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ARTIGO ORIGINAL

Accuracy of Gasometry in Electrolyte Evaluation

Precisão da Gasometria na Avaliação do Ionograma

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Palavras-chave
Cloro/sangue; Criança; Gasometria; Potássio/sangue; Sódio/sangue

ABSTRACT

Introduction: The measurement of sodium, potassium and chloride can be done through a serum or gasometric sample. The fast availability of results would make gasometry the ideal method. However, the data on the accuracy of gasometry is not consensual.

Methods: Prospective observational study of children aged 28 days to 17 years who underwent elective surgery at a Pediatric Surgery Service during one year. We compared sodium, potassium and chloride values in serum and gasometry samples collected simultaneously.

Results: Sixty five children with a median age of 10 years (IQR 3.6-15), 77% male. 161 determinations of sodium, 154 of potassium and 143 of chloride were obtained. There was a mean difference in sodium, potassium and chloride values between the two methods of 1±1.89 mmol/L, 0.3±0.19mmol/L and -5±1.81 mmol/L, respectively. There was a strong correlation between sodium (r=0.64) and chloride (r=0.78) and very strong with potassium (r=0.9). It was possible to establish a linear regression and obtain a correction factor between the two methods.

Conclusion: There is a very strong correlation between the measurements of gasometry and serum potassium, allowing both methods to be used if a correction factor of +0.25 is applied to the gasometry value. Although the correlation was not as good with sodium, gasometry was precise enough to be used in clinical practice. Chloride values should be interpreted cautiously as significant variations may occur.

RESUMO

Introdução: O doseamento de sódio, potássio e cloro pode ser efetuado através de uma amostra sérica ou de gasometria. A rapidez no resultado tornaria a gasometria no método ideal. Contudo, a literatura não é consensual quanto à sua precisão.

Métodos: Estudo observacional prospetivo de crianças com idades entre 28 dias e 17 anos submetidas a cirurgia eletiva num Serviço de Cirurgia Pediátrica, durante um ano. Comparámos a determinação de sódio, potássio e cloro em amostras séricas e de gasometria colhidas em simultâneo.

Resultados: Sessenta cinco crianças com idade mediana de 10 anos (IQR 3,6-15), 77% do sexo masculino. Obtiveram-se 161 determinações de sódio, 154 de potássio e 143 de cloro. Verificou-se uma diferença média na medição de sódio, potássio e cloro entre os dois métodos, respetivamente, de 1±1,89 mmol/L, 0,3±0,19 mmol/L e -5±1,81 mmol/L. Encontrou-se uma correlação forte nas medições de sódio (r=0,64) e cloro (r=0,78) e muito forte na de potássio (r=0,9). Para todos, foi possível estabelecer uma regressão linear e obter um fator de correção que permite a conversão entre os dois métodos.

Conclusão: Existe uma correlação muito forte entre os valores de potássio da gasometria e séricos, permitindo que ambos sejam usados se um fator de correção de +0,25 for aplicado ao valor da gasometria. Embora a correlação não tenha sido tão boa para o sódio, a gasometria foi suficientemente precisa para ser usada na prática clínica. Os valores de cloro devem ser interpretados com cautela, pois podem ocorrer variações significativas.

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INTRODUCTION

Electrolytes such as sodium (Na^+), potassium (K^+) and chloride (Cl^-) are essential elements to homeostasis, being involved in many metabolic functions of the body. The determination of their concentrations in the blood provides important information about osmotic and body acid-base balance.[1]

Sodium is the major extracellular cation and its main functions are the maintenance of fluid distribution and the osmotic pressure of the vascular compartment.[1] Potassium is the major intracellular cation and is crucial for neurological and muscular cellular activity.[1] Chloride, in turn, is the major extracellular anion and is also involved in the balance of extracellular fluid distribution.[1]

Changes in these serum electrolyte levels can be caused by multiple situations. These changes can lead to the imbalance of homeostasis mechanisms and may lead to various manifestations, including life-threatening situations, such as cardiac arrhythmias and cardiac arrest, in the case of potassium imbalances, and cerebral edema, as with sodium imbalances.[1] Hyponatremia (sodium <135 mmol/L) is one of the most common electrolyte abnormalities in hospitalized and non-hospitalized patients.[2]

