Hamilton, F. W., Penfold, C. M., Ness, A. R., Stevenson, K. P., Atkinson, C., Day, A. M., ... Tyrrell-Price, J. (2018). Can Quantab titrator sticks reliably predict urinary sodium? *Clinical Nutrition ESPEN*, *23*, 217-221. https://doi.org/10.1016/j.clnesp.2017.09.011

University of Bristol - Explore Bristol Research

General rights

Original article

Can Quantab titrator sticks reliably predict urinary sodium?

Fergus W. Hamilton [a], Chris M. Penfold [b, c, *], Andrew R. Ness [b, c], Kirsty P. Stevenson [d],
Charlotte Atkinson [b, c], Andrew M. Day [d], Gregory M. Sebepos-Rogers [e],
Jonathan Tyrrell-Price [f]

[a] Emergency Department, Dunedin Hospital, Otago, New Zealand
[b] National Institute for Health Research (NIHR), Biomedical Research Centre Nutrition Theme, University Hospitals Bristol NHS Foundation Trust, University
of Bristol, Bristol, UK
[c] School of Oral and Dental Sciences, University of Bristol, Bristol, UK
[d] Department of Biochemistry, University Hospitals Bristol NHS Foundation Trust, Bristol, UK
[e] Oxford University Hospitals NHS Foundation Trust, Oxford, UK
[f] Department of Gastroenterology and Nutrition, University Hospitals Bristol NHS Foundation Trust, Bristol, UK

ARTICLE INFO

SUMMARY

Background & aims: Urinary sodium concentration is a commonly used marker for extracellular fluid depletion which is often associated with dehydration. A point of care test for urinary sodium may reduce delays in clinical decision making by offering more timely guidance leading to improved salt and fluid management. We compared laboratory assessed urinary sodium with a potential point of care measure of urinary chloride in a variety of in- and outpatient specialities, to explore its use as an indicator of low urine sodium.

Methods: Urinary chloride concentrations were estimated using a Quantab titrator stick in samples from patients that had been sent for urinary sodium assays. We validated the results of this titrator stick with laboratory-assessed sodium concentrations by deriving correlation coefficients between these methods and using limits of agreement testing. We determined the optimal titrator stick cut-point for identifying low urinary sodium (urinary sodium <20 mmol/L) by maximising the product of the sensitivity and specificity. This level of urinary sodium was used to mirror the British Society of Gastroenterology guidance on short bowel patients Nightingale and Woodward, 2006.

Results: We obtained laboratory urinary sodium concentration and Quantab stick chloride measures on 127 samples. Twenty three percent had a urinary sodium below 20 mmol/L so were regarded as biochemically dehydrated. A threshold of <4.3 on the Quantab scale had a positive predictive value for low sodium of 56% (95%CI 40%—71%) and a negative predictive value of 94% (95%CI 87%—98%).

Conclusions: These data suggest that the Quantab stick could be used as a point of care test to aid fluid and salt management decisions in an outpatient setting. Further work to explore the use of the titrator stick in specific patient populations at risk of salt and water depletion is justified.

1. Introduction

Sodium concentration in the urine is controlled by a complex set of endocrine and renal systems, and influenced by a number of factors [2]. In healthy people it is a marker of short-term salt (sodium chloride) intake [3]. In people who are unwell it can be used as a measure of sodium homoeostasis or (de)hydration. As people become dehydrated, the body attempts to retain fluid. The kidney does this by retaining sodium (and chloride) through both active transportation and passive diffusion through electrochemical gradients created by active transportation. Low urinary sodium levels are therefore a marker of salt depletion which can be used to assess dehydration, particularly in the presence of extracellular fluid losses. This marker is used routinely in people with intestinal failure and on home parenteral nutrition (HPN) as many cannot hydrate themselves orally so are dependent on intravenous

* Corresponding author. NIHR Bristol Biomedical Research Centre (Surgical Innovation Theme), Musculoskeletal Research Unit, Learning & Research, University of Bristol, Southmead Hospital, Westbury on Trym, Bristol, BS10 5NB, UK. Fax: +44 117342 0239.
E-mail address: Chris.penfold@bristol.ac.uk (C.M. Penfold).

replacement [1,4]. Home intestinal failure patients are spread across a wide geographical area so could benefit from a near patient test. In clinical practice a urine sodium concentration below 20 mmol/L is frequently used as a threshold to indicate clinical assessment. A low urinary sodium is likely to represent biochemical dehydration but has other causes including hyponatraemia, renal dysfunction and hyperaldosteronism. In these circumstances fractional excretion of sodium and response of urinary sodium to fluid filling may be more instructive.

