Acid-based disturbances due to perioperative fluid therapy with slightly alkalized and acid-based neutral balanced crystalloids: a comparative study

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ABSTRACT

The study aimed at comparing the effects of perioperatively administered balanced crystalloid infusion solutions, containing varied quantities of metabolizable anions, on homeostasis. In the prospective randomized open label study, patients were assigned to Plasmalyte (PL) and Ringerfundin (RF) Groups. The infusion solutions were parenterally administered at 1000 mL/6 hours. Arterialized capillary blood was sampled at the time of transfer to the Intensive Care Unit (ICU) (Time 0), and again at both 2 and 6 hours from Time 0. The collected blood was tested for blood gas parameters. A total of 112 patients were enrolled in the study. There was no significant difference (P=0.329) in baseline pH values between the same-sized PL and RF Groups, with median pH values of 7.34 and 7.32, respectively. Similarly, no significant differences were seen in pH values measured after 2 hours (P=0.436), with median values of 7.38 for the PL Group and 7.37 for the RF Group. Finally, no significant differences were observed after 6 hours (P=0.528), with median values of 7.41 and 7.40, respectively. Over time, pH values increased significantly in both groups (P≤0.001). There were no significant changes in either baseline base excess, actual bicarbonate, standard bicarbonate, partial pressure O2 and CO2 values, measured after 2 and 6 hours between the PL and RF Groups. The study failed to show differences between the balanced solutions Plasmalyte, in 5% glucose, and Ringerfundin, on the effects of pH and other acid-base parameters in patients receiving postoperative care following elective surgery.

Key words: crystalloids, fluid therapy, Plasmalyte, Ringerfundin, acid base, internal environment

INTRODUCTION

Fluid therapy is an integral part of perioperative care for surgical patients. The intervention aims to maintain adequate circulating volume which, together with the normal function of the cardiovascular and respiratory systems, is essential for perfusion and oxygenation of tissues and prevents the development of complications associated with hypovolemia, hypoxemia and hypoperfusion. Impaired tissue perfusion with acidosis also contributes to capillary leak syndrome, further aggravating hypovolemia. (1) The key issues in perioperative fluid management are not only a determination of adequate volume and timing of administration but also the type of infusion solution used. (2-4)

The aim of the article is to add to the discussion on selecting appropriate crystalloid solutions as crystalloids constitute a substantial volume of perioperative fluid replacement. Relatively less attention is paid to colloid solutions, although their use is also a matter of ongoing lively debate and suggests that succinylated gelatin should be preferred. As for crystalloids, the use of so-called balanced solutions is currently strongly recommended over unbalanced fluids or normal saline. (5,6)

At the forefront of clinical practice are two commercially produced medicines, Plasmalyte (Baxter Healthcare) and Ringerfundin (B. Braun). The two products differ in composition and thus, theoretically, in indications and expected effects. The older Plasmalyte was originally designed as slightly alkalizing, with a pH of 6.5-8.0, as compared with the newer Ringerfundin with a pH of 5.1-5.9. A more important difference, however, is in potential base excess (BEpot), that is, their ability to influence the body's pH after being metabolized. The BEpot values for Plasmalyte and Ringerfundin are +26 mmol/L and 0 mmol/L, respectively. This means that Ringerfundin was designed as acid-base neutral and should be perceived as more physiological by the organism.

OBJECTIVE

The study aimed at analyzing changes in the internal environment of the organism following perioperative administration of a balanced alkalizing crystalloid solution,

as compared with a balanced pH-neutral crystalloid.