Therefore, the measurement of these electrolytes is frequently required in clinical p ractice. The accuracy and the prompt availability of the results are essential factors in their determination, mainly in emergency and critical care settings as well as in surgery context, in which the dynamic physiological status of patients can lead to sudden changes of these electrolytes and life-threatening situations.[3-6] Thus, an early diagnosis of electrolytes imbalance and an adequate correction can improve patient outcomes.[3]

One of the most commonly used laboratory methods for measuring electrolytes is the serum ionogram analysis, usually through a blood sample obtained by venipuncture, which is subsequently analysed in laboratory (LAB) through a system of ion-selective electrodes (ISE). An ISE uses the unique properties of certain membranous materials to develop an electric potential for the measurement of ions in solution. The electric potential of the membrane is determined by the difference between the concentration of the ion to be tested in the test solution and a fixed concentration of the ion in the internal filling solution. The electric potential is measured and processed to obtain the concentration of the ion to be tested. There are direct and indirect ISEs and an important difference between them is that in the second one a dilution of the sample is performed before the analysis.[3]

Serum ionogram measurement is performed by indirect ISEs and results usually takes more than thirty minutes, which may be unsatisfactory in emergent situations. On the other hand, in gasometric analysis (GAS) the results can be obtained significantly faster because the sample is not diluted pre-analytically (direct ISE) and the measurement is done directly from the obtained whole blood sample.[3]

The use of gasometry has become common in clinical practice. However, an additional sample is usually sent to be evaluated in the laboratory because the latter is considered standard.[2] The available data about the accuracy of GAS and the equivalence between LAB and GAS is often dubious.[2] There are studies that concluded that the two methods are equivalent,[7,8] others refer that they are equivalent only to potassium[9,10] and others still state that they are significantly different.[5,11] The variability of the conclusions may be due to a combination of factors, namely:

a) Different types and models of ISE systems between different hospitals, as well as different calibrations of the measuring instruments and the corresponding analytical results.[2,5]

b) Heparinization: syringes used in gasometry contain heparin, thereby diluting and increasing the sample volume, which decreases the electrolyte assay obtained in GAS.[2,12] In addition, heparin itself binds to electrolytes decreasing the measurement of these in the GAS.[2] Heparin therefore introduces a negative bias, mainly in relation to sodium and potassium because they are positive ions, with greater affinity to bind to heparin. This does not occur in the LAB has the samples are not heparinized.[13]

c) Transport conditions, in particular, time and storage temperature of the samples, are determinant factors for analytical assay. Thereby, their variability can result in variations between different hospitals.[3] Analytical assessments are recommended to be carried out as early as possible. Studies indicate that the pre-analytical phase, within the set of all phases involved in the analytical evaluation, is the most susceptible to errors, with a total of 46% to 68.2% errors occurring at this stage.[24]

d) Total proteins: LABs' indirect ISE overestimates electrolyte measurements in situations of hypoproteinemia,[2] which is frequent in critically ill patients.[12] In these patients, measurements made using direct ISE (GAS), which is not affected by serum protein concentration, may be more accurate. In critically ill patients the measurements performed with the two methods differed significantly, as their clinical interpretation and the therapeutic decision.[23]

The variability in the measurement of electrolytes between GAS and LAB in different hospitals and its clinical relevance demand a comparison between the two measurement methods. The aim of this study is, therefore, to determine the accuracy of sodium, potassium and chloride measurements in gasometry and serum ionogram in a pediatric population.

MATERIAL AND METHODS

Study Population

Within the scope of a research performed at our hospital (Centro Hospitalar Universi-tário Lisboa Norte), entitled

"Fluids in the perioperative in pediatric age - which fluid is the most appropriate? Prospective, randomized and blinded clinical trial", we analysed data of the patients included between October 2017 and October 2018.

The clinical trial was approved by the local Ethics Committee (number 102/17) and in-cluded children submitted to elective surgery in a Pediatric Surgery Service in Lisbon. Inclusion criteria were: age over 28 days and under 18 years, need for intravenous fluids until the morning of the day after surgery and ability to understand the Portuguese lan-guage. Exclusion criteria were: signs or symptoms of intracranial hypertension; kidney failure requiring dialysis; renal pathology that causes excessive renal sodium excretion; patients requiring life support techniques such as extracorporeal membrane oxygenation; need for intravenous fluids before surgery; significant changes in serum (Na^+<130 or >150 mmol/L, Cl^-<95 or >110 mmol/L) and base excess <-7 or >7 mmol/L. Patients who met all the inclusion criteria and who did not present any exclusion criteria were invited to participate by signing an informed consent. The privacy and anonymity of partici-pants were guaranteed through protected databases in which patients' personal data were not included.

