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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Does fluid resuscitation with balanced solutions induce electrolyte and metabolic abnormalities? An in vitro assessment

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Abstract

Background: Popular intravenous fluids in clinical use may have an impact on electrolyte concentration and metabolic balance and should be considered as powerful pharmacological agents. There is a growing body of evidence that fluid therapy should be more individualised and preferably based on balanced solutions.

Aim: We sought to investigate the impact of three commonly used balanced fluids on electrolytes and metabolic equilibrium in an in vitro setting.

Methods: Study group comprised 32 healthy male volunteers (without history of any acute/chronic disorder or known metabolic abnormality), aged 21–35 (29 ± 4) years, weight 59–103 (81.2 ± 9.8) kg, from whom blood samples were withdrawn. The whole blood was diluted in 4:1 ratio with the study solutions to make an end-concentration of 20 vol.% of each solution. The test solutions included balanced crystalloid (Plasmalyte®, Baxter, Poland [PL]), succinylated gelatin (Geloplasma®, Fresenius Kabi, Poland [GEL]) and 6% HES 130/0.4 (Volulyte®, Fresenius Kabi, Poland [HES]).

Results: All fluids caused comparable degree of haemodilution. PL and GEL decreased (104 mmol/L, interquartile range [IQR] 103–105; and 106 mmol/L, IQR 105–107.5, respectively), whereas HES increased the concentration of Cl^- to 109 (IQR 108–110) mmol/L. PL and HES decreased (136, IQR 136–137 mmol/L; and 138 mmol/L, IQR 137–139, respectively), whereas GEL increased the Na^+ level to 140.5 (IQR 140–141) mmol/L. PL and HES decreased osmolality (277.2 mOsm/kg, IQR 275.7–278.4; and 280.9 mOsm/kg, IQR 279.3–282.0, respectively). GEL increased it to 285.7 (IQR 283.7–286.8) mOsm/kg. All test solutions caused a similar statistically significant ($p < 0.05$) drop in base excess and bicarbonate concentration, and these fell outside the reference values. Due to its composition, GEL caused a significant increase in lactate concentration. HES and GEL caused a statistically significant drop in strong ion difference value. Due to high lactate level, the effect of GEL was most pronounced.

Conclusions: Balanced intravenous solutions should be safe in terms of their impact on human plasma electrolyte and metabolic equilibrium when administered to replace up to 20% of blood volume. In metabolic acidosis, balanced succinylated gelatin should be used with caution. Therefore, arterial blood gas analysis should be performed in patients in whom significant amounts of fluid are administrated, preferably with assessment of Cl^-, Na^+, lactate concentrations as well as pH, osmolality, and strong ion difference.

Key words: resuscitation fluid, balanced crystalloid, balanced colloid, acid-base balance, strong ion difference

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INTRODUCTION

Fluid administration is probably the most common therapeutic intervention in perioperative and intensive care medicine. Intravenous fluids are used for maintenance of fluid balance, replacement of volume losses, and augmentation of intravascular volume when relative volume depletion exists [1]. Popular intravenous fluids in clinical use may have an impact on electrolyte concentration and metabolic balance, and each resuscitation fluid should be considered as a powerful pharmacological agent [2].

There is a growing body of evidence that fluid therapy should be more individualised and preferably based on bal-

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Table 1. Composition of test solutions according to manufacturer information in comparison with human plasma and undiluted sample

Parameter	Reference values in human plasma	Baseline values in studied population	PlasmaLyte (PL)	Volulyte (HES)	Geloplasma (GEL)
Na^+ [mmol/L]	135–145	139.5 (138–140)	140	137	150
K^+ [mmol/L]	4.5–5.5	3.95 (3.9–4.1)	5.0	4.0	5
Mg^{+2} [mmol/L]	0.8–1.0	–	1.5	1.5	1.5
Cl^- [mmol/L]	94–111	108 (107–109)	98	110	100
CH_3COO^- [mmol/L]	–	–	27	34	–
$C_6H_{11}O_7^-$ [mmol/L]	–	–	23	–	–
Lactate [mmol/L]	1.0–2.0	1.35 (1.1–1.6)	–	–	30
Osmolality [mOsm/kg]	291	284.6 (282–286)	295	286.5	295
pH	7.35–7.45	7.36 (7.34–7.38)	7.4 (6.5–8.0)	5.7–6.5	5.8–7.0
Ca^{+2} [mmol/L]	1.0–1.3	1.22 (1.2–1.24)	–	–	–
HCO_3^- [mmol/L]	23–27	23.5 (22.8–24.2)	–	–	–

