PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Li, Qian; Xu, Ming; Zhou, Jian-Xin

VERSION 1 - REVIEW

REVIEWER	Alejandro Rabinstein Mayo Clinic, Rochester, MN USA
REVIEW RETURNED	07-Mar-2014

GENERAL COMMENTS	- The doses of osmotic agents you are proposing to compare are not equiosmolar (i.e. the same volumes of mannitol 20% and HS 3% have different tonicity). This might affect the relationship between serum and calculated Osm or at least should lead to lower Osmolar gaps in the HS group. Thus, the design as written will not allow you to answer the question reliably. - In addition to this methodological concern (which should be fixable), I question the practical usefulnes of the investigation (the primary hypothesis should be confirmed, but not sure what that will change) and even more so how the study proposal for this small study needs to be published... - Not sure I can see any benefit in using calculated rather than measured Osm even if both prove to be comparable. Both require blood draws and the cost of running a full electrolyte panel to calculate Osm will not be lower than measuring the Osm in most centers. Using arterial blood gas for immediate measurement is typically much more expensive. - The hemodynamic and fluid variables to be considered as study endpoints should be specified more clearly - I assume comparing the formulas for calculating osmolality to see which one is more accurate is going to be another study endpoint, yet it is not listed. - How the incidence of re-operation matters in this study is not clear to me and I would not consider a study endpoint, even if clinically very important. If you want to include a clinical endpoint, then at a minimum your osmotic therapies should be equiosmolar and they are not. - I would like to see in the rationale of the study what would be the potential practical benefit to learn that the primary hypothesis is true (i.e. the osmolar gap is indeed smaller with HS)

REVIEWER	Michel W Bojanowski, MD, FRCSC Centre Hospitalier de l'Université de Montreal Montreal, Qc, Canada
REVIEW RETURNED	17-Mar-2014

GENERAL COMMENTS	Hyperosmolar therapy is an essential element in the management of increased intracranial pressure (ICP). Mannitol and hypertonic saline solutions are two effective agents used for this purpose, often in cases where time is needed to prepare for a more definitive treatment. Ideally these agents are administered according to precise measurements of the ICP, although neurological clinical status and/or imagery may be used to warrant their need. Usually they are given in bolus and repeated according to the status of the monitored ICP or according to the patient's clinical response. The use of these agents must be closely monitored since exaggerated hyper-osmolality may lead to medical complications, particularly renal insufficiency. Different formulae are used to calculate the osmolality, but the most accurate result is measured using a cryoscopic technique. Since there is a difference between the calculated result and the measured one, it is important to know how reliable the calculation is in cases when an accurate measurement is not available. Any study that addresses this issue is relevant. In this paper, Li Qian et al proposes a protocol for a prospective, randomized, double blind controlled study to determine the accuracy of serum osmolality estimation after the administration of a hyperosmolar agent. They hypothesize that expected osmole gap would be lower when using 3.1% sodium chloride solution as opposed to mannitol. The statistical methods are appropriate and include an agreement analysis of the results since simple correlation between calculated and measured osmolality may not always imply that there is good agreement between the two methods to evaluate each of these two agents. It is not surprising to expect that the osmol gap would be smaller when using a hypertonic saline solution since, contrary to mannitol, Na+ is itself part of the formula in the calculated measure. However in this study, it is not clear whether the measurements for each patient will be done only after the first administration of the agent or each time the agent is administered. In clinical practice, hyperosmolar agents are usually given several times to maintain a hyperosmolar state. Since repeated doses may lead to physiological changes, the accuracy of serum osmolality estimation, which is the goal of this study, may potentially change over time and, thus, have an impact in the conclusions of the study.

VERSION 1 – AUTHOR RESPONSE

Reviewer Name Alejandro Rabinstein

The endpoints don't seem to match with those in the registry
Responses: Has been corrected in revised manuscript.

The doses of osmotic agents you are proposing to compare are not equiosmolar (i.e. the same volumes of mannitol 20% and HS 3% have different tonicity). This might affect the relationship between serum and calculated Osm or at least should lead to lower Osmolar gaps in the HS group. Thus, the design as written will not allow you to answer the question reliably.
Responses: We use 20% mannitol (1098 mosmol/kg) and 3.1% sodium chloride solution (1054 mosmol/kg) in the study. The two agents are nearly equal in osmolality.

