are withdrawn from the study should have the reason(s) for their withdrawal recorded

9.4.5 Subject replacement policy

Withdrawn subjects will not be replaced.

9.4.6 Screening failures

Patients who fail to meet the inclusion and exclusion criteria are defined as screening failures. The investigator will maintain a Screening Log which includes screen failures. The log will document the subject number, subject initials, demographics and the reason(s) for excluding the patient from the study. This log will be kept in the Investigator's Study File. It will be used to determine systematic bias in selection of patients for entry into the study.

10. TREATMENT AND STUDY PROCEDURES

10.1 Description of study fluid/intervention

Standard 500cc Half saline bottle (INFUSOL ® HS) will be used as study fluid. To create a high SID fluid with SID of 75, 75mEq/L of sodium bicarbonate will be added to the 500cc bottle of half saline, which is equivalent to 37.5mls of 8.4% sodium bicarbonate.

10.2 Comparator of study fluid/intervention

Standard 500cc bottle Hartmann's solution (INFUSOL ® HM) which contains sodium chloride 600mg/100ml and calcium chloride 27mg/100ml, potassium chloride 40mg/100ml, sodium lactate 320mg/ml.

10.3 Dosage and administration

Group 1: 30ml/kg of IVD half-normal saline with addition of 75mEq/L sodium bicarbonate

Group 2: 30ml/kg of IVD Hartmann's Solution.
The rate of infusion of study fluids will be given depending on treating physician clinical judgement.

The study fluids will be given via volumetric infusion pump available in Emergency Department Hospital Pulau Pinang.

10.4 Investigational product supply and handling

10.4.1 Supply, packaging and labelling

Each study fluid will be labelled with the following information:

10.4.1.1 Manufacturer's identification
10.4.1.2 Protocol number
10.4.1.3 'For Clinical Trial Use Only' statement
10.4.1.4 Randomisation number
10.4.1.5 Subject's ID
10.4.1.6 Quantity of bottles
10.4.1.7 Storage conditions
10.4.1.8 Expiry date

10.4.2 Storage

The investigational product must be stored in accordance with the manufacturers' instructions. Required conditions for storage will be printed on the medication label. Until the investigational product is dispensed, it must be stored at room temperature below 30^{o}C.
Investigational product should be kept under adequate security by the investigator and only accessible to authorised study personnel.

10.4.3 Dispensing

Upon dispensation, the investigator must write the following in the Investigational Product Dispensing Log: subject ID and initials and date dispensed, total bottles dispensed, batch number and expiry date of product.

10.4.4 Accountability

The investigator or designee must maintain current and accurate record of the receipt, inventory and dispensing, including shipping invoices, of all study supplies. The Investigational Product Accountability Log must include:

- Date received
- Name of study medication and dosage
- Amount currently in storage area
- Label ID number or batch number/Lot number
- Name and initial of person responsible for each investigational product inventory entry/movement
- Amount dispensed to and returned by each subject, including unique subject identifiers
- Amount transferred to another area for dispensing or storage
- Non-study disposition (eg. Lost, wasted, broken)
- Amount destroyed at study site
- Accountability logs must be available for inspection by CRC monitor at any time. Upon completion/termination of the study, unused investigational product must be returned to the sponsor or CRC for reconciliation and destruction.

10.5 Concomitant medication/ treatment

The rate of infusion, time of initiating antibiotics, inotropes will not be interfered by commencement of study fluid.

10.6 Treatment allocation and randomization

- Patients were assigned in a 1:1 ratio by means of randomization using online randomizer, http://www.randomiser.com/.
- The code is saved in the randomization log which will only be secured by an pharmacist assigned by the Principal Investigator.
- Each time when patient is recruited, a trained pharmacist or senior nurse or senior medical officer who is not involved directly in the treatment of the subject will open the randomization log and prepare the test fluid according to the randomization log.
- The following information will be recorded during randomization:
  a. Study ID (assigned during study initiation)
  b. Subject's screening status
  c. Date of informed consent signed by subject
  d. Subject's ID no.
  e. Upon successful randomization, the subject will be assigned a randomization number and study fluid. Document the subject's ID no. and randomization no. on the Patient Enrolment Log and Patient Identification List.

