September 13, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12649-review.doc).

Title: Perioperative hyponatremia in children – a narrative review

Author: Cheme Andersen and Arash Afshari

Name of Journal: *World Journal of Critical Care Medicine*

ESPS Manuscript NO: 12649

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewers

Reviewer 02584466

Major suggestions

A) Avoid repeating the same statements in the Abstract, Core Tip, and Discussion. Choose the appropriate section for these statements.

We thank the reviewer for the suggestion. In order to avoid repeating the same statements in the Abstract, Core Tip and Discussion, the following changes have been made:

The abstract has been changed to: "For more than 50 years, hypotonic fluids (crystalloids) have been the standard for maintenance fluid in children. In the last decade, several studies have evaluated the risk of hyponatremia associated with the use of hypotonic versus isotonic fluids in children, leading to an intense debate. Children undergoing surgery have several stimuli for ADH release, such as pain, nausea, vomiting, narcotic use and blood loss. The body's primary defence against development of hyponatremia is the kidneys' ability to excrete free-water. Renal water handling is generally controlled via ADH (antidiuretic hormone). Increased levels of ADH can cause hyponatremia. Hyponatremia defined as plasma sodium level of < 136 mmol / L draws excess water into the cells causing them to swell. This manifests as central nervous system symptoms such as lethargy, irritability and seizures. The risk of symptomatic hyponatremia is higher in children than in adults and certain categories of children require special attention. Symptomatic hyponatremia in children is an emergency and early diagnosis, prompt treatment and close monitoring is essential to reduce morbidity and mortality. The widespread use of hypotonic fluids in children undergoing surgery is a matter of concern and more focus on this topic is urgently needed. In this paper, we review the literature and describe the impact of perioperative hyponatremia in children."

The Core Tip has been changed to: "Hospital acquired hyponatremia is common and children undergoing

surgery are at particular risk. They tend to develop hyponatremic encephalopathy at higher serum sodium concentrations than adults and they have a poorer prognosis. Intraoperative fluids for children should be isotonic as the use of hypotonic fluids induce a higher risk of hyponatremia and hyponatremic encephalopathy. Symptomatic hyponatremia should be corrected with 3% NaCl and close monitoring of the patient and serum sodium level is mandatory to prevent brain herniation and neurological damage from cerebral ischemia."

The Discussion has been changed to: "Several pediatric studies have shown that the use of hypotonic fluids in comparison to isotonic fluids is related to a higher risk of hyponatremia. Thus, it is very hard to justify the use of hypotonic fluids as standard maintenance fluid in children during surgery. An ideal intraoperative fluid for children should have a tonicity and sodium concentration close to the physiological range in children in order to avoid hyponatremia[81]. An addition of 1-2.5% instead of 5% glucose in order to avoid hypoglycaemia, lipolysis or hyperglycaemia is recommended and should also include metabolic anions (i.e. acetate, lactate or malate) as bicarbonate precursors to prevent hyperchloraemic acidosis. Most children need 2-3 mEq / kg / 24 hours of sodium chloride and the target serum sodium is between 135-140 mmol / L.

One specific group of children with an increased risk of hyponatremia are the critically ill children and more specifically children in need of postoperative admission to intensive care units (ICUs)[82,83,84,85,86,87,88]. In general, causes of hyponatremia in critically ill children admitted to ICUs can be categorized in two groups. The first group includes children with normo- or hypervolemic conditions caused by heart failure, iatrogenic induced hyponatremia (secondary to excessive water and / or salt insufficiency), renal insufficiency or SIADH (syndrome of inappropriate ADH secretion)[89]. The second category are children with hypovolemia, which can be caused by an extra-renal volume loss (gastric, diarrhea, burn wounds, interstitial leakage), renal loss (polyuria after acute kidney failure, adrenocortical insufficiency) or excessive use of diuretics.

Hypotonic maintenance fluids in children remain widely used despite several studies indicating increased risk of hyponatremia[90,91,92,93]. Children develop hyponatremic encephalopathy at higher serum sodium concentrations than adults and have a poorer prognosis. It continues to be a risk affecting morbidity and mortality in children and the symptoms are easily neglected as common symptoms secondary to surgery and general anesthesia[94,43].

Monitoring serum sodium levels in patients maintained by fluid infusion is critical, and certainly in children undergoing surgery as they are more vulnerable to hyponatremia than adults. In case of symptomatic hyponatremia close monitoring of serum sodium levels is mandatory as hyponatremic encephalopathy can rapidly progress[95,96,97,98,99,100].