anced solutions [3]. Although normal saline (NS, 0.9% sodium chloride) is still the most commonly prescribed solution, it may lead to hyperchloraemia and metabolic acidosis due to its supraphysiological chloride content [4, 5]. In consequence, deterioration of renal blood flow, reduction in gastric mucosal blood flow, proinflammatory cytokine production, and immunomodulation may appear [5, 6]. Because NS contains a significant amount of sodium, it can also induce hypernatraemia when administered in an uncontrolled way [3].

The osmolarity of intravenous fluids causes water shifts through cellular membranes and leads to disturbances of metabolic equilibrium, which usually differ between crystalloids and colloids. These effects are preferably analysed using the Peter Stewart approach, which focuses on strong ion difference (SID) assessment. Intravenous fluids with different SID values produce various derangements of acid-base status. Generally, fluids with SID>HCO_3^- produce alkalosis, fluids with SID<HCO_3^- produce acidosis, and if the SID of a fluid equals HCO_3^-, pH is unchanged [7].

Therefore, we sought to investigate the impact of three commonly used balanced fluids on electrolyte and metabolic equilibrium in an *in vitro* setting.

METHODS

The study was approved by the Bioethics Committee of the Medical University of Silesia in Katowice (KNW/0022/KB1/158/15/16). Written informed consent was obtained from 32 healthy volunteers (with no history of any acute/chronic disorder or known metabolic abnormalities), aged 21–35 (29 ± 4) years, weight 59–103 (81.2 ± 9.8) kg, from whom blood samples were withdrawn. Females were excluded due to possible additional blood loss associated with menstruation and proven impact of hormonal variations on coagulation. No drugs were allowed for seven days and no alcohol or strenuous physical exercise for one day before blood sampling.

Haemodilution

The test solutions included balanced crystalloid (Plasmalyte®, Baxter, Poland [PL]), succinylated gelatin (Geloplasma®, Fresenius Kabi, Poland [GEL]), and 6% HES 130/0.4 (Volulyte®, Fresenius Kabi, Poland [HES]) (Table 1). The whole blood was diluted 4:1 with the study solutions to make an end-concentration of 20 vol. % of each solution, equivalent to an infusion of about 1 L of test solution to a 70-kg person. Taking into account the mean weight of volunteers (81.2 ± 9.8 kg), the average amount of study solution administered in this recreated scenario was 15 mL per kg.

Sampling

Venous blood samples were drawn via a 16 G or 18 G indwelling cannula (Vasofix® Certo, B. Braun AG, Melsungen, Germany) from an antecubital vein of a non-dominant arm. The first portion of blood (2 mL) was discarded to minimise the effect of NS used as a flushing solution. Four blood samples were drawn: baseline (12.5 mL, BL) and three blood samples (10 mL), diluted at the ratio of 4:1 with each test solution (PL, HES, GEL) to make 20 vol.% end-concentrations. The dilution process was carried out immediately after blood sampling. Samples were collected in 1.7-mL heparin blood tubes (safePICO Aspirator, Radiometer, Brønshøj, Denmark) pre-heparinised with 80 IU of dry electrolyte-balanced heparin for venous blood gases. Samples were processed immediately after collection using the ABL 800 FLEX blood gas analyser (Radiometer, Brønshøj, Denmark) and included determination of pH, base excess (BE), bicarbonate (HCO_3^-), haemoglobin, and electrolytes (Na^+, Cl^-, Ca^{+2}). SID was calculated using the following formula: SID = $[Na^+] + [K^+] + [Ca^{+2}] - [Cl^-] - [lactate]$.