Procedures and equipment

Each patient was submitted to venipuncture for blood collection in three different moments: in the operative room before starting fluids, at the end of surgery, in the morning of the day after surgery. The venous sample from each blood collection, was divided and placed in a safePICO Aspirator from Radiometer®, for GAS analysis and in a Serum Gel Sarstedt Monovette® for LAB. At our hospital, serum ionogram is performed in an indirect ISE module of the Roche cobas® 8000 (USA) analyser. System maintenance procedures are performed daily, at the end of a series of samples or after high sample processing. Calibration is carried out every 24 hours, after the use of ISE Cleaning solution, after changing the reagent bottles and after the replacement of any electrode. Regarding the direct ISE GAS analyser, the system is the ABL800 FLEX - Radiometer Medical ApS (Denmark), whose calibrations are performed automatically and periodically, at scheduled time. Calibrations beyond the scheduled time can also be performed manually. Reference intervals considered for the different ions were: sodium from 135 to 145 mmol/L; potassium from 3.5 to 5.1 mmol/L and chloride from 98 to 107 mmol/L. Values below these intervals were considered hyponatremia, hypokalemia and hypochloremia, respectively. Values above these intervals were considered hypernatremia, hyperkalemia and hyperchloremia, respectively. The interpretation of the results was based on the regulation of clinical laboratories according to the United States Clinical Laboratory Improvement Amendments (US-CLIA),[15] which establishes the conditions of variability accepted between analytical results. According to US-CLIA, a difference of 4 mmol/L for sodium, 0.5 mmol/L for potassium and 5% for chloride is acceptable between different methods of measurement. Several studies comparing LAB and GAS in the measurement of the ionogram used the US-CLIA variability ranges as a reference for the interpretation of results.[5,8,9]

Statistical methods

The statistical analysis was performed using SPSS software version 24 (IBM® Corp., Armonk, NY, USA) and samples T-Test, Pearson correlation coefficient and linear re-gression analyses were used. It was also intended to access the proportion of paired samples whose measurements exceeded the variability tolerated by US-CLIA.

RESULTS

A total of 65 patients were included. The median age was 10 years old (IQR 3.6-15) and 77% were male. Given the three evaluations for each patient, a total of 195 pairs of ionograms were expected. However, we ended up obtaining a total of 161 pairs of evaluations of sodium, 154 of potassium and 143 of chloride. This reduction was attributed to several factors, patient drop out before the third determination (34 samples excluded), samples processed in the emergency laboratory, which does not perform chloride measurements (18 chloride samples were excluded), hemolysis (7 potassium samples were excluded).

The mean values obtained by LAB and GAS are presented in Table 1.

Table 1. Mean value and difference in means in mmol/L of the measurements of sodium, potassium and chloride by LAB and GAS and the range of variability accepted by US-CLIA

Electrolyte	LAB Mean Value ± SD	GAS Mean Value ± SD	Difference in Means	US-CLIA range	*p*-VALUE
Na^+	139 ± 2.15	138 ± 2.29	1 ± 1.89	4	<0.001
K^+	4,3 ± 0.43	4,0 ± 0.42	0.3 ± 0.19	0,5	<0.001
Cl^-	103 ± 2.64	108 ± 2.80	-5 ± 1.81	5,15	<0.001

LEGENDA:
SD - standard deviation

The difference in means between the two methods was 1 mmol/L (SD 1.89 mmol/L) for sodium, 0.3 mmol/L (SD 0.19 mmol/L) for potassium and -5 mmol/L (SD 1.81 mmol/L) for chloride. Sodium and potassium results are within the US-CLIA range but chloride is not, if taking into account its standard deviation.

The proportion of measurements whose differences were superior to the range of varia-bility accepted by US-CLIA is presented in Table 2.