METHODS

Study design

The study was designed as a single-center, randomized, interventional, prospective study and approved by the University Hospital Olomouc and Faculty of Medicine and Dentistry, Palacký University Olomouc Ethics Committee. Patients included in the study were not required to give informed consent. The study was entered in the ClinicalTrials.gov database under the number NCT02691676. It comprised patients over 18 years of age undergoing surgery at the hospital's Department of Surgery I and subsequently placed in an Intensive Care Unit (ICU) bed. As there were no limitations concerning the type of surgery, these involved a wide range of abdominal and thoracic procedures; however, all of them were elective procedures. No patients were critically ill, being classified as American Society of Anesthesiologists (ASA) III or less. Sample collection and processing

To determine the present status of the internal environment, arterialized capillary blood was drawn from the fingertip at the time of patient transfer from the operating room to ICU (Time 0), and again at 2 hour (Time 2) and 6 hour intervals (Time 6) from Time 0. The blood specimen was tested in the laboratory using the Astrup method to measure the following parameters: pH, BE, actual bicarbonate (aBi), standard bicarbonate (sBi), partial pressure of oxygen (pO2) and carbon dioxide (pCO2). These values were entered into a table and statistically analyzed. Patients Arms were adjusted for age and length of surgery to allow their comparison.

INFUSION SOLUTIONS

The following infusion solutions were parenterally administered using a central or, more frequently, peripheral venous catheter:

Arm 1: Plasmalyte in 5% glucose infusion solution (PL), manufactured by Baxter Healthcare as slightly alkalizing (Na+ 140; K+ 5.0; Mg2+ 1.5; Cl- 98; acetate 27; gluconate 23)

Arm 2: Ringerfundin infusion solution (RF), manufactured by B. Braun as acid-base neutral (Na+ 145; K+ 4.0; Mg2+ 1.0; Ca2+ 2.5; Cl- 127; acetate 24; malate 5.0).

At the time of transfer to the ICU, patients were randomized into PL and RF Arms. Parenteral administration of the two solutions was initiated immediately after collection of the first blood sample at 166mL/hour. Thus, all patients received 1000 mL of infusion solution over 6 hours. Patients requiring more rapid fluid replacement due to postoperative hypovolemia were excluded from the study. Patients were routinely rewarmed with a warm air blanket and received humidified oxygen via a face mask or, in case of good oxygenation, via a nasal cannula.

STATISTICAL ANALYSIS

The data was processed with the IBM SPSS Statistics v. 22 statistical software. The significance of changes in parameters over time in both groups was assessed using paired Student's t-test with the Bonferroni correction. The baseline values, as well as those obtained after 2 and 6 hours in the PL and RF Groups, were compared with a two-sample t-test and Mann-Whitney U test. The association between changes in the parameters was assessed with Spearman's rank correlation. The normality of data was verified with the Shapiro-Wilk test. All tests were performed at a level of significance of 0.05. The Spearman's rank correlation (r) may range between -1 and +1. Values close to zero mean that a change in pH does not correlate with a change in that particular parameter. In such a case, the level of significance is $P \geq 0.05$. The closer r is to +1 or -1, the stronger the association. In case of a significant correlation, $P < 0.05$.

RESULTS

Patients

The sample comprised 112 patients. The two Arms (Pl and RF respectively) were homogeneous with respect to both patient age (P=0.549) and length of surgery (P=0.481). In the PL Arm (n=56), the median patient age was 65 years (range, 22-86 years) and the median length of surgery was 1.5 hours (range, 0.5–5.5 hours). In the RF Arm (n=56), the median age was 35 years (range, 32–89 years) and the median length of surgery was 1.5 hours (range, 0.5–3.5 hours).

pH values

There were no significant differences in baseline pH values between the two Arms (P=0.329). The median pH values for the PL and RF Arms were 7.34 (range, 7.18–7.51) and 7.32 (range, 7.16–7.46). Similarly, no significant differences were seen in pH values measured after 2 hours (P=0.436), with median values of 7.38 (range, 7.2–7.5) for the PL Arm and 7.37 (range, 7.2–7.5) for the RF Arm.

Finally, no significant differences were observed after 6 hours (P=0.528), with median values of 7.41 (range, 7.24–7.53) and 7.40 (range, 7.29–7.46) for the PL and RF Arms, respectively (figure 1).