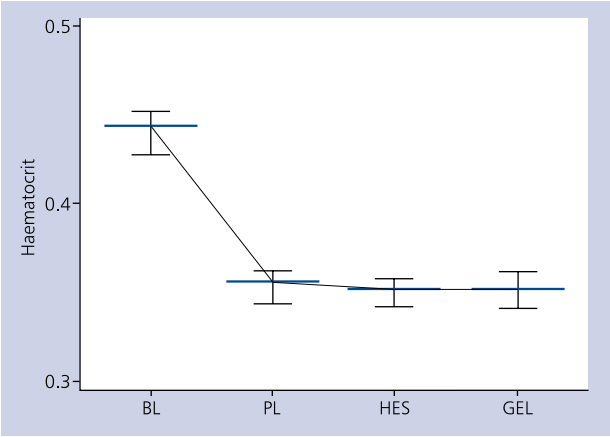

Figure 1. Impact of test solution on haemodilution

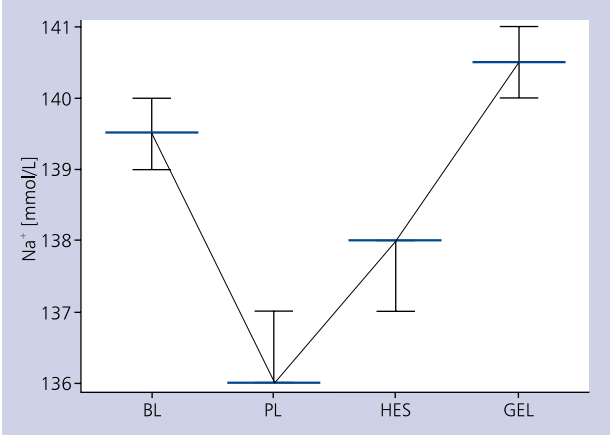

Figure 3. Impact of test solutions on Na^+ concentration

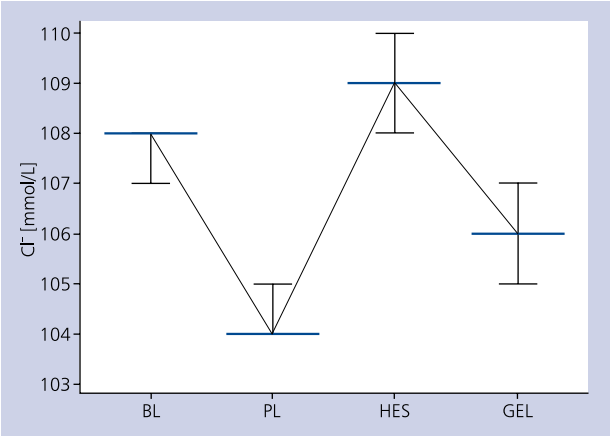

Figure 2. Impact of test solutions on Cl^- concentration

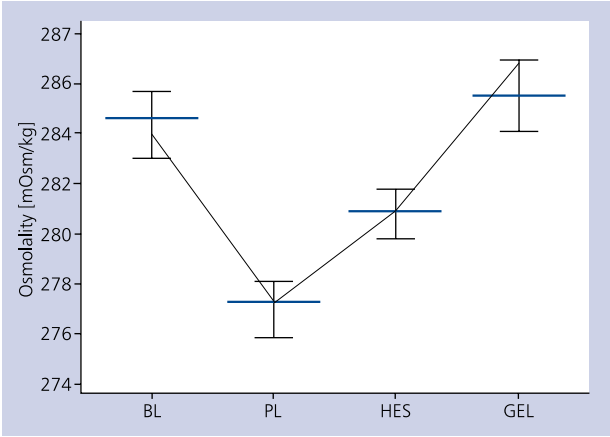

Figure 4. Impact of test solutions on osmolality

Statistical analysis

The statistical analysis was performed using MedCalc software (Version 16.1 2016, MedCalc Software bvba, Belgium). Quantitative data are presented as mean ± standard deviation (normally distributed variables) or median and interquartile range (IQR) (those with skewed distribution). The type of distribution was verified using Shapiro-Wilk test. The differences between undiluted samples and study solutions were analysed using repeated analysis of variance (ANOVA) or Friedman test. Post-hoc analysis was performed when appropriate. The level of statistical significance was set at $p < 0.05$.