The linear regression between the two methods of electrolyte

Table 2. Proportion of measurements whose differences obtained between LAB and GAS results were superior to the range of variability accepted by US-CLIA

Na^+	**3.1 %**
K^+	**3.9 %**
Cl^-	**36.4 %**
% (DIFFERENCES LAB – GAS) > (Δ US-CLIA)	

measurement was established and is represented in the Fig.s 1, 2 and 3. The corresponding regression equations were obtained:

Na^+ LAB = 0.625 × Na^+ GAS + 51.25 (r = 0.64)

K^+ LAB = K^+ GAS + 0.25 (r = 0.90)

Cl^- LAB = 0.833 × Cl^- GAS + 11.67 (r = 0.78)

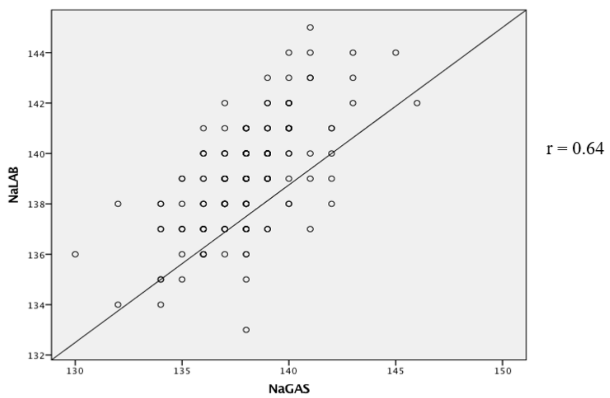

Figure 1. Scattered graph plotted to show the correlation between LAB sodium and GAS sodium

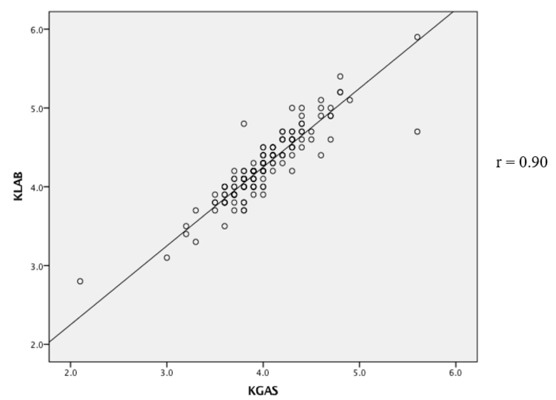

Figure 2. Scattered graph plotted to show the correlation between LAB potassium and GAS potassium

DISCUSSION

The results of this study revealed statistically significant differences between LAB and GAS in the measurement of sodium, potassium and chloride, but the difference in means was within the range accepted by US-CLIA for sodium and potassium. The clini-cal importance of these differences is distinct for each analysed electrolyte.

Sodium

The difference in means between the methods is within

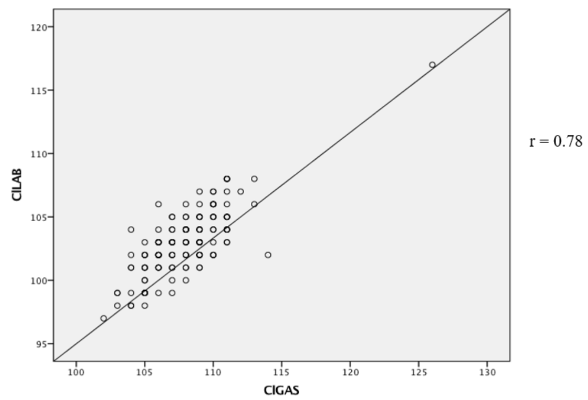

Figure 3. Scattered graph plotted to show the correlation between LAB chloride and GAS chloride

the range accepted by US-CLIA. Additionally, we consider this difference to be clinically tolerable and the proportion of measurements that did not meet the acceptance range was small. Thus, we consider that sodium measurements can be performed by both methods and other studies have found similar conclusions.[7,8] Nonetheless, sodium had the weakest correlation between GAS and LAB measurements of the three electrolytes studied.

Potassium

Since the difference in means between the two methods is in the accepted range by US-CLIA, LAB and GAS can be considered equivalents in measuring potassium. However, we consider that the difference observed (0.3 ± 0.19 mmol/L) can be associated with different clinical approaches, mostly when the results are at the extremes of the normal range. Potassium was the electrolyte with the strongest correlation (r=0.90, very strong correlation), and the regression equation obtained allows, with a significant degree of reliability, to convert the result of one method into another. (K^+LAB = K^+GAS + 0.25). Interpretation of potassium results should always be cautious, because although LAB is the reference method for the ionogram analysis it has been found that serum potassium values are consistently higher than in plasma's, which can be related to many factors, particularly:

a) The platelet release of potassium during the coagulation that happens in the pre-analytical phase.[16] The higher the platelet count, the greater the error.[1,17]

b) Hemolysis. When detected its measurement is frequently discarded.[17]

c) Presence of marked leukocytosis, which is related to both pseudohyperkaliemia[18] and pseudohypokalemia.[19] This phenomenon can be explained by the large number of circulating blood cells combined with the fragility of the cell membrane of cells in rapid proliferation which makes them susceptible to lysis during the coagulation and centrifugation of the samples before being analysed by LAB, with the release of intracellular potassium. Similar phenomena are also described in cases of erythrocytosis, as in polycythemia vera.[20]

d) Time elapsed in the pre-analytical phase and the exposure temperature of the sample. This causes deregulation of the Na^+/K^+-ATPase pump activity and the release of potassium from the cellular elements of the blood.[14]

e) Contamination. EDTA (ethylenediamine tetraacetic acid) and trisodium citrate are two anticoagulants used in collection tubes for complete blood count and coagulation study, respectively.[16] During blood collection, the tubes containing these substances should be used after the ionogram tube, due to the risk of contamination of the latter, since these substances may falsely increase the measurement of potassium. Other substances may have the same effect, namely povidone iodine and benzalkonium chloride, used in sterilization.[16]

Fictitious changes in potassium have important clinical relevance, since corrections may lead to marked changes in potassium and, consequently, to life-threatening conditions.[1] Furthermore, false measurements considered to be within the reference range may not correspond to normokalemia, delaying electrolyte correction. Although GAS does not include a pre-analytical control to provide information about the status of the sample (occurrence of hemolysis, for example), it could be preferable to LAB because there are less interferences, which mostly occur during the pre-analytical phase. It would be useful, though, the availability of prompt information about hemolysis in GAS in order to avoid inaccuracies.[5,11]

Chloride

For chloride, the difference in means exceeded the range of variability accepted by the US-CLIA if taking in account the standard deviation. Therefore, the two methods were not considered equivalent, which is consistent with previous studies described in the literature, in which LAB and GAS differed substantially.[22,23] The measurement of chloride has particular interest in detecting metabolic alterations by calculation of the anion gap (AG).[21] Geerts N *et al*, in a retrospective study with 529 patients, concluded that chloride measurements obtained by LAB were significantly lower (-4 mmol/L) than those obtained by GAS, and therefore the AG calculation through LAB was overvalued. The reasons for the difference are unknown, but are assumed to be in part due to the direct chloride ISE activity.[23] Makiishi T *et al* investigated this disparity and concluded that there is a directly proportional relationship between chloride and bicarbonate concentrations measured by LAB, with lower measurements of chloride occurring in situations of metabolic acidosis and higher measurements in metabolic alkalosis.[24] This may be related to the selectivity of the chloride ISE, whose ion exchange membrane can be influenced by other anions, such as bicarbonate, phosphorus and lactate.[25] Since the measurements made by direct ISE is not affected by anionic oscillation in the blood, GAS could actually be more accurate than LAB, especially in clinical situations associated with metabolic derangements.[22,23]

The correlations of the measurements between LAB and GAS obtained for each electrolyte, which are considered "strong" for sodium and chloride and "very strong" for potassium, indicate a concordance between LAB and GAS. This concordance makes conversion possible between LAB and GAS by applying a correction factor according to the linear regression equations.

Study limitations

One of the limitations of this study is the enrollment from a single research center, with the results of electrolyte measurements in LAB and GAS being exclusively obtained through two measurement systems used in the hospital where the study was carried out: the Roche Cobas® 8000 ISE system (LAB) and the ABL800 FLEX - Radiometer Medical ApS system (GAS). Measurements made on other systems may not match the same results given that the sensitivity, specificity and calibrations may be specific. Nevertheless, these systems are widely used, making the results of this study applicable to hospitals where identical systems are being used.

Another limitation is related to the population studied. Considering that all patients included in this study were hospitalized for elective surgery, the laboratory results were predominantly within the reference range, remaining uncertain the accuracy of GAS in the context of excess or deficit of electrolytes.

CONCLUSION

There is a very strong correlation between the measurements of potassium in GAS and LAB, allowing both methods to be used if a correction factor of +0.25 is applied to the potassium GAS value. Although the correlation was not as good with sodium GAS was precise enough to be used in clinical practice. Chloride values should be interpreted cautiously as significant variations may occur.

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