10.7 Blinding & emergency unblinding procedures

All the investigators, treating physician and subjects will be blinded to the study fluid which is given during the treatment.
Generally there should be no need to unblind the allocated study fluid. Unblinding should only be done only in those rare cases in the event that an AE which knowledge of the identity of the test drug is necessary to manage the subject's condition, the treating physician will call the Principal Investigator who will review actual type study fluid given to that subject, identify the test drug

immediately. The Principal Investigator will decide whether unblinding is required.
A detailed report with the date and reason for identifying the study drug will be prepared by the Principal Investigator and informed to IEC. This report must be signed by the treating physician and the Principal Investigator.

Except in the rare emergency cases, the treatment blind will be maintained until all subjects have completed the treatment and the database has been cleaned and locked.

10.8 Baseline assessment and laboratory tests

Baseline parameters and laboratory tests as below will be captured in entry form:

- Social demographics, weight and height
- Co-morbid factors
- Primary disease
- Drug history
- Laboratory data

10.9 Discontinuation and interruption of study fluid infusion

Study fluid may be discontinued depending on the clinician's judgement. If the study fluid needs to be discontinued, the total amount of test fluid will be recorded and patient will be excluded from the analysis.

10.10 Assessment of efficacy

The outcomes of the study are assessed using specific efficacy parameter:

10.10.1 Primary end-point: change in pH and bicarbonate level post study fluid infusion

10.10.2 Secondary end-point: change in lactate level post study fluid infusion

10.11 Assessment of safety

Safety assessments will consist of:

10.11.1 Monitoring and recording all adverse events and serious adverse events

10.11.2 Development of acute pulmonary edema

10.11.3 30 days all-cause mortality

10.11.4 Development of acute kidney injury

11. ADVERSE EVENTS

There should be criteria for observing, recording and reporting AE. If AE would endanger a patient, he/she should be excluded from the study and treated appropriately. The trial should also be stopped if too many AE are observed.

11.1 Definitions

11.1.1 Adverse event (AE)

Any untoward medical occurrence in a subject administered an investigational product and which does not necessarily have a causal relationship with treatment. An AE can therefore be any unfavourable and unintended sign, symptom, laboratory observation or disease temporally associated with the use of the investigational product, whether or not related to the investigational product.

The following should be reported as AE:

- Treatment emergent symptoms which include:
  - Medical conditions or signs or symptoms that was absent before starting study treatment.
  - Medical conditions or signs or symptoms present before starting study treatment and worsen (increase severity or frequency) after starting study treatment.
- Abnormal laboratory values or tests that induce clinical signs or symptoms or require therapy.
- Any adverse experience even if no drug has been administered, for example during run in or wash out phase of the study.
- For studies involving a marketed drug in an established indication, AE includes significant failure of expected pharmacological or biological action.
- Any doubtful event should be treated as an AE.

11.1.2 Unexpected adverse event

Any adverse event not reported in the safety section of the Investigator's Brochure or if the event is of greater frequency, specificity or severity.

11.1.3 Serious adverse event (SAE)

Any adverse event occurring that:

- Results in death
- Is a life threatening adverse experience defined as any adverse event that places the subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. Note that this does not include a reaction that had it occurred in a more severe form, it would have caused death.
- Results in subject hospitalisation or prolongation of existing hospitalisation.