RESULTS

All fluids being investigated caused similar degree of haemodilution (Fig. 1).

Baseline chloride concentration was 108 (IQR 107–109) mmol/L. All test solutions caused statistically significant changes of chlorides (Fig. 2). PL and GEL decreased (104 mmol/L, IQR 103–105; and 106 mmol/L, IQR 105–107.5, respectively), whereas HES increased the concentration of Cl^- to 109 (IQR 108–110) mmol/L.

Baseline Na^+ level was 139.5 (IQR 138–140) mmol/L. All test solutions caused statistically significant changes of Na^+ concentration (Fig. 3). PL and HES decreased (136, IQR 136–137 mmol/L; and 138 mmol/L, IQR 137–139; respectively), whereas GEL increased the Na^+ level to 140.5 (IQR 140–141) mmol/L.

Osmolality of undiluted blood was 284.65 (IQR 282–285.95) mOsm/kg. PL and HES caused statistically significant changes in osmolality (Fig. 4). PL and HES decreased the osmolality (277.25, IQR 275.7–278.45 mOsm/kg; and 280.9 mOsm/kg, IQR 279.3–282.05; respectively), whereas GEL increased it to 285.7 (IQR 283.7–286.8) mOsm/kg. All values remained within reference range.

As far as the acid-base balance is concerned, a statistically significant drop in pH was noted for HES and GEL, although the pH drop after dilution with GEL was more significant compared to HES (Fig. 5). All pH values after mixing with test solutions stayed within normal range.

