Author’s response to reviews

Title: The impact of phosphate balanced crystalloid infusion on acid-base homeostasis (PALANCE study): study protocol for a randomized controlled trial

Authors:

Judith-Irina Pagel (judith.pagel@med.uni-muenchen.de)
Nikolai Hulde (nikolai.hulde@med.uni-muenchen.de)
Tobias Kammerer (tobias.kammerer@med.uni-muenchen.de)
Michaela Schwarz (schwarz@chkmb.de)
Daniel Chappell (daniel.chappell@med.uni-muenchen.de)
Alexander Burges (Alexander.Burges@med.uni-muenchen.de)
Klaus Hofmann-Kiefer (Klaus.Hofmann-Kiefer@med.uni-muenchen.de)
Markus Rehm (Markus.Rehm@med.uni-muenchen.de)

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Author’s response to reviews:

We thank the Editor and the referee for the review of our protocol and the helpful comments. We have revised the manuscript according to their suggestions. The alterations are formatted as underlined text in the manuscript.

Please find below our point-to-point reply.

Editor:

1. Please make sure you have described all SPIRIT items. When an item is truly “not applicable”, it is to your advantage to provide a succinct explanation so that the readers understand the rationale for not addressing the item on the SPIRIT checklist in their protocol.

Thank you for your recommendation. We have reevaluated the SPIRIT checklist as suggested and address each point in the checklist or refer to a page in the manuscript. Therein, we provide explanations for each item that we have labeled as “not applicable” before. Specifically, explanations have been added for items 11c, 17b, 23, 26b and 33.
2. Please fully define all your outcomes following the framework described in Zarin NEJM 2011;364:852-60. Your outcome definition should include these 5 elements: the domain (name of the outcome), specific measurement, metric, method of aggregation, and time point.

Thank you for pointing this out. We have revised the definition of our outcomes and have included all 5 elements in the outcome list as suggested.

3. Please write your methods and procedures using active voice.

We have completely revised the methods section accordingly.

Reviewer #1:

Reviewer #1: I thank the authors for their valuable and interesting protocol. Though very interesting it has some flaws that should be addressed at latest once the results of this study are ready for publishing.

Thank you very much for your review and your very important and valuable comments and questions.

1. What is your definition of major abdominal surgery? 120 minutes is a very short duration for "major" surgery. Do these patients undergo laparatomy or do you also include patients with laparoscopic or transvaginal approaches? I am not sure if a procedure of less than 120minutes can be called "major". You only include gynceological patients? What happens if the surgery is not terminated at the time point 120, does the study continue?

Thank you for your very valuable comment. We understand from reading your comment that this section of the manuscript lacks information and clarity. We recruit only female patients from the GYN department who are scheduled for major abdominal surgery i.e. laparotomy. By routine, these patients will undergo placement of a central venous and arterial line. Laparoscopic or transvaginal approaches are not included. In most cases, the procedures take longer than 120min. The time frame of 120min, however, refers to our observation period, independently from the duration of surgery. After induction of anesthesia we observe the patients for 120min and if the procedure takes longer, which is likely, the patients remain in the study, of course. The administration of the study drug, e.g. phosphate as well as study specific blood draws will only take place during these 120 min of the procedure. Afterwards the anesthetist responsible for the patient will continue according to good clinical practice and clinical standards. The next time point of the PALANCE study will take place on the next day during the postoperative period. We have now revised the sections “Anaesthesiologic management and postoperative care” and “Trial population and selection criteria” and improved this section accordingly.

2. The amount of fluid (30ml/kg ideal body weight/h) you plan to infuse is extremly high! Fluid overload is associated with increased mortality and infectious complications; I would strongly suggest to either lower the amount of fluid infused or make a strong argument as to why such hugh amounts are necessary.
Thank you for your comment. Please find our reply to No2 together with the statement to comment No. 3

3. Power calculation: You based your power calculation on a study using 4000ml/h. Was that study performed in an experimental setting? I cannot imagine that in any OR 4000ml of fluids per hour of surgery are infused! Therefore I am not sure if this study can be used for power calculation as it obviously is not even near current clinical practice and even with 30ml/kgIBW/h of infusion you have far lower fluid volumes than with 4000ml/h for 2 hours. Maybe use your clinic’s data on Ionosteril instead of this study.