Urinary sodium is a reliable test, however it can only be performed in a biochemistry laboratory. For people with disease living in the community (for example on home parenteral nutrition) there is a need for them to visit a local healthcare facility to provide or deliver a sample. The sample then has to be transferred to the local laboratory and analysed, after which the results are sent to clinicians in order for them to act on it. Such procedures can result in delays of 1—2 days between providing a sample and the treatment response. Furthermore the collection of repeated samples to monitor (de)hydration or the response to changes in management requires considerable time and effort.

An accurate and reliable point of care test for urinary sodium that is simple to use could improve care for people living in the community who need to assess their hydration status regularly (for example people on home parenteral nutrition), by reducing delays in clinical decision making. Urinary chloride however, may also be a suitable indicator of urinary sodium concentration. Previous studies have shown that the Quantab titrator stick chloride measure correlates highly with sodium in urine [5—8]. In this study we have assessed whether this titrator stick can identify people with a urinary sodium of <20 mmol/L (the cut-off point commonly used to indicate dehydration).

2. Materials and methods

We compared laboratory assessed urinary sodium concentration with Quantab titrator test stick measures of chloride in hospital urine samples that had been sent for urinary sodium assays over a five-month period (December 2014 to April 2015). We collected routinely available data on the demographics (age and sex) of the patient, the reason for the request and the clinical team requesting the assay. This study was reviewed by the University Hospitals Bristol NHS ethics committee and judged not to need full ethical approval as we were not changing therapy or collecting confidential data.

Our laboratory serves a tertiary teaching hospital in Bristol, UK. This hospital provides care for patients with intestinal failure, adult medical patients from the surrounding area (except for renal medicine), and provides regional paediatric care. Urine samples were from a wide variety of inpatient and outpatient specialities, and a small number were from primary care. Samples were collected in plain universal containers and processed centrally in the Biochemistry lab. All samples were processed by one investigator (KS), and were stored routinely for 5 days then discarded.

2.1. Laboratory assessed urinary sodium and chloride

Our laboratory uses the Cobas 8000 analyser (Roche, West Sussex, UK). This system uses ion selective electrodes to calculate the number of ions in a given solution, and can produce rapid and accurate measurements of sodium and chloride. Our analyser had a lower limit of 20 mmol/L, therefore any sample with a concentration of less than 20 mmol/L of sodium or chloride was assigned the value of 20 mmol/L in the statistical analysis. The upper limit was not reached.

2.2. Chloride titrator stick

We used the Quantab chloride titrator stick (HACH Lange, Salford, UK) to estimate urinary chloride concentration. The sticks have been used commercially for non-medical purposes (including testing swimming pools and concrete manufacture) for over thirty years, and cost approximately USD 0.75 per stick. They consist of a plastic strip with a capillary column in the centre containing sodium dichromate, which has a non-reversible reaction with chloride ions resulting in a colour change (black to white) [5]. The stick is placed in a sample (minimum around 1 ml), and the fluid rises by capillary action, causing a colour change in about 10 min. There is a printed graduation on the stick allowing this change to be quantified. Sticks are read using the provided scale, from 1.8 to 8.2. According to the manufacturer provided conversion scale this corresponds to a chloride ion concentration range of 298—6525 mg/L (8.4—184 mmol/L). As previous studies have shown inter-rater variability to be negligible [5], a single investigator (KS), blinded to the biochemical assay result, read all sticks in this study. All sticks were read at 20 min. Sticks that showed no change or with results below the valid range of the scale were recorded as missing.