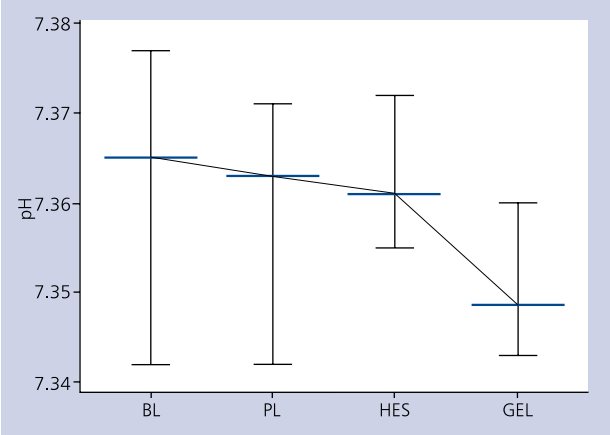

Figure 5. Impact of test solutions on pH

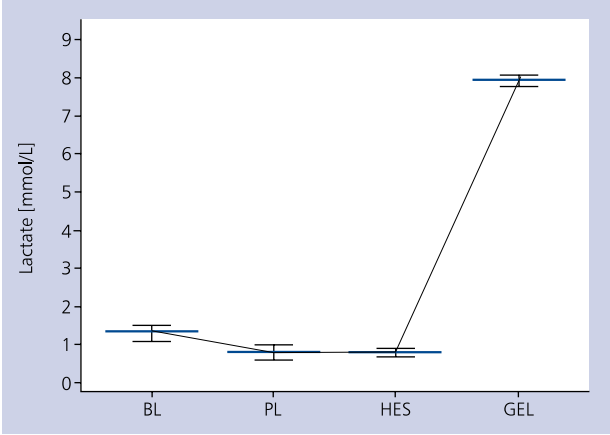

Figure 8. Impact of test solutions on lactate concentration

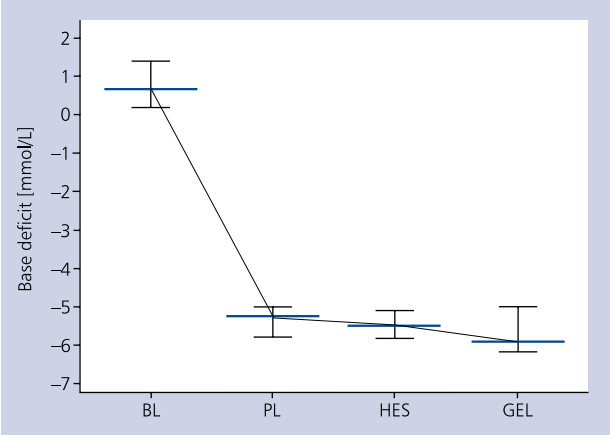

Figure 6. Impact of test solutions on base excess

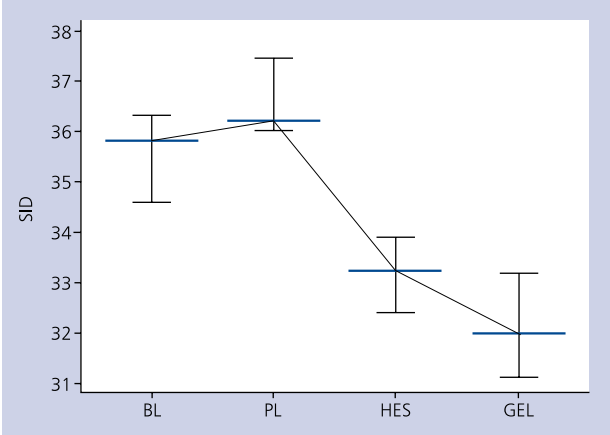

Figure 9. Impact of test solutions on strong ion difference (SID)

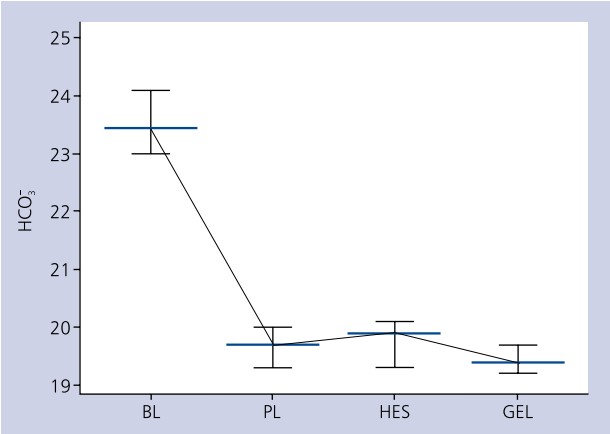

Figure 7. Impact of test solutions on HCO_3^- concentration

All test solutions caused similar statistically significant drop in base excess (Fig. 6). Similar changes were observed for bicarbonate concentration, with the lowest value seen after mixing with GEL (Fig. 7). Both parameters fell outside reference values for all test solutions.

Baseline lactate level was 1.35 (IQR 1.10–1.60) mmol/L. The impact of test solutions on its concentration is depicted in Figure 8. Due to its composition, GEL caused the most significant abnormalities.

Baseline SID was 35.82 (IQR 34.15–36.53) mEq/L. The impact of test solutions on blood SID is shown in Figure 9. HES and GEL caused a statistically significant drop in SID value. Due to high lactate level, the effect of GEL was the most pronounced.

DISCUSSION

In this experimental ex vivo study we confirmed that commonly used balanced fluids had little impact on electrolyte composition of human plasma. Moreover, their effect on the acid-base balance was mild and similar between investigated solutions.

There are numerous intravenous solutions available for fluid management, broadly divided into crystalloids and colloids. Crystalloids have different electrolyte composition and dependent on the type contain Na, Cl, K, Ca, Mg, and some organic anions like lactate, acetate, gluconate, or bicarbonate. Crystalloids freely pass through vascular endothelial membranes. Colloids are aqueous solutions of starch, gelatin, or albumin. Their particles are suspended in different carrier solutions, usually NS or balanced electrolytes. The large size of macromolecules limits their free passage through vascular endothelium. Therefore, one ought to remember that different fluids may have quite different impacts on osmolality, electrolyte, and acid-base balance.