The following hospitalisations are not considered to be SAEs:

- Elective treatment for a condition unrelated to study indication or study treatment
- Occur on an emergency outpatient basis and do not result in admission (unless fulfilling other criteria in SAE definition)

- Part of normal treatment or monitoring of the study indication and are not associated with any deterioration in condition.
- Results in a significant or persistent disability or incapacity defined as any event that results in a substantial and/or permanent disruption of the subject's ability to carry out normal life functions.
- Is a congenital anomaly or birth defect
- Is any instance of overdose, either accidental or intentional (suspected or confirmed)
- Is any other important medical event, based upon appropriate medical judgement that may jeopardize the subject or may require medical or surgical intervention to prevent or avert one of the outcomes listed above.

11.2 Detecting and documenting AE

Information about all AEs, whether volunteered by the patient, discovered by investigator questioning or detected through physical examination, laboratory test or other means, would be recorded on the Adverse Event Page of the CRF and followed up as appropriate.

When eliciting experiences of AE from a subject, ask a standard non-leading question like "Do you feel different in any way since starting the new treatment/the last visit?" This question will be put to the subject in his/her own language at each study visit.

Each AE should be described by:

a) Nature of AE

This should be documented in terms of a medical diagnosis(es). When this is not possible, the AE should be documented in terms of signs and/or symptoms observed by the investigator or reported by the subject.

b) Duration

Start and end dates

c) Assessment of causality

The investigator should attempt to explain each AE and assess its relationship, if any, to the study treatment. Causality should be assessed using the following definitions:

- Very likely
  - The AE follows a reasonable temporal sequence from study treatment administration
  - Abates upon discontinuation of study treatment
  - Reappears on repeated exposure (re-challenge)
- Probable
  - The AE follows a reasonable temporal sequence from study treatment administration
  - Abates upon discontinuation of study treatment
  - Cannot reasonably be explained by known characteristics of the subject's clinical state

- Possible
  - The AE follows a reasonable temporal sequence from study treatment administration
  - But could have been produced by the subject's clinical state or other mode of therapy administered to the subject
- Doubtful
  - The temporal association between study treatment and AE is such that the study treatment is not likely to have any reasonable association with the observed event
- Very unlikely
  - The AE is definitely produced by the subject's clinical state or other mode of therapy administered to the subject

The degree of certainty with which an AE is attributed to study treatment or alternative cause like natural history of disease or concomitant treatment should be guided by the following considerations:

- Time relationship between treatment and occurrence of AE
- De-challenge and re-challenge information, if applicable
- Known pharmacology of the drug
- Dose response relationships
- Lack of alternative explanations i.e. no concomitant drug used and no other inter-current disease
- Reaction of similar nature being previously observed with this drug or class of drug
- Reaction having often been reported in literature for similar drug

d) Severity of AE

- Mild: awareness of signs or symptoms, but they are easily tolerated
- Moderate: enough discomfort to cause interference with usual activity
- Severe: incapacitating, with inability to work or do usual activity

Note that a severe AE is not necessarily serious. The term severe is a measure of the intensity while a serious AE is determined based on regulatory criteria. A life threatening AE is an SAE.

11.3 Reporting SAE

Information about all SAE will be recorded on the Serious Adverse Event Page of the CRF. All events documented in the SAE Form must be reported within 24 hours to Principal Investigator by telephone. The investigator should not wait to receive additional information to fully document the SAE before notifying Principal Investigator. A fax SAE form detailing relevant aspects of the SAE in question should follow telephone report of SAE. The investigator should also comply with the applicable regulatory requirements related to the reporting of unexpected serious drug reactions to the regulatory authorities. Where applicable, information from relevant medical records and autopsy reports should be obtained.

Any death or congenital abnormality, if brought to the attention of the investigator within 6 months after cessation of study treatment, whether considered treatment related or not, should be reported to CRC.

Study contact for reporting SAE:

Name: Dr Yeoh Chun Chiat
Department: Emergency Department
Tel: 019 - 9316939
E-mail: ccyeoh@ummc.edu.my

24 hour contact information for physicians on call will be provided to each site prior to study initiation.

