Mini Review

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Which laboratory technique is used for the blood sodium analysis in clinical research? A systematic review

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Abstract

Background: Circulating sodium is analyzed by flame spectrometry and indirect or direct potentiometry. The differences between estimates returned by the three techniques are often relevant. It is unknown whether peer-reviewed international publications focusing on this parameter provide information about the technique. Objectives of the study were to ascertain if information about the employed technique is provided.

Content: A search in the National Library of Medicine for articles whose title contains "hyponatr[a]emia" was performed. We restricted the search to clinical reports including 10 or more humans published in the 2013–2015 and 2017–2019 periods. Authors of papers not reporting the technique were contacted to obtain this information. The study design and journal quartile ranking of each article were also evaluated.

Summary: For the final analysis, we included 361 articles (2013–2015, n=169; 2017–2019, n=192). Information about the laboratory technique was given in 61(17%) articles. Thanks to our inquiry, we collected this information for 116(32%) further reports. Indirect potentiometry was the most frequently used technique, followed by direct potentiometry. Spectrometry was used in a small minority of studies. Study design, journal ranking and study period did not modulate the mentioned frequency.

Outlook: Most articles focusing on hyponatremia do not provide information on the laboratory technique. This parameter is nowadays analyzed by indirect or, less frequently, direct potentiometry. The figures are similar for high and low impact factor journals and for the 2013–2015 and the 2017–2019 periods. Many authors, reviewers and editors likely assume that the results of this parameter are not influenced by the technique.

Keywords: bias; direct potentiometry; error of measurement; indirect potentiometry; ion; sodium.

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Introduction

Disorders of blood sodium (Na^+) are common in humans [1]. This laboratory parameter is nowadays analyzed in diluted samples by flame spectrometry and indirect potentiometry or in undiluted samples by direct potentiometry. A growing body of evidence points out that the three methods sometimes show a poor (>4 mmol/L) agreement. Nonetheless, most clinicians are not aware of the discrepancies among the different laboratory techniques and use them interchangeably [2–5]. It is unclear, however, whether clinical research studies focusing on Na^+ in blood provide information about the technique utilized for its determination. Objectives of this systematic review of the literature are to ascertain if information about the laboratory technique is provided; which is the most frequently employed technique; and if the attitude is stable over time.

Methods

Literature search strategy

To increase the rigor of the work [6], we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses, a recognized set of items for reporting [7]. A computerized literature search in the National Library of Medicine for original full-text articles whose title contains "hyponatr[a]emia" was performed in autumn, 2020. We restricted the search to full reports published in English-language journals from 2013 to 2015 and from 2017 to 2019 and to original articles including 10 or more humans.

Selection criteria – data extraction

Two of us independently but in an unblinded fashion extracted the data from the articles. Disagreements were resolved by consensus and arbitrated by a third author. We used a predefined database to extract from each report following information: (1) study classification (observational vs. interventional), (2) data collection (retrospective vs. prospective), (3) number of subjects tested for circulating Na^+ (n=10–99; n=100–499; n≥500), (4) study setting (intensive care vs. other settings), and (5) the utilized laboratory technique (indirect potentiometry, flame spectrometry, direct potentiometry). We contacted with respect to this information the corresponding author of each paper not reporting the laboratory technique and sent a reminder 2 months later to non-responders.

Finally, we used the Journal Citation Reports (Clarivate Analytics' Web of Science™) to extract the highest journal impact factor quartile ranking of each article in the year of publication [8].

Analysis

Data are presented both cumulatively and separately for the period 2013–2015 and 2017–2019. The χ^2-test and the Wilcoxon–Mann–Whitney test with the post-hoc Bonferroni adjustment were used to analyze categorical data. The level of statistical significance was set at $p<0.05$.

Results

Search results

The literature search process is reported in Figure 1. For the final analysis, we included 361 articles (see Supplementary Material). One hundred and sixty-nine articles appeared between 2013 and 2015, and 192 between 2017 and 2019. They were published from the following continents: 134 from Asia (Japan, n=34; South Korea, n=23; India, n=20; China, n=17; Israel, n=8; Taiwan, n=8; Turkey, n=7; Iran, n=5; Pakistan, n=5; Saudi Arabia, n=3; Singapore, n=2; Indonesia, n=1; Vietnam, n=1), 114 from North America (United States, n=104; Canada, n=10), 102 from Europe (Italy, n=20; Spain, n=14; Germany, n=9: France, n=8; Sweden, n=8; Switzerland, n=7; Belgium, n=6; Denmark, n=6; Austria, n=4; Netherlands, n=4; Poland, n=4; Czech Republic, n=3; United Kingdom, n=3; Ireland, n=2; Finland, n=1; Greece, n=1; Portugal, n=1; Serbia, n=1), five from Australia, four from South America (Argentina, n=2; Brazil, n=2), and two from Africa (South Africa, n=1; Egypt, n=1).