The type and amount of a resuscitation fluid may have impact on patient outcomes [1, 4, 5]. There is no evidence that resuscitation with colloids is beneficial compared to resuscitation with crystalloids in patients with trauma, burns, or following surgery, while the use of hydroxyethyl starch might even increase mortality (OR 1.10; 95% CI 1.02–1.19) [8]. Rochwerg et al. [9], in their meta-analysis, also showed increased risk of renal replacement therapy in patients receiving starch solutions (OR 1.39; 95% CI 1.17–1.66) and no difference between balanced crystalloid, NS, and albumin. The most recent Surviving Sepsis Campaign guidelines from January 2017 strongly recommend at least 30 mL/kg of crystalloids as the fluid of choice for initial resuscitation and subsequent intravascular volume replacement in patients with sepsis and septic shock, using either balanced solutions or NS [10]. Fluid therapy should be guided by frequent and reliable assessment of haemodynamic parameters using clinical examination and both non-invasive and invasive haemodynamic monitoring [10]. Of note, the same amount of a particular intravenous fluid might have quite different effects in different patients.

Fluids may also have an impact on electrolyte balance and acid-base balance. Crystalloids are manufactured as hypertonic, isotonic, and hypotonic in relation to plasma osmolality, and are also categorised into balanced and unbalanced solutions. Balanced solutions have a composition similar to human plasma and SID of approximately 24 mEq/L, which is achieved by the addition of different buffering agents, e.g. bicarbonate, lactate, or acetate [1]. Balanced solutions have been postulated as alternatives to unbalanced solutions (i.e. NS). In experimental studies NS was found to cause electrolyte disturbances (hypernatraemia, hyperchloraemia) and metabolic acidosis (due to SID of 0 mEq/L), with its clinical sequelae of impaired kidney function, coagulation abnormalities, and inflammatory response [11]. Plasma-Lyte A as a calcium-free balanced crystalloid solution has been shown to produce lesser metabolic derangements in the population of trauma patients [12]. Zhou et al. [13], in an experimental model of abdominal sepsis in rats, showed lesser metabolic acidosis and lower chloride concentration with Pasma-Lyte compared to NS. The authors showed also higher risk of acute kidney injury and mortality in the group receiving NS. McFarlane et al. [14] in open abdominal surgery showed metabolic acidosis and hyperchloraemia with NS compared to Plasma-Lyte. In our study, all test-balanced solutions caused no or mild (hyperchloraemia after dilution with HES) disturbances in ionic composition of plasma. Although NS is still the most popular intravenous fluid in clinical use, there is a trend towards growing use of balanced solutions, which are not fully researched. Our intention was to investigate solely this type of fluid to make our results more homogeneous.

The impact of balanced crystalloid and two balanced colloids in our study showed similar, mild disturbances in acid-base balance as evidenced by classic parameters of acid-base balanced, like pH, BE, HCO_3^-. The impact of balanced colloids on acid-base balance, as shown by SID, was more pronounced compared to the balanced crystalloid (36.21 [35.71–37.78], 33.24 [32.22-34.38] and 31.99 [30.48––33.53] for PL, HES, GEL, respectively). The effect of GEL in this respect was more pronounced compared to HES due the presence of lactate as a buffering agent. It should be remembered that another popular resuscitation fluid, Ringer's lactate, may also elevate lactate levels [15, 16].

Limitations of the study

Our experimental study has several limitations, which should be taken into account in data interpretation. First of all, it was impossible to assess the impact of fluids in a true physiological scenario, which significantly differs between individuals, is dynamic, and multifactorial. Secondly, fluid dose (approx. 20 mL/kg) might be insufficient to discover between-fluid differences. Thirdly, we did not use NS as an unbalanced comparator of our findings. Fourthly, in our study we used peripheral venous blood, whereas for analysis of acid-base disturbances in clinical medicine the optimal is arterial blood. Also, we implemented gender criterion for patients' exclusion, which might have an impact on the external validity of our results in the female population. Finally, although the type of intravenous fluid may have a direct effect on the patient's metabolic equilibrium, there are other factors influencing metabolic status that should be controlled when an in vivo study is performed, including shock, hypoxaemia, anaemia, diabetes, poisoning, liver failure, or acute kidney injury. We tried to minimise their impact performing an in vitro study in healthy subjects.

CONCLUSIONS

Balanced intravenous solutions should be safe in terms of their impact on human plasma electrolyte and metabolic equilibrium when administered to replace up to 20% of blood volume. In metabolic acidosis, balanced succinylated gelatin should be used with caution. Therefore, arterial blood gas analysis should be performed in patients in whom significant amounts of fluid are administrated, preferably with assessment

of Cl^-, Na^+, lactate concentrations as well as pH, osmolality, and strong ion difference.