Correlation between changes in pH and changes in pCO2, pO2, BE, aBi and sBi after 2 hours

There were no significant differences in pH changes after 2 (P=0.486) or 6 hours (P=0.177) between the PL and RF Arms. Over time, pH values increased significantly in both Arms (P=0.001 for all comparisons).

BE, aBi, sBi, pO2 and pCO2 values

There were no significant changes in either baseline BE, aBi, sBi, pO2 and pCO2 values or those measured after 2 and 6 hours between the PL and RF Arms. Table 1 shows the significance of Student's t-test or Mann-Whitney U test and documents the level of statistical significance of P-values for differences in the studied parameters when comparing the PL and RF Arms. Differences in the parameters at Time 0, +2 and +6 hours between the two Arms did not reach statistical significance.

PL Arm

A change in pH was significantly correlated with changes in pO2 (r=0.299), BE (r=0.442) and sBi (P=0.503).

RF Arm

A change in pH was significantly correlated with changes in BE (r=0.608) and sBi (r=0.663).

Correlation between changes in pH and changes in pCO2, pO2, BE, aBi and sBi after 6 hours

PL Arm

A change in pH was significantly correlated with changes in pCO2 (r=-0.512), BE (r=0.670) and sBi (P=0.575).

RF Arm

A change in pH was significantly correlated with changes in pCO2 (r=-0.696), BE (r=0.811) and sBi (r=0.856). For the RF Arm, stronger correlations were found between a change in pH and changes in the other parameters (figures 2 to 6)

Table 1. Significance of tests (P-value) for comparison of blood gases and other parameters in both arms: Plasmalyte (PL) and Ringerfundin (RF)

PL vs. RF Arms	pH	BE	aBi	sBi	pO2	pCO2
Baseline values (Time 0)	0.329	0.579	0.344	0.924	0.822	0.069
Time 2	0.436	0.751	0.372	0.690	0.125	0.129
Time 6	0.528	0.759	0.440	0.581	0.842	0.213
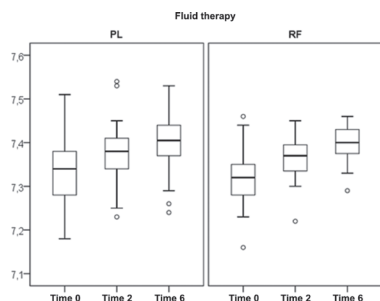
Figure 1. pH values in the Plasmalyte (PL) and Ringerfundin (RF) Arms at Time 0, +2 and +6 hours (pH development for both arms)
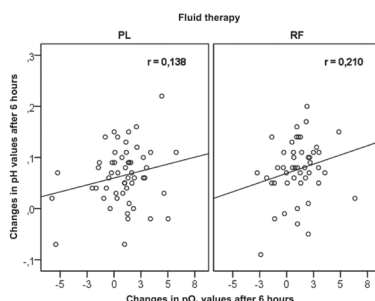

Figure 2. Changes in pH and partial pressure of Oxygen (pO2) values in the Plasmalyte (PL) and Ringerfundin (RF) Arms after 6 hours (non-significant correlations)
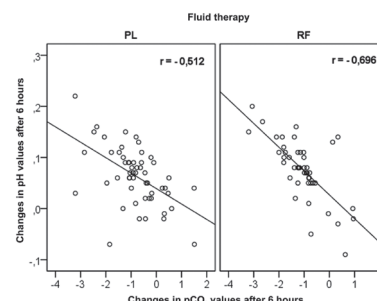

Figure 3. Changes in pH and partial pressure of carbon dioxide (pCO2) values in the Plasmalyte (PL) and Ringerfundin (RF) Arms after 6 hours (significant correlations)
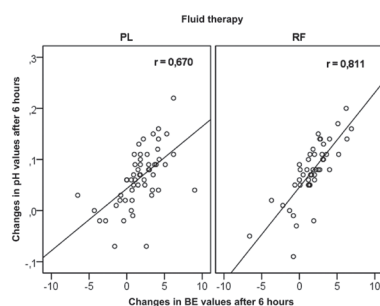