Findings

The characteristics of the 361 articles are given in Table 1. In approximately three quarters of them, 100 subjects or more were studied. Furthermore, about 60% of the articles were published in the first or second journal impact factor quartile. Information about the laboratory technique was given within the paper in no more than 61 (17%) of the articles. Thanks to the post-publication email inquiry, we collected this information for 116 (32%) further cases. The study classification, the type of data collection, the number of study participants per publication, and the journal impact factor quartile were not statistically different in the 2013–2015 and in the 2017–2019 period.

Indirect potentiometry was by far the most frequently used (71%) laboratory technique, followed by direct potentiometry (17%). Flame spectrometry was used only in a small minority (1.1%) of studies (Table 2). This trend was similar in the 2013–2015 and in the 2017–2019 period. Direct potentiometry was more frequently (42 vs. 15%; [$p<0.05$]) utilized in studies including intensive care patients (Table 3).

Data on the association between the frequency of reports with information regarding the laboratory Na^+-method and the type of study design or data collection, number of participants per study, intensive care vs. non-intensive care studies, or journal quartile ranking, are reported in Figure 2. No significant difference in the frequency of articles with or without information regarding the laboratory Na^+-method was noted between observational or interventional studies and between studies with retrospective or prospective data collection. Similarly, the mentioned frequency was not modulated by the numbers of subjects included in each

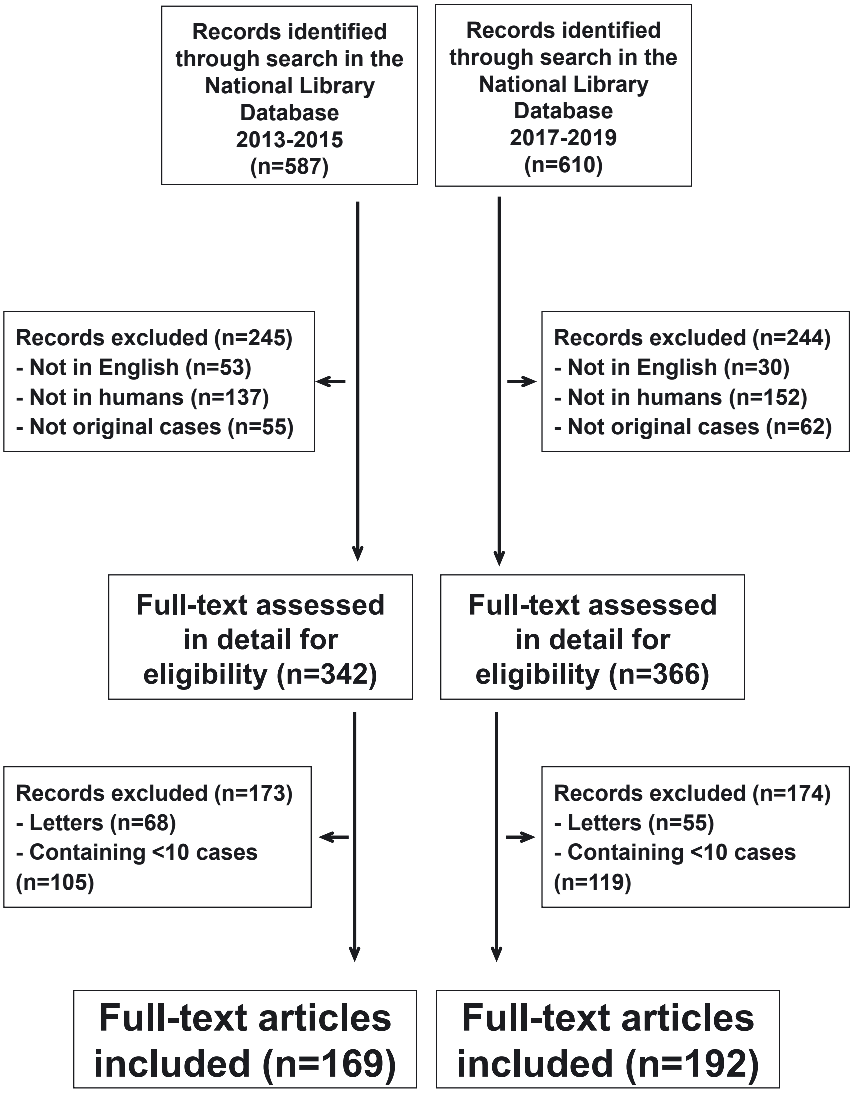

Figure 1: Laboratory technique used for the determination of circulating Na^+ in clinical research. Flowchart of the literature search process.

report, by the study setting and by the journal quartile ranking.