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Conflict of interest: *The study was supported by the 2015 annual grant of the Polish Cardiac Society funded by the Adamed corporation.*

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Czy resuscytacja płynowa z wykorzystaniem roztworów zbilansowanych wywołuje zaburzenia elektrolitowe i metaboliczne? Badanie *in vitro*

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Streszczenie

Wstęp: Powszechnie dostępne w praktyce klinicznej roztwory infuzyjne wpływają m.in. na stężenie elektrolitów i parametry metaboliczne osocza, tym samym powinny być postrzegane jako środki farmakologiczne o określonym wpływie na homeostazę ustrojową. Istnieje coraz więcej danych, że taki rodzaj terapii powinien być dobierany indywidualnie do pacjenta, z uwzględnieniem wskazań oraz przeciwskazań klinicznych, i oparty na roztworach zbilansowanych, czyli zbliżonych swym składem do osocza.

Cel: Celem niniejszej pracy była ocena wpływu trzech najczęściej stosowanych roztworów zbilansowanych płynów (krystaloidu i dwóch koloidów) na równowagę elektrolitową i metaboliczną w warunkach eksperymentalnych *in vitro*.

Metody: Badaną grupę stanowiło 32 zdrowych mężczyzn (ujemny wywiad w kierunku chorób ostrych i przewlekłych, farmakoterapii oraz zaburzeń metabolicznych), w wieku 21–35 (29 ± 4) lat, o masie ciała 59–103 (81,2 ± 9,8) kg, od których pobrano próbki krwi z zachowaniem należnych standardów laboratoryjnych. Krew pełna była następnie rozcieńczana w stosunku 4:1 z roztworami testowymi, aby uzyskać 20-procentowe stężenie końcowe każdego roztworu. Roztwory testowe stanowiły: zbilansowany krystaloid (Plasmalyte®, Baxter, Polska [PL]), sukcynylowana żelatyna (Geloplasma®, Fresenius Kabi, Polska [GEL]) oraz 6% HES 130/0,4 (Volulyte®, Fresenius Kabi, Polska [HES]).

Wyniki: PL i GEL zmniejszyły (odpowiednio do 104 mmol/l, przedział międzykwartylowy [IQR] 103–105 oraz 106 mmol/l, IQR 105–107,5) stężenie chlorków, podczas gdy HES zwiększył stężenie jonów Cl^- do 109 (IQR 108–110) mmol/l. PL i HES zredukowały (odpowiednio do 136 mmol/l, IQR 136–137 oraz 138 mmol/l, IQR 137–139) stężenie Na^+, podczas gdy roztwór GEL zwiększył stężenie sodu do 140,5 (IQR 140–141) mmol/l. PL i HES zmniejszyły osmolalność osocza (odpowiednio do 277,2 mOsm/kg, IQR 275,7–278,4 oraz 280,9 mOsm/kg, IQR 279,3–282,0). GEL zwiększyła osmolalność do 285,7 (IQR 283,7–286,8) mOsm/kg. Wszystkie roztwory testowe spowodowały podobne, istotne statystycznie ($p < 0,05$), zmniejszenie niedoboru zasad (BE) oraz stężenia wodorowęglanów poniżej wartości normatywnych. Z powodu swojego składu GEL spowodowała istotny wzrost stężenia mleczanów w próbkach. HES i GEL wywołały istotny statystycznie spadek wartości różnicy silnych jonów, jednak z powodu dużej zawartości mleczanów efekt GEL był najbardziej zaznaczony.

Wnioski: Roztwory zbilansowane są bezpieczne w kontekście ich wpływu na równowagę elektrolitową i metaboliczną, gdy są stosowane do zastąpienia utraty krwi w ilości do 20% jej objętości. Przy współistniejącej kwasicy metabolicznej zbilansowany roztwór sukcynylowanej żelatyny powinien być stosowany z ostrożnością.

Słowa kluczowe: płyn nawadniający, zbilansowany krystaloid, zbilansowany koloid, równowaga kwasowo-zasadowa, różnica silnych jonów

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