11.4 Treatment and follow up of AE

Treatment of any AE is at the sole discretion of the investigator who should follow up subjects with AE until the event has resolved or until the condition has stabilised. Otherwise appropriate medical care should be arranged for the patient. Abnormal tests should be repeated until they return to baseline levels or an adequate explanation of the abnormality has been found. Any follow up information should be reported to Principal Investigator as soon as it becomes available.

- Pregnancy

A female subject must be instructed inform the investigator if she becomes pregnant within 90 days after given the study fluids. Monitoring of the subject should continue until conclusion of the pregnancy. The investigator should report all pregnancies to Principal Investigator within 24 hours of being notified of the pregnancy.

The partner should be counselled and followed as described above.

11.5 Safety update

Should the side effects reported are serious or unexpected and very likely, probably or possibly related to the study fluid, the Principal Investigator will immediately submit a copy of this information to the IRB/IEC. The IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

12 STUDY CONDUCT

12.1 Study procedures

Any deviation from the study procedures described below will be considered protocol deviation and will be notified to Principal Investigator.

12.1.1 Baseline data and laboratory investigation

Once a patient is recruited as study subject, the following data will be collected at baseline:

- Subject's demography: date of birth/age, national registry identification card number, sex, race, height (cm) and weight
- Background and medical history which includes any diagnosed medical conditions within the previous 12 months, history of medication and medical procedures within the previous 30 days of entry into the study.
- Vital signs

  The following vital signs assessments will be performed:
  - Body weight (kg) or estimated body weight (kg) if patient unable to stand up and height (cm), no shoes in light clothing
  - Pulse in beats/min, taken at the radial artery over 60 seconds.
  - Blood pressure will be measured with a mercury sphygmomanometer at least 2 measurements should be taken with a 2 minute interval between measurements.
  - BP should be measured by the same treating physician whenever possible and on the same arm. All measurements should be to the nearest 2 mmHg. Diastolic BP is determined at Phase V (i.e. disappearance of the Korotkoff sound).
  - Capillary refilling time is time taken for color to return to an external capillary bed after 5-second pressure is applied to cause blanching.

Blood pressure, pulse rate and capillary refill time will be recorded from the initiation of treatment, every 30-minute interval, till 30ml/kg study fluids completed or at 2 hours after initiation of study fluid infusion.
A provisional diagnosis before admission to the ward will be recorded.

12.1.2 Randomisation

- Patients were assigned in a 1:1 ratio by means of randomization using online randomizer, http://www.randomiser.com/.
- The code is saved in the randomization log which will only be secured by an assigned pharmacist.
- Each time when patient is recruited, a trained pharmacist or senior nurse or senior medical officer who is not involved directly in the treatment of the subject will open the randomization log and prepare the test fluid according to the randomization log.
- The following information will be recorded during randomization:
  - Study ID (assigned during study initiation)
  - Subject's screening status
  - Date of informed consent signed by subject
  - Subject's ID no.
  - Upon successful randomization, the subject will be assigned a randomization number and study fluid. Document the subject's ID no. and randomization no. on the Patient Enrolment Log and Patient Identification List.

12.1.3 Follow up

All subject will be followed up in the ward and the following data will be recorded:

- any AE or SAE related to study fluids administration
- BUSEC taken within 48 hours of hospital admission
- any death within 30 days and its cause
- discharge date

12.2 Criteria for stopping subject treatment

Study fluid may be discontinued depending on the clinician's judgement as followed

- subject develops acute pulmonary edema
- subject has clinically improved and does not need further fluid resuscitation
- any situation that the treating physician believes that any further infusion of study fluid might worsen the clinical condition of the subjects

  If the study fluid needs to be discontinued, the total amount of test fluid will be recorded and patient will be excluded from the analysis.

12.3 Sample handling and analysis

12.3.1 Collection

Blood gas analysis will be obtained from peripheral veins, central veins from subjects, kept in plastic syringes preloaded with measured heparin. Blood for electrolytes and creatinine (BUSEC) level will be obtained as the same manner and will be kept in the plain tube, labeled. Total blood taken for a subject will be 5mls, which includes 0.5mls each for blood gas anaylsis(immediately before and after the study fluid is given) and 2mls each for BUSEC (immediately before and within 48 hours after the study fluid is given).