In addition to this methodological concern (which should be fixable), I question the practical usefulnes of the investigation (the primary hypothesis should be confirmed, but not sure what that will change) and even more so how the study proposal for this small study needs to be published...
Responses: As we stated in the introduction section of the manuscript, monitoring of serum osmolality is of clinical importance during hyperosmolar therapy to determine clinical efficacy, adjust dosage and avoid side effects. However, routine measurement of serum osmolality is not feasible at bedside in clinical setting. Clinicians usually estimate serum osmolality by serum osmoles (including serum sodium, potassium, urea, and glucose), and these osmoles are routinely measured by bedside blood gas analysis, especially in ICU. Although, theoretically, the correlation of measured and calculated serum osmolality during hypertonic saline infusion might be better than mannitol, no study has been performed to demonstrate the correlation.

I'd prefer a statistician to quickly review the statistical part
(Should be reviewed by a PharmD as well)

Not sure I can see any benefit in using calculated rather than measured Osm even if both prove to be comparable. Both require blood draws and the cost of running a full electrolyte panel to calculate Osm will not be lower than measuring the Osm in most centers. Using arterial blood gas for immediate measurement is typically much more expensive.
Responses: Blood gas analysis is a routine measurement in the ICU, and usually contains the measurement of blood sodium, potassium and glucose concentration. Calculation of osmolality by these components will avoid additional blood draws and decrease the cost.

The hemodynamic and fluid variables to be considered as study endpoints should be specified more clearly.
Response: Changes of haemodynamic and fluid balance variables will elucidate the influence of these two agents on status of circulation. (added in revised manuscript)

I assume comparing the formulas for calculating osmolality to see which one is more accurate is going to be another study endpoint, yet it is not listed.
Response: Have been added in revised manuscript.

How the incidence of re-operation matters in this study is not clear to me and I would not consider a study endpoint, even if clinically very important. If you want to include a clinical endpoint, then at a minimum your osmotic therapies should be equiosmolar and they are not.
Response: Have been omitted.

I would like to see in the rationale of the study what would be the potential practical benefit to learn that the primary hypothesis is true (i.e. the osmolar gap is indeed smaller with HS)

Response: Although, theoretically, the osmole gap during hypertonic saline infusion might be smaller than mannitol, no study has been performed to demonstrate how much of the osmole gap with hypertonic saline infusion.

Reviewer Name Michel W Bojanowski, MD, FRCSC

Hyperosmolar therapy is an essential element in the management of increased intracranial pressure (ICP). Mannitol and hypertonic saline solutions are two effective agents used for this purpose, often in cases where time is needed to prepare for a more definitive treatment. Ideally these agents are administered according to precise measurements of the ICP, although neurological clinical status and/or imagery may be used to warrant their need. Usually they are given in bolus and repeated according to the status of the monitored ICP or according to the patient's clinical response. The use of these agents must be closely monitored since exaggerated hyper-osmolality may lead to medical complications, particularly renal insufficiency.
Different formulae are used to calculate the osmolality, but the most accurate result is measured using a cryoscopic technique. Since there is a difference between the calculated result and the measured one, it is important to know how reliable the calculation is in cases when an accurate measurement is not available. Any study that addresses this issue is relevant.
In this paper, Li Qian et al proposes a protocol for a prospective, randomized, double blind controlled study to determine the accuracy of serum osmolality estimation after the administration of a hyperosmolar agent. They hypothesize that expected osmole gap would be lower when using 3.1% sodium chloride solution as opposed to mannitol.
The statistical methods are appropriate and include an agreement analysis of the results since simple correlation between calculated and measured osmolality may not always imply that there is good agreement between the two methods to evaluate each of these two agents.
It is not surprising to expect that the osmol gap would be smaller when using a hypertonic saline solution since, contrary to mannitol, Na+ is itself part of the formula in the calculated measure.
However in this study, it is not clear whether the measurements for each patient will be done only after the first administration of the agent or each time the agent is administered. In clinical practice, hyperosmolar agents are usually given several times to maintain a hyperosmolar state. Since repeated doses may lead to physiological changes, the accuracy of serum osmolality estimation, which is the goal of this study, may potentially change over time and, thus, have an impact in the conclusions of the study.
Response: Indeed, we will study the change of serum osmolality during single dose of hyperosmolar agent infusion. We enroll the patients after elective intracranial surgery admitted to ICU for overnight monitoring. Single dose of hyperosmolar agent is usually administered in these patients in our institute. We agree the reviewer's comment that repeated doses of hyperosmolar agents will influence the accuracy of serum osmolality estimation. We will perform further study to clarify osmolality estimation in this situation.