2.3. Statistical analysis

We described the demographics of the study sample using means (and standard deviations) or medians (and inter-quartile ranges and ranges) for continuous data, and proportions for categorical data, as appropriate. Validation of the Quantab titrator sticks comprised direct comparisons of the two methods, and determination of the optimal Quantab titrator stick cut-off to identify people who are biochemically dehydrated based on laboratory-assessed urinary sodium concentrations.

For the direct comparison of the Quantab titrator stick results with the laboratory assessed results we converted the stick readings to mmol/L using the manufacturer provided scale. We derived a correlation coefficient between the two methods and assessed their agreement using limits of agreement testing to calculate a Bland-Altman statistic. For the purposes of these comparisons we replaced any converted Quantab titrator stick results <20 mmol/L with 20 mmol/L (n = 24), in order to be compatible with the processing of laboratory results <20 mmol/L outlined previously.

In order to determine the optimal Quantab titrator stick cut-point to identify people classified as possibly dehydrated according to biochemical assays we defined our 'gold standard' for dehydration as laboratory measured urinary sodium <20 mmol/L. We selected the Quantab titrator stick cut-off point which maximised the product of the sensitivity and specificity, as outlined by Liu et al. [9].

2.4. Sensitivity analyses

To determine whether the direct comparison of the Quantab titrator stick results with the laboratory assessed results was affected by the replacement of values below the minimum limit of the laboratory equipment with 20 mmol/L, we exclude these values and repeated these analyses. In order to determine whether our findings were biased by comparing sodium concentrations with chloride concentrations, we also compared the dipstick chloride with the laboratory measured chloride in those samples where it had been requested (n = 51). We derived correlation coefficients between chloride measured in the laboratory and chloride estimated by the Quantab titrator stick, and between sodium and chloride concentrations measured in the laboratory. We determined the optimal Quantab titrator stick cut-off point based on dehydration defined using laboratory measured chloride concentration

<20 mmol/L, and compared the agreement between dehydration defined using laboratory measured sodium and chloride concentrations using kappa statistics. To assess the potential applicability of the stick across a range of dehydration prevalences we used the values of sensitivity and specificity for our optimal Quantab stick cut-off point to calculate the negative predictive values (NPV) and positive predictive values (PPV) for theoretical dehydration prevalences from 10% to 50%. We also repeated these analyses in the subgroup of people aged <16 years to ensure the results were valid in different age groups. Statistical analysis was performed using STATA 14, (Statacorp, Texas) and the *batplot* [10] and *cutpt* [11] commands.

3. Results

3.1. Demographics

167 urine samples were brought to the laboratory for analysis during the data collection period. 87 of these (52%) were from women, 106 (63%) were from adults, and the median age was 49 years (IQR 9–71 years). The main requesting specialities were: adult gastroenterology (21%), adult medicine (15%), paediatric neurosurgery (15%), paediatric endocrinology (8%), and oncology (7%). A variety of other specialities accounted for the remaining requests. The commonest indications were investigation of hyponatraemia (30%), investigation of cerebral salt wasting (15%), monitoring of home parenteral nutrition (15%), and only 4% to investigate suspected dehydration. No specific indication was recorded by the clinical team in 35% of cases.

3.2. Urinary sodium measurements

We obtained laboratory measurements of urinary sodium concentration on 166 of the 167 samples, and we took dipstick measurements of the chloride concentration of 151 of these samples. We excluded 12 samples with laboratory measured sodium concentrations above the maximum range of the test sticks, and 12 further samples with test stick results which were outside the valid range for conversion to chloride concentrations (n = 5 below the minimum and n = 7 above the maximum). A total of 127 samples had both measurements. In 51 samples we also had laboratory urinary chloride concentration as it had been requested by the clinical team.

Twenty-nine samples (22.8%) were found to have a sodium concentration <20 mmol/L and were therefore considered to be biochemically dehydrated (Table 1). The median laboratory measured sodium concentration was 50 mmol/L (IQR 23–87 mmol/L) compared with 58 mmol/L (IQR 27–96 mmol/L) chloride for the converted Quantab titrator test (Table 1). The scatter plot between these two measures shows an association, as expected. However, there is a high degree of variability, particularly for low Quantab titrator test results (Fig. 1). The correlation between laboratory measured sodium concentration and the Quantab titrator test results, converted into concentrations of chloride, was r = 0.62.
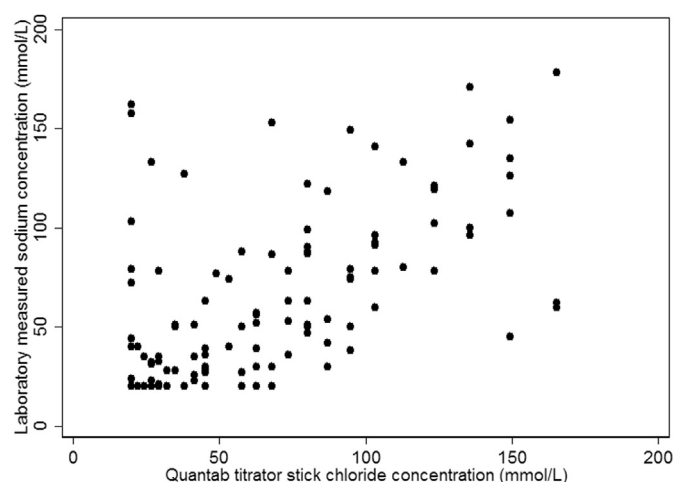

Fig. 1. Scatter plot of laboratory assessed sodium concentrations with converted Quantab titrator stick chloride concentrations.

The limits of agreement testing (Fig. 2) indicate that if the Quantab titrator sticks were used as an indication of urinary sodium concentration, it was overestimated by a mean of 3.1 mmol/L (95% limits of agreement = −69.3–75.4 mmol/L). Disagreements between the two methods occurred at both high and low laboratory measured sodium concentrations.

The optimal cut-off point for the Quantab titrator stick to indicate a sodium of <20 mmol/L was <4.3 units. 43 (34%) of the Quantab titrator stick results were below this threshold. This cut-off point corresponded to an NPV of 94.0% (95%CI 86.7%–98.0%), a PPV of 55.8% (95%CI 39.9%–70.9%), a sensitivity of 82.8% (95%CI 64.2%–94.2%) and a specificity of 80.6% (95%CI 71.4%–87.9%).

3.3. Sensitivity analysis

The correlation and agreement between laboratory measured sodium concentration and the Quantab titrator test results differed only slightly after the exclusion of 37 samples in which either the laboratory-assessed sodium or the converted Quantab titrator stick results were <20 mmol/L (r = 0.63, mean difference = 7.5 mmol/L, 95% limits of agreement = −60.7–75.7 mmol/L). The correlation between laboratory measured sodium and chloride concentrations was r = 0.79. The limits of agreement testing indicate that laboratory measured chloride concentrations were slightly higher than the sodium concentrations with a mean difference of 5.1 mmol/L (95% limits of agreement = −64.3–74.5 mmol/L). The optimal cut-off point for the sticks compared with urinary chloride <20 mmol/L was also <4.3 units, and the agreement between dehydration defined using laboratory measured sodium and chloride concentrations was substantial (92.2% agreement, κ = 0.75, P < 0.001). The subset of samples which were laboratory tested for both sodium and chloride concentrations were more likely to be

Table 1
A description of the laboratory and Quantab test stick results, and their conversion into mmol/L.

	Urine Na$^+$ (mmol/L) (n = 127)	Urine Cl$^-$ (mmol/L) (n = 51)	Quantab stick result (n = 127)	Quantab stick Cl$^-$ (mmol/L)[a] (n = 127)
Median	50	60	5.6	58
IQR	23–87	23–88	3.8–6.8	27–95
Range	20–178	20–160	1.8–8.0	8.4–165
Number (%) biochemically dehydrated[b]	29 (22.8%) (<20 mmol/L)	10 (19.6%) (<20 mmol/L)	43 (34%) (<4.3)	24 (18.9%) (<20 mmol/L)

[a] Converted using manufacturers guidelines.