12.3.2 Labelling of blood samples

- The standard labels provided by hospital Pulau Pinang laboratory should be used to label each sample.
- Any hand written additions to the labels should be made using indelible ink
- Labels should not be attached to caps.

12.4 Laboratory analysis

All blood gas will be analysed as point-of-care using ABL 800 machine in the emergency department hospital Pulau Pinang. In the other hand, blood for electrolytes and creatinine level will be analysed at the hospital Pulau Pinang laboratory.

13. DATA MANAGEMENT

All the data will be stored in a password encrypted computer which only the principle and co-investigators has access to it. The data will be analysed by SPSS software using the same computer. Once data analysis is completed, the data will be transferred to password encrypted CD and will be kept in the high security safe in the Emergency Department, Hospital Pulau Pinang for next 5 years and will be destroyed after that. Subjects will not be given to any access to any patient's information and study data.

14. STATISTICAL METHODS

14.1 Sample size and power considerations

Sample size is calculated using PS software. The sample size calculation assumed the following: α value 0.05, power of 0.95 and standard difference of 0.05 from previous study. It's power to detect 0.03 difference in pH between 2 study fluids. The calculated sample size was 73 patients each arm with total sample size 150.

14.2 Randomisation

Randomization is made using online randomizer (http://www.randomiser.com/). Patient will be randomised to receive either Hartmann's solution or half saline with addition of 75mEq/L sodium bicarbonate, ratio is 1:1.

14.3 Analysis

Data analysis will be performed using the SPSS program. Descriptive analysis will be used to describe demographic and disease characteristics of the patients. Percentages and frequencies will be used for categorical variables while means and standard deviations will be calculated for continuous variables. The significance level is set at p-value less than 0.05.

The mean difference of blood pH, bicarbonate level and lactate level between the two study fluids will be analyzed using Independent T-test (normally distributed) or Mann-Whitney Test (non-normally distributed). The all-cause mortality at 30 days, development of pulmonary edema and incidence of acute kidney injury will between the two study fluids will be analyzed using binary logistic regression. The length of stay in hospital between the two study fluids used will be analyzed using Independent T-test (normally distributed) or Mann-Whitney Test (non-normally distributed).

15 ADMINISTRATIVE MATTERS

15.1 Notification of regulatory authorities

All necessary arrangements for the registration and approval of this study with the responsible authorities and the disposition of the required data and document will be undertaken by the Principal Investigator.

15.2 Study initiation

Investigators involved in this study must not enrol any patient prior to completion of a formal meeting conducted by the Clinical Research Associate of CRC. This meeting will include an inventory of study supplies, a detailed review of the protocol and CRF, training on study procedures and other procedures required of GCP. Investigators who are not GCP certified will undergo GCP training during the study.

15.3 Protocol deviation

Any protocol deviation will be documented by the Principal Investigator with rectification as soon as possible. The investigator should be notified immediately. With the exception of emergency situations, no changes or deviations in the conduct of this protocol will be permitted without the prior approval from the Principal Investigator. In the event of any emergency, the

investigators will institute any medical procedures deemed appropriate. All such procedures must be promptly reported to Principal Investigator.

15.4 Study documentation

The investigator must maintain adequate and accurate records to document the conduct of the study and substantiate the study data. These documents are Essential Documents and Source Documents.

15.4.1 Essential documents

These are documents that permit evaluation of the study and the quality of the data produced. The Essential Documents are:

- Signed protocol amendments
- Sample CRFs
- IRB/IEC approval letter, including a dated list of IRB/IEC membership and members' affiliation
- Informed consent form
- CV of investigator and co-investigator
- Correspondences with IRB/IEC, sponsor and CRC
- Interim reports to IRB/IEC
- Site signature log
- Monitor visit log
- Screening log
- Other appropriate documents in accordance with GCP guidelines.