Discussion

The results of this systematic review may be summarized in three points. First, the majority of original articles with focus on hyponatremia published in journals referenced in the National Library of Medicine database do not provide information on the laboratory technique. Second, blood Na^+-analysis is nowadays measured by indirect or, less frequently, direct potentiometry. On the other hand, flame spectrometry, at one time the most common method, is no more ordinarily employed. Third, these figures are almost identical for the 2013–2015 and the 2017–2019 periods, for reports published in high and low impact factor journals, for studies performed in intensive and non-intensive care setting, and for reports including a high or a low number of cases. It is therefore concluded that many authors, reviewers and editors take for granted that the results of blood Na^+-analysis are not influenced by the utilized laboratory technique.

Na^+ has traditionally been measured as concentration (mmol/L) by flame spectrometry in diluted plasma or serum. Potentiometry is inherently different because it does not detect concentration but activity. Following dilution of plasma or serum in a large volume, however, indirect potentiometry yields and excellent estimate of the concentration. The recommended name for this quantity is

Table 1: Characteristics of the 361 articles included in this analysis.

	All	2013–2015	2017–2019
Publications, n	361	169	192
Study classification			
Observational, n (%)	274 (76)	130 (77)	144 (75)
Interventional, n (%)	87 (24)	39 (23)	48 (25)
Data collection			
Prospective, n (%)	136 (38)	71 (42)	65 (34)
Retrospective, n (%)	225 (62)	98 (58)	127 (66)
Subjects per publication			
10–99, n (%)	91 (25)	48 (28.5)	43 (22)
100–499, n (%)	127 (35)	54 (32)	73 (38)
≥500, n (%)	143 (40)	67 (39.5)	76 (40)
Journal impact factor quartile			
First, n (%)	101 (28)	60 (35)	41 (21)
Second, n (%)	114 (31)	44 (26)	70 (36)
Third, n (%)	54 (15)	20 (12)	34 (18)
Fourth, n (%)	35 (10)	18 (11)	17 (9)
None, n (%)	57 (16)	27 (16)	30 (16)
Na^+-determination – laboratory technique			
Information published, n (%)	61 (17)	32 (19)	29 (15)
Information only after inquiry, n (%)	116 (32)	46 (27)	70 (36)
Information unavailable, n (%)	184 (51)	91 (54)	93 (49)

Table 2: Methods employed for the measurement of circulating Na^+ in 177 articles.

	All	2013–2015	2017–2019
Indirect potentiometry, n (%)	126 (71)	56 (74)	70 (71)
Direct potentiometry, n (%)	30 (17)	14 (18)	16 (16)
Indirect or direct potentiometry, n (%)	19 (11)	8 (10)	11 (11)
Flame spectrometry, n (%)	2 (1.1)	0 (0.0)	2 (2.0)

"total Na^+" concentration [4, 5]. The Na^+-analysis by direct potentiometry (i.e. in undiluted samples) appropriately reflects the activity of this ion and is biophysically and clinically more relevant than the concentration. However, by convention, the International Federation of Clinical Chemistry and Laboratory Medicine [4, 5] recommends for this quantity the term "ionized Na^+" and to report it in concentration (mmol/L).

Several studies performed in adults [9–11], children [12], infants [12, 13] and neonates [13, 14] demonstrate relevant discrepancies between the Na^+-estimates returned by direct and indirect potentiometry. Generally, discordances between techniques result from random error, calibration bias or interference specific to one technique.

Table 3: Methods employed for the measurement of circulating Na^+ in intensive care and non-intensive care studies.

	Non-intensive care (n=165)	Intensive care (n=12)
Indirect potentiometry, n (%)	120 (73)	6 (50)
Direct potentiometry, n (%)	25 (15)	5 (42)[a]
Indirect or direct potentiometry, n (%)	18 (11)	1 (8.3)
Flame spectrometry, n (%)	2 (1.2)	0 (0.0)

[a]$p<0.05$ vs. non-intensive care studies.