Figure 4. Changes in pH and Base excess (BE) values in the Plasmalyte (PL) and Rinferfundin (RF) Arms after 6 hours (significant correlations)
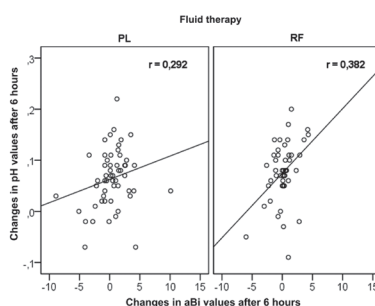

Figure 5. Changes in pH and actual bicarbonate (aBi) values in the Plasmalyte (PL) and Ringerfundin (RF) Arms after 6 hours (significant correlations)
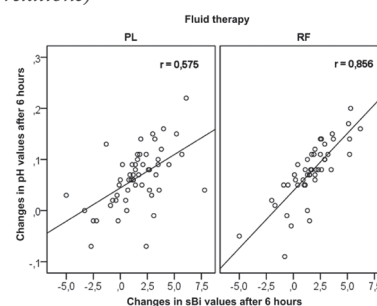

Figure 6. Changes in pH and standard bicarbonate (sBi) values in the Plasmalyte (PL) and Ringerfundin (RF) Arms after 6 hours (significant correlations)

DISCUSSION

Results suggest that with regard to changes in blood gas parameters, both Plasmalyte, in 5% glucose, infusion solution and Ringerfundin infusion solution are equally suitable for postoperative hydration therapy. The study showed no significant differences in the analyzed parameters between the two solutions; in particular, adjustments in pH were completely analogical in both patients Arms. It is well known that improvements in blood gas parameters following surgery are contributed to by other factors, especially correction of hypothermia and restoration of normal respiration. The analysis of summarized data obtained from the entire study sample also showed significant correlations between changes in pH and increased pO2 at two (six) hours after surgery and decreased pCO2 at 6 hours postoperatively. On the other hand, no significant associations were found between changed pCO2 values and changes in BE, aBi and sBi after 2 hours. At 6 hours postoperatively, changes in pCO2 were significantly correlated with changes in aBi but not with changed BE and sBi values.

When compared with unbalanced fluids, balanced solutions have the advantage that, apart from more or less optimal amounts of sodium, potassium, magnesium and other minerals, they also contain metabolizable organic anions such as acetate, gluconate, malate or lactate, capable of balancing variations in the internal environment of the organism. This is mainly the buffering effect that reduces ionic and pH changes.

The commercially available fluids vary not only in the amounts of organic anions and pH but also in the amounts of individual metabolizable anions. The composition of crystalloid solutions is reflected in the direct effect on pH of the organism, its ability to buffer changes and the overall impact on minerals in the body.

These solutions have also been shown to have renoprotective effects which are likely to be related to their osmotically induced diuretic effect. (7) However, they may also stress the organism by increased oxygen consumption and resting energy expenditure as they are metabolized. (2) Depending on their variations, individual crystalloid solutions may show various therapeutic effects. As for the solutions used in this study, it should be mentioned

that Ringerfundin has a calcium content greater than zero and a documented slightly better effect on potentiation of diuresis, nor is it associated with an increase in bilirubin concentration. (8)

In case of Plasmalyte, its theoretically stronger alkalizing effect can be used to advantage by increasing the supply of metabolizable anions. This, however, was not confirmed by the present study although the results could be different following more intensive fluid resuscitation. Some experimental studies have documented the fact that a portion of the administered anions may be excreted by the kidneys without being involved in metabolic processes in any way. This is mainly relevant to gluconate. In vivo, however, the buffering, or alkalizing, ability of the solution may not correspond with the theoretical assumptions, (7,9) as shown in the present study as well.