The investigator will maintain an Investigators Study File. This file shall be used to facilitate and ensure filing of all relevant and Essential Documents during and after the study. The investigator will be responsible for keeping the Investigator's Study File updated and ensuring that all required documents are filed. The file will be inspected during monitoring visits.

15.4.2 Source documents

These are original hospital records, clinical charts, subject screening checklist, original laboratory reports, memoranda, pharmacy dispensing records, recorded data from automated instruments, transcriptions certified after verification as being accurate, microfiches, photographic negatives, microfilm, magnetic or electronic media, x-rays, subjects' files, and records kept at the pharmacy, at the laboratories and at medico-legal departments involved in the study.

The investigator must maintain source documents for each patient in the study. All information on CRFs must be traceable to these source documents:

- Patient identification list
- Curriculum vitae
- Site signature/authorization log

15.5 Patient identification list/Enrolment log

The investigator has to maintain a list of all enrolled patients containing the full name, date of birth, date of enrolment, and the randomization number. The list has to show an unequivocal study identification number. The list will be filed in the Investigator's Study File on site.

15.6 Curriculum vitae

The investigator will provide curriculum vitae showing his/her experience in the area of the proposed study. These should be filed at CRC as well as in the Investigator's Study File on site.

15.7 Site signature/authorization log

The investigator must maintain a Signature Log to document signatures and initials of all staff authorized to make entries and/or corrections on CRFs and other study related records or documents. The log will be filed in the Investigator's Study File.

15.8 Monitoring the study

The investigator agrees to cooperate with any monitor from the IEC to ensure that any problems detected in the course of these monitoring visits are resolved.

15.9 Audits and Inspections

The investigators should make available the various records of the trial to health authority inspectors after appropriate notification. The verification of CRFs data will be made by direct inspection of source documents.

15.10 Retention of documents

The investigator shall arrange for the retention of all study documents and records, including subject records, screening log, signed informed consent forms and the patient identification list for at least 3 years after completion or discontinuation of the study.

If the investigator moves or retires, he/she must nominate someone in writing to be responsible for archiving. Archived data may be held in microfiche or electronic record, provided a back up exists and a hard copy can be obtained from it if required.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made with the sponsor or CRC to store these in a sealed container(s) outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storage outside of the site.

15.11 Finance

This is a self-funded study.

15.12 Study Termination and Site Closure

Reasons that may require termination of the study include:

- It becomes apparent that patient enrolment is unsatisfactory with respect to quality or quantity.
- Date recording is inaccurate and/or incomplete
- Deliberate violation of the signed protocol

Should Principal Investigator decide to terminate the study, the investigator will complete the CRFs as far as possible.

15.13 Confidentially

Patients' data are kept strictly confidential by the investigator or any person connected with the work and shall not be disclosed to any third party without the prior written consent of the principle investigator.

15.14 Publication policy

Any proposed publication or presentation (eg. manuscript, abstract or poster) for submission to journal or scientific meeting should be sent to Director General of Health at least 45 days prior to submission for manuscripts, and at least 21 days prior to submission to publishers for abstracts.

15.15 Anticipated subject accrual and duration of the study

This study is expected to start in 2017. The projected study timetable for the study is as follows:

- First patient enrolled is expected in 1st Feb 2017
- Last patient enrolled is expected in 31st Dec 2017

The planned date of last outcome is 31st Jan 2018.

These accrual rates are based on reasonable planning expectations. The investigator should however continually compare the actual and expected accrual rates, and make every effort to ensure that they are as closely matched as possible. If the investigator anticipates major problems with recruitment, or delay in the expected completion date, he/she should discuss this with the CRC staff as early as possible.

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17 APPENDICES

- Data collection forms
- Patient information sheet (in English)
- Patient information sheet (in Bahasa Malaysia)
- Patient's informed consent (in English)
- Patient's informed consent (in Bahasa Malaysia)