This complex problem which is unfortunately still an ongoing clinical challenge deserves more attention by clinicians not only in an academic context but more importantly in clinical settings as there is ample evidence to support fluid therapy strategies that can reduce the risk of serious consequences for children. Additionally, the medical industry and researchers are urged to put more efforts into developing more appropriate balanced iv solutions for children (table 3) of different ages and different conditions as there continues to be a great variability in the number of solutions available across various regions and countries and with inadequate research on development of new solutions."

B) Attempt to be precise in every statement. The readers should not have to guess the meaning of various sentences. Example: Page 6 "However, there was a greater variation (in what?) among children with the most severe level of pre-operative hyponatremia"

We agree with the reviewer that every statement should be precise. In regard to the sentence mentioned we have changed it to: "However, there was a greater variation in serum sodium levels among children with the most severe level of pre-operative hyponatremia."

C) The language of the manuscript needs intense revision by an expert. This will have the advantage of improving the clarity of many statements.

The language has been revised by an expert and the text have been revised.

a) What is a "basic" salt solution? (page 5, top). Provide its strength.

We thank the reviewer for pointing this out. Basic salt solution is normal saline. The text has been changed to: "This method was simplified in 1986 by Berry, proposing delivery of a bolus of 0.9% normal saline solution to otherwise healthy children over the first hour of surgery[14]."

b) What are "large" and "very large" changes in serum sodium levels in the first few weeks of life? (Page 7, top). Provide ranges of these changes.

The ranges have been provided: "Additionally, there seems to be an adverse association between large (8-13 mEq/L) and very large (>13 mEq/L) changes in serum sodium levels in the first few weeks of life and the risk of impaired functional outcomes at 2 years of age, and in particular neuromotor impairment[70]."

c) Change "...should have an osmolality close to the physiological range....(page 8, second paragraph) to "should have a sodium concentration...". It is important to dissociate in this instance between solutes that are metabolized rapidly and those that are not. For example, the osmolarity of 5% glucose solution is close to the normal range. After it is metabolized, the children are left with a large water load.

This is an important point and we thank the reviewer for pointing this out. The text has been changed to: "An ideal intraoperative fluid for children should have a tonicity and sodium concentration close to the physiological range in children in order to avoid hyponatremia[81]."

d) Monitoring of the serum sodium concentration is critical for managing perioperative patients, indeed all patients who are maintained by fluid infusion. This should be stressed in the Discussion
We have thank the reviewer and agree with the mentioned suggestion. The following text has been inserted in the discussion: "Monitoring serum sodium levels in patients maintained by fluid infusion is critical, and certainly in children undergoing surgery as they are more vulnerable to hyponatremia than adults. In case of symptomatic hyponatremia close monitoring of serum sodium levels is mandatory as hyponatremic encephalopathy can rapidly progress[95,96,97,98,99,100]."

e) Representative cancer types should be added to the Cancer row in Table 2.
Representative cancer types have been added: "Lung cancer (especially small-cell lung cancer), brain tumor, leukemia, lymphoma, pancreas cancer, prostate cancer, ovary cancer, neuroendocrine tumor, squamous cell carcinoma"

f) I did not see any mention in the text of Table 3, which is very important.
Table 3 has been referred to in the discussion: "Additionally, the medical industry and researchers are urged to put more efforts into developing more appropriate balanced iv solutions for children (table 3) of different ages and different conditions as there continues to be a great variability in the number of solutions available across various regions and countries and with inadequate research on development of new solutions."

Reviewer 01971138

A) I have a few suggestions for improving the manuscript. Most of these involve sentence structure, but one change is very important. The authors say that IV solutions should have the same osmolality as plasma. Instead, they should have said the same "tonicity" as plasma. 5% dextrose in water as the same osmolality as plasma but would be disastrous in a post-operative patient.

We thank the reviewer for the comment. The text has been changed to: "An ideal intraoperative fluid for children should have a tonicity and sodium concentration close to the physiological range in children in order to avoid hyponatremia[81]."

B) My suggested changes are incorporated in the text.

The suggested changes in the abstract, core tip and introduction have been made albeit the text in these sections have been edited again to reply to suggestions by reviewer 02584466.

Editor's comments

Thank you for your comments. We have addressed all the comments.

A running title has been provided.

The references in the text have been made in superscript.

A total of 100 references are used.

The references have been set up and follows BPG's Revision Policies for Review.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Critical Care Medicine*.

Sincerely yours,

Cheme Andersen, MD
Department of Anaesthesiology
Juliane Marie Centre
Rigshospitalet
Blegdamsvej 9
2100 Copenhagen
Denmark
E-mail: chemeandersen@gmail.com