In any case, the two solutions should not differ in their metabolic demands on the organism. (8) The etiological causes of postoperative acid-base disturbances are multifactorial. Even administration of an acid-base neutral solution has a positive effect on postoperative adjustments in pH through improved microcirculation and tissue metabolism. Yet severely acidotic patients may benefit from the targeted potentially alkalizing effect of Plasmalyte. This, however, was not confirmed by the present study, as the sample comprised no severely acidotic patients.

A separate issue is to determine the optimum volume of fluid replacement. The classical approach, that is, a standard, relatively high dose of crystalloids exceeding the perioperative fluid loss, generally leads to hyperhydration and, in patients predisposed to the development of edema, a perioperative weight gain of as much as 7–10 kg. (11,12) Hyperhydration is associated with a range of adverse consequences, such as increased inflammatory response of the organism, impaired healing of wounds and anastomoses and higher rates of inflammatory, respiratory and circulatory complications. (11-14)

In patients undergoing major surgery, the current trend is perioperative fluid restriction, also contained in the ERAS protocol. It aims at replacing the actual fluid loss only, both by bleeding which may be roughly estimated and by evaporation from the skin, wound and airways, ranging from 0.5 to 1.0 mL/kg/hour. The fluid-restrictive strategy refers to fluid volumes of 5–15 mL/kg/hour administered during the surgery or < 3.3 mL/kg/hour administered on the day of surgery. (15,16) The strategy appears to be beneficial mainly in major surgeries lasting more than 3 hours. (4,17)

In such procedures, the optimal strategy is personalized fluid replacement based on objective parameters such as the mean arterial pressure, pulse rate, urine output, central venous pressure and, if possible, inferior vena cava ultrasound. These parameters may give a more accurate estimate of the actual amount of intravascular fluid or its hemodynamic adequacy so that fluid administration may be controlled based on the response to the therapy.

However, mostly healthy adults undergoing less extensive and shorter surgeries (e.g. hernioplasty, cholecystectomy or mastectomy) were shown to benefit from a more liberal strategy (40 mL/kg/hours as compared with 15 mL/kg/hour), with lower incidence rates of postoperative nausea, vomiting and dizziness, as well as improvements in general well-being and other subjective recovery measures. (18) A feasible method for an approximate estimate of fluid loss is regular weighing of patients. Naturally, estimating the needed fluid amounts is not as good as the use of semi-invasive monitoring of hemodynamic parameters, such as LiDCO, NiCO, PiCCO or Vigileo. However, these methods are of real benefit only to patients with severe comorbidities or to certain types of procedures. Moreover, they are still not routinely available in all centers.

The present study was limited by the fact that capillary blood analysis, particularly in the early postoperative period, may not be fully representative of the internal environment of the organism. This, however, should not influence the comparison of the two solutions as the type of sampling was identical in both subgroups. Moreover, there are studies with similar results yielded by analyzing blood gases from both capillary and arterial blood. While pCO2 and pH are exactly the same with both types of sampling, some variation in values may be assumed in case of pO2, especially if blood is drawn from the fingertip. To obtain pO2 values, sampling blood from the earlobe is more convenient10.

Another limitation is the fact that all patients were administered the same amount (1000 mL) of the crystalloid solutions irrespective of their body weight. Finally, body temperature was not measured and recorded at the time intervals of the study. In the Plasmalyte Arm, the Plasmalyte in 5% glucose infusion solution was used. The results can also be applied to the use of Plasmalyte without 5% glucose, because 5% glucose does not alter the Plasmalyte ionic composition or bases quantity.

CONCLUSION

Despite theoretical variations in the effect of the balanced solutions Plasmalyte in 5% glucose and Ringerfundin on the pH of humans, our study failed to show different effects on changes of pH and other acid-base parameters in patients receiving postoperative care following elective surgery. A potential preference for one or the other infusion solution is only reasonable in a limited number of surgical patients in whom balanced solutions constitute a part of pharmacotherapy of homeostatic imbalance rather than fluid replacement.

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