We have stated that we base our power calculation on a study using 4000ml over 120min, i.e. 2000ml/ hour (Hofmann-Kiefer et al., 2012, European Journal of Medical Research, Ref22). The study was in fact conducted in gynecology patients at our clinic. An ideal bodyweight of 70kg would result in a max of 4200ml over 120min, which is very similar to the maximum of fluids that were necessary to keep the patients hemodynamically stable in the study of Hofmann-Kiefer et al. on which our power calculations are based. We may further explain our rationale for the fluid regime in the PALANCE study:

We like to point out that we recruit a distinct patient cohort in the PALANCE study. The recruited patients mostly suffer from carcinoma of the ovaries and are undergoing laparotomy. These patients have a higher demand for fluids. We understand the dose of 30ml/kg/ideal bodyweight as a maximum amount of fluid that is given over 120min. This is in concordance with previous studies using similar regimes (please refer to Ref 22: Hofmann-Kiefer et al., 2012, European Journal of Medical Research, and new Ref 33: Rehm et al, 2017, der Anaesthesist). Rehm et al show exemplary in their review the time course for fluid and blood loss as well as the substitution of fluids in a patient suffering from ovarian carcinoma undergoing laparotomy over time. Therein, they calculate this patient’s fluid demand and provide bedside calculations for such a procedure. It is very likely, that, over the time course of 120min, these patients suffer from a blood loss of 1000ml or more. According to current clinical practice, a blood loss should be replaced in a ratio of 4-5:1 with crystalloids (Rehm et al, 2017, der Anaesthesist, new Ref 33). Furthermore, one has to consider losses via urine excretion and insensible perspiration. Taken together, our approach using 30ml/kg/ideal bodyweight seems to fit well for this patient cohort. As mentioned above, previous studies conducted at our institution and with the same patient cohort, used a similar approach (Hofmann-Kiefer et al., 2012, European Journal of Medical Research, Ref 22). The authors showed that a maximum of 30ml/kg/ bodyweight was necessary to keep patients hemodynamically stable and distinct acid-base alterations were described. They furthermore showed that after 120min, Stewart parameters of acid-base shifted as predicted. Based on their fluid regime and the observed shifts, we aim now to counteract precisely those alterations using the proposed sodium glycerophosphate regime. Therefore, we need not only to choose the right cohort of patients, but also similar conditions where these acid-base shifts take place. In the Editorial to one of the earliest studies conducted at our institution (Scheingraber S, Rehm M et al, Rapid saline infusion produces hyperchloremic acidosis in patients undergoing gynecologic surgery. Anesthesiology 1999; 90:1265–70), considering the fluid and volume losses during major gynecological surgeries, the authors Donald S. Prough and Akhil Bidani specifically welcomed the amount of fluid given (5000ml over 120min) in this study setting. Nevertheless, we understand that the reader might struggle at first with the unusual high amount.
We have added the term “maximum” to the dose and have added the information provided here to the manuscript on page 11 as well as the new reference (Rehm M et al, 2017, der Anaesthesist, new Ref 33). We sincerely hope our strategy and rationale for the amount of fluids given in this study have become clear.

4. Even though the topic is scientifically very interesting, I am not sure of its clinical relevance. Additionally I think the issue of changes in acid-base homeostasis and the benefits of perioperative phosphate supplementation should be investigated separately.

Thank you for your comment. The Stewart concept of acid base describes the relationship of phosphate supplementation for the maintenance of a stable acid base homeostasis. Although this concept is scientifically acknowledged, its implementation in clinical practice is still not well established. Since we realize from the comment that the relationship between phosphate supplementation and changes in acid-base homeostasis have not been made clear enough, we may point out again the Stewart equation for [A-]:

\[ [A-] = [Alb \times (0.123 \times \text{pH} - 0.631)] + [Pi \times (0.309 \times \text{pH} - 0.469)] \]

and the relationship between [A-] and pH:

\[ [A-] \downarrow \rightarrow \text{Alkalosis and/or } [A-] \uparrow \rightarrow \text{Acidosis} \]

As described in the equations, phosphate is specifically important for an adequately balanced acid-base and its supplementation might prevent the known disturbances of fluid administration and thus destabilization of [A-] from happening. Key aspect of the planned investigation is to test the applicability of a phosphate balanced crystalloid solution in order to maintain acid-base homeostasis based on Stewart’s concept. Although the general benefits of perioperative phosphate supplementation would be worth investigating in a separate study, it is the exact focus of our trial to investigate the relationship between phosphate supplementation and acid-base homeostasis. We will also look at possible additional benefits arising from phosphate supplementation, as described in the manuscript. The main endpoint of the study, however, is to stabilize [A-] and as such, the pH via the preemptive application of phosphate. In previous studies, the shifts of acid-base in this specific patient cohort have already been described (please see Ref. 22) and in fact delivered the base for the present trial (please also have a look at the response to comment No 3). Therefore, the aim is to study phosphate supplementation and acid-base disturbances together. The prevention of acid-base shifts in these patients maybe highly beneficial and the other estimated benefits of phosphate supplementation have been described in the manuscript on pages 6-7. Furthermore, as a minor goal, we sincerely hope to direct the clinician’s attention towards the applicability of Stewart’s concept of acid base for clinical practice.