The difference between direct and indirect potentiometry (or flame photometry) with Na^+ is mainly caused by the water exclusion effect. It occurs uniquely with indirect potentiometry (or flame spectrometry) when the portion of serum occupied by lipids and proteins relevantly differs from the typical value of 7% [3–5, 11]. It is known since the eighties [2, 3, 5, 10] that when Na^+ is determined by indirect potentiometry (or flame spectrometry), above-normal protein (e.g.: multiple myeloma) or lipid (e.g.: hypertriglyceridemia) concentration increases the water exclusion effect and results in artifactually low values (pseudohyponatremia). What is less recognized but more common [5, 9–14], is that below-normal albumin [18], the most important protein in blood, decreases the water exclusion effect and results in artifactually normal values in true hyponatremia (pseudo-normonatremia) or in artifactually high values in true normonatremia (pseudo-hypernatremia). Below-normal albumin is common in conditions such as renal or intestinal protein-losing disorders, liver cirrhosis, poor nutrition, heart failure, severe infections and conditions characterized by an increased capillary permeability [15, 16].

One feature that is important for neonates and infants is the blood sample size, which is smaller with indirect potentiometry or flame spectrometry than with direct potentiometry.

Interestingly, the variability in Na^+-values obtained by the different methods is usually not taken into consideration in meta-analyses and systematic reviews focusing on this ion, including three reports published last year [17–19].

The major limitation of this study relates to the fact that we exclusively evaluated reports focusing on hyponatremia. However, we believe that the selection of reports on hypernatremia would not have relevantly changed the outcome of the analysis. The main strength relates to the inclusion of more than 350 reports and to the inquiry among the authors of the reports to obtain information about the laboratory method used for the determination of Na^+.

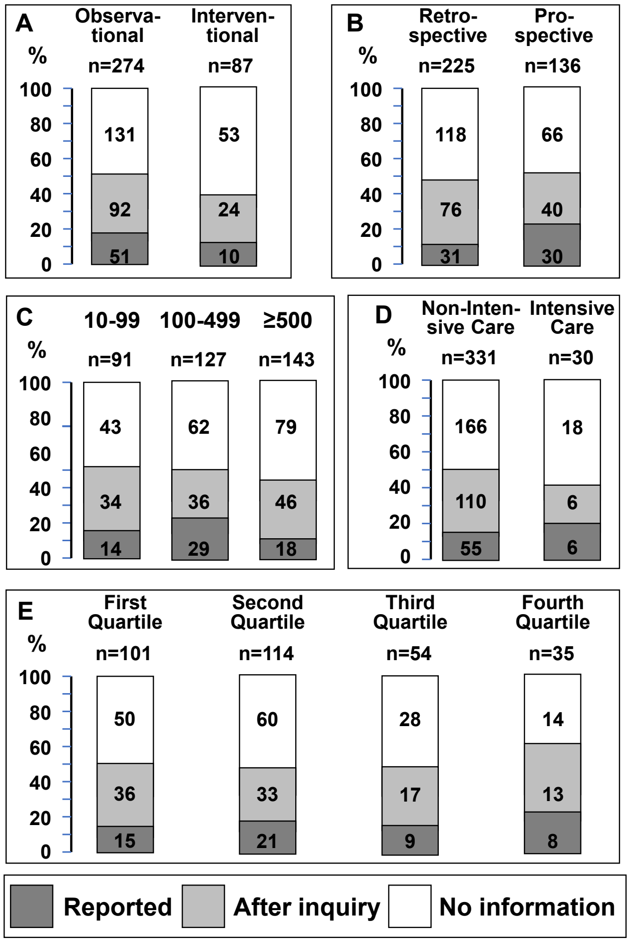

Figure 2: Association between the frequency of reports with information regarding the laboratory Na^+-method and study design (A), data collection (B), number of participants per study (C), intensive care vs. non-intensive care studies (D), or journal quartile ranking (E; the journal impact factor quartile was unavailable for 57 articles).

Conclusions

The choice of the method for measuring Na^+ may have a substantial impact on result and the direct-potentiometric measurement is considered the most accurate technique. Because a given laboratory may be unable to analyze Na^+ by direct potentiometry, it is essential that readers of a publication are made aware of the method used to measure Na^+. There is need of a broader awareness of this fact in the community of scientists working in the field of electrolytes. Many authorities, including the International Federation of Clinical Chemistry and Laboratory Medicine, encourage to more and more abandon the indirect technology [4]. Modern high-throughput laboratory platforms are not compatible with direct potentiometry. Hence, the usefulness of algorithms to correct Na^+ analyzed by indirect potentiometry for lipids and proteins is currently evaluated [5, 10, 20].

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Supplementary Material: The online version of this article offers supplementary material (https://doi.org/10.1515/cclm-2021-0293).