

BMJ Open Correlation of measured and calculated serum osmolality during mannitol or hypertonic saline infusion in patients after craniotomy: a study protocol and statistical analysis plan for a randomised controlled trial

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ABSTRACT

Introduction: Brain oedema is a major complication after craniotomy. Hyperosmolar agents have been used as the medical treatment for this condition.

Measurement and estimation of serum osmolality during hyperosmolar agent infusion is of clinical importance to evaluate clinical efficacy, adjust dosage and avoid side effects. However, several studies have shown that calculated serum osmolality may lead to a systematic bias compared with direct measurement. In the present study, mannitol or hypertonic saline (HS) will be used in patients after elective craniotomy. We aim to determine the accuracy of serum osmolality estimation during the application of hyperosmolar agent.

Methods and analysis: The study is a prospective, randomised, double-blinded, controlled, parallel-group design. Adult patients requiring the use of hyperosmolar agents for the prevention or treatment of postoperative brain oedema are enrolled and assigned randomly to one of the two treatment study groups, labelled as 'M group' and 'HS group'. Patients in the M and HS groups receive intravenous infusion of 125 mL of either 20% mannitol or 3.1% sodium chloride solution, respectively. Data will be collected immediately before the infusion of study agents, 15, 30, 60, 120, 240 and 360 min after the start of infusion of experimental agents, which includes serum osmolality, concentration of serum sodium, potassium, urea and glucose. Serum osmolality will be measured by means of freezing point depression. Estimated serum osmolality will also be calculated by using four formulas published previously. Osmole gap is calculated as the difference between the measured and the estimated values. The primary endpoint is the correlation of measured and estimated serum osmolality during hyperosmolar agent infusion.

Ethics and dissemination: The study was approved by the International Review Board (IRB) of Beijing Tiantan Hospital, Capital Medical University. Study findings will be disseminated through peer-reviewed publications and conference presentations.

Strengths and limitations of the study

- The main strength of the study is that: We will demonstrate the correlation of measured and calculated serum osmolality during mannitol and hypertonic saline infusion. The accuracy of serum osmolality estimation during the application of hyperosmolar agents will be investigated in this study, and this will help to determine clinical efficacy, adjust dosage and avoid side effects.
- The main limitation of the study is that: The accuracy of serum osmolality estimation is only determined during single dose of hyperosmolar agent infusion. Since repeated doses may lead to physiological changes, the accuracy of serum osmolality estimation may potentially change over time.

Trial registration number: ClinicalTrials.gov identifier: NCT02037815.

INTRODUCTION

Brain oedema and elevated intracranial pressure (ICP) are potentially devastating complications following various types of intracranial operations,¹⁻³ and appropriate treatments improve cerebral perfusion and reduce damage by local compression of brain tissue.^{4 5} Hyperosmolar agents have been used to ameliorate brain oedema and intracranial hypertension during and after craniotomy, and mannitol and hypertonic saline (HS) are the two most extensively studied and most frequently used in the clinical practice.⁶⁻¹⁰ Although recent meta-analyses suggested that HS might be more effective than mannitol in

controlling intracranial hypertension, no significant differences have been found in the neurological outcome and side effects between the two agents.^{11–14}

The primary mechanism of hyperosmolar agents to control brain oedema is based on the increased osmotic gradient across the blood–brain barrier during drug infusion, and this helps in the removal of water from brain tissue to the vascular space.¹⁵ Clinical studies showed that an osmotic gradient between blood and brain of just above 10 mOsmol/kg was effective in reducing ICP.¹⁶ In clinical practice, serum osmolality can be used as a surrogate measure of the effect of hyperosmolar agents, with either mannitol or HS. The initial target of serum osmolality is often set at 300–320 mOsmol/kg.⁹ Acute renal failure might develop when serum osmolality exceeds 320 mOsmol/kg during mannitol infusion.¹⁷ Therefore, measurement of serum osmolality during hyperosmolar agent infusion is of clinical importance to determine clinical efficacy, adjust dosage and avoid side effects.

Serum osmolality is often measured in laboratory by cryoscopic technique as the reference method.¹⁸ However, in a clinical setting, routine measurement of serum osmolality is not feasible at bedside, neither in the intensive care unit (ICU) nor in the neurosurgical ward. In this situation, clinicians usually estimate serum osmolality by using formulas derived from serum osmoles that can be measured by bedside blood gas analysis or routine laboratory chemical analysis, such as serum sodium, potassium, urea and glucose.¹⁹ However, several studies have shown that during mannitol infusion, calculated serum osmolality may lead to a systematic bias compared to direct measurement.^{20–22} This poor correlation of calculated and measured osmolality during mannitol infusion might be due to the osmole gap, which is the difference between the two values. Up to now, few studies have been carried out to determine the accuracy of estimation of serum osmolality during HS infusion.²¹

In the present study, mannitol or HS will be used in patients after elective craniotomy. Serum osmolality will be measured and calculated during drug infusion. The aim is to determine the accuracy of serum osmolality estimation during the application of hyperosmolar agents. We hypothesise that the correlation of measured and calculated serum osmolality during infusion of HS is better than mannitol.

METHODS AND ANALYSIS

Study design overview

The present study is a prospective, single-centre, randomised, double-blinded, two-arm trial in patients after elective craniotomy.

Study setting and population

The study setting is neurosurgical ICU (30 beds), Beijing Tiantan Hospital (1100 beds), Capital Medical University, Beijing, China.

All patients after elective intracranial surgery admitted to our ICU are screened daily for study eligibility.

Inclusion criteria are:

1. Age between 18 and 65 years;
2. Within 24 h of operation;
3. Require the use of hyperosmolar agents for the prevention or treatment of postoperative brain oedema.

Exclusion criteria are:

1. History of diabetes;
2. History of alcohol abuse;
3. Herniation of brain;
4. Unstable haemodynamic condition: systolic blood pressure (BP) less than 90 mm Hg or need for continuous infusion of vasopressor;
5. Presence of oliguric renal failure;
6. Serum sodium concentration below 130 mmol/L or above 155 mmol/L;
7. Enrolled in another trial.

Consecutive patients are randomly assigned to receive 20% mannitol (M group) or 3.1% sodium chloride solution (HS group). Hyperosmolar agents (20% mannitol or 3.1% sodium chloride solution) are routinely used in our clinical practice for the prevention and treatment of postoperative brain oedema in patients after craniotomy. Indications include ICP above 25 mm Hg, brain oedema shown by CT, poor neurological status due to brain oedema and bulging of brain during operation. Hyperosmolar agents are initiated in some cases because of clinical decline or elevated ICP, but in many others they are instituted based on CT results or empirically.

Randomisation, allocation concealment and blind

The study has a prospective, randomised, double-blinded, controlled, parallel-group design. Consecutive patients are randomly assigned 1:1 to one of the two treatment groups, labelled as 'M group' and 'HS group'. Randomisation is based on a computer generated random digits table and follows a concealed process using sealed and numbered envelopes that allocate the patient to either of the two arms of the study. Patients may be randomised into this study only once, unless they were discharged from the hospital and were readmitted beyond 180 days of the first enrollment.

Twenty per cent mannitol (1098 mOsmol/kg) and 3.1% sodium chloride solution (1054 mOsmol/kg) are nearly equal in osmolality. This enables us to perform blind during the study. After enrollment of the patient, 125 mL 20% mannitol or 3.1% sodium chloride solution will be filled into a sterile 250 mL glass bottle by a pharmacist. Patients and all study personnel except the investigative pharmacist are blind to treatment assignment. The details of the series are unknown to any of the investigators and are contained in a set of opaque and sealed envelopes, each bearing on the outside only the number.

Data collection and trial intervention

At study entry, data on demography, body mass index, history of illness, diagnoses of the patients and the

reason for use of hyperosmolar agents are collected. The surgical site, operation time, type and amount of hyperosmolar agents used during 24 h before the study drug infusion are recorded. Acute Physiology and Chronic Health Evaluation II score (APACHE II) is calculated. Venous blood sample (3 mL) is obtained and concentrations of serum glucose, triglyceride, cholesterol, albumin, globulins, total serum protein and blood urea nitrogen (BUN) are measured by standard central laboratory device.

All enrolled patients are randomised 1:1 to receive 125 mL of either 20% mannitol (M group) or 3.1% sodium chloride solution (HS group). Both fluids are infused via central venous line in 15 min by using an infusion pump. Vital signs, which include heart rate, respiratory rate, non-invasive BP and pulse oxygen saturation (SpO₂) are continuously monitored. Type of fluid intake, cumulative fluid intake, cumulative urine output and cumulative fluid balance are documented immediately before the infusion of study agents (T0), 15 min (T1), 30 min (T2), 60 min (T3), 120 min (T4), 240 min (T5) and 360 min (T6) after the start of infusion of experimental agents. At the same time points, 3 mL arterial blood sample and 10 mL urine sample are collected. Serum and urine osmolality are measured by means of freezing point depression.¹⁸ Blood values of sodium, potassium, glucose and lactate are measured using an ICU bedside blood gas analyser. Urine specific gravity and concentration of sodium are also measured by standard central laboratory devices.

Calculation of serum osmolality and osmole gap

We use four formulas to estimate serum osmolality¹⁹

$$2 \times [\text{Na}^+] \quad (\text{Formula 1})$$

$$2 \times ([\text{Na}^+] + [\text{K}^+]) + \text{BG} + \text{BUN} \quad (\text{Formula 2})$$

$$2 \times [\text{Na}^+] + 0.9 \times \text{BG} + 0.93 \times \text{BUN} \times 0.5 \quad (\text{Formula 3})$$

$$1.9 \times ([\text{Na}^+] + [\text{K}^+]) + \text{BG} + \text{BUN} \times 0.5 + 5 \quad (\text{Formula 4})$$

[Na⁺], serum sodium concentration (mmol/L); [K⁺], serum potassium concentration (mmol/L); BG, blood glucose concentration (mmol/L); BUN, blood urea nitrogen concentration (mmol/L).

Osmole gap is calculated as the difference between the measured values and each of the estimated values shown above.

Study endpoints

The primary endpoint is the correlation of measured and estimated serum osmolality during the infusion of hyperosmolar agent. The differences between the measured and each of the calculated values from different

formulas are compared. Other endpoints include changes in the following values during the infusion of experimental agents: serum and urine osmolality, serum and urine sodium concentration, urine specific gravity, and haemodynamic and fluid balance variables. Changes in haemodynamic and fluid balance variables will elucidate the influence of these two agents on status of circulation.

Current sample size justification

Primarily, we hypothesise that the peak serum osmole gap during HS infusion would be lower than that during mannitol infusion. Previous investigation showed that by using the formula 2 listed above, the peak serum osmole gap during mannitol infusion was 25 mOsmol/kg in patients with brain injury.²⁰ It is expected that the serum peak osmole gap would decrease to 15 mOsmol/kg during the infusion of 3.1% sodium chloride solution. Using the Power and Sample Size Calculation program, we will need to enrol 15 patients in each group to be able to reject the null hypothesis that the mean peak serum osmole gap of the two experimental groups is equal with a probability (power) of 0.8. The type I error probability with testing this null hypothesis is 0.05.

Statistical analysis

All analyses will be according to the intention-to-treat principle, that is, all randomised patients will be analysed in the groups to which they were originally allocated and will be blinded to treatment assignment.

Categorical variables will be presented as numbers and percentages and analysed by the χ^2 test. Continuous variables will be checked for normal distribution and presented as mean and SD or median and IQR as appropriate. Comparison of continuous variables will be performed by using Student t test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables.

We will use Bland and Altman's²³ limits of agreement analysis to clarify the accuracy of estimated serum osmolality calculated by each of the four formulas listed above. Bias is defined as the mean of the difference between measured and calculated values (measured minus calculated). Upper and lower limits of agreement are defined as bias \pm 1.96 SD of the mean bias. The relationship between measured and calculated serum osmolality is also determined with linear regression analysis, and to visualise the results, calculated values are plotted against measured values.

We use repeated measures of analysis of variance for comparing serum osmole gap, serum and urine osmolality, serum and urine sodium concentration, urine specific gravity and haemodynamic and fluid balance variables across different time points (T0–T6) between the two groups (M and HS groups).

All tests of significance will be at the 5% significance level. Analyses are conducted using SPSS V.17.0.

DISSEMINATION

Ethical aspects and informed consent

The trial complies with the latest Declaration of Helsinki. The study was registered on 16 January 2014 at the ClinicalTrials.org (NCT02037815).

Patients, within 24 h of craniotomy, are often unable to provide consent, so written informed consent is obtained from patients' relatives. Immediately after a patient's admission, the ICU physician will introduce the family to the study coordinator. The physician will make sure the family knows the credentials of the study coordinator, and informs them that this person is going to discuss a research programme being conducted, and that this person is qualified to do so. The study coordinator will take the family to a place where they can talk confidentially. Every relevant aspect of the project will be described. The study coordinator will stop frequently, ask if there are any questions and request that the family to repeat in their own words what is being discussed, to make sure they understand.

The study coordinator will explain the following details:

1. The patient may experience brain oedema during the postoperative period, and hyperosmolar agents are needed in this situation.
2. Twenty per cent mannitol and 3.1% sodium chloride solution are standard of care in our institute.
3. According to scientific literatures, HS may be more effective than mannitol for the treatment of elevated ICP. However, there are no differences in clinical outcome and occurrence of side effects between these two agents.
4. Indications and side effects of mannitol and HS will be introduced in detail.
5. The objective of this study is to determine the accuracy of serum osmolality estimation during the application of mannitol and HS.
6. About 30 mL of blood sample will be obtained during the study.

The study coordinator will be especially careful to assure the family that they are free to decline consent without consequences and that they can withdraw consent at any time without impact on treatment. Family members will be provided with contact information of the study coordinator, local coinvestigator and the local ethical committee. Written consent will be obtained in the presence of a witness.

Dissemination plan

Results of the trial will be submitted to international peer-reviewed journals. Results will also be presented at national and international conferences relevant to subject fields.

TRIAL STATUS

The first patient was enrolled on 20 January 2014. The study will be completed in June 2014.

SUMMARY

During hyperosmolar agent infusion, serum osmolality monitoring is important to determine clinical efficacy, adjust dosage and avoid side effects. In the present study, mannitol or HS will be used in patients after elective craniotomy. Serum osmolality will be measured and calculated during drug infusion. The aim is to determine the accuracy of serum osmolality estimation during the application of a hyperosmolar agent. The results of the present study will provide basic information for estimation of serum osmolality during hyperosmolar therapy.

Contributors QL and J-XZ participated in the design of the study and drafted the manuscript. MX participated in the design of the study. All authors edited the manuscript and read and approved the final version of the manuscript.

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Competing interests None.

Patient consent Obtained.

Ethics approval Institutional Review Board of Beijing Tiantan Hospital affiliated to Capital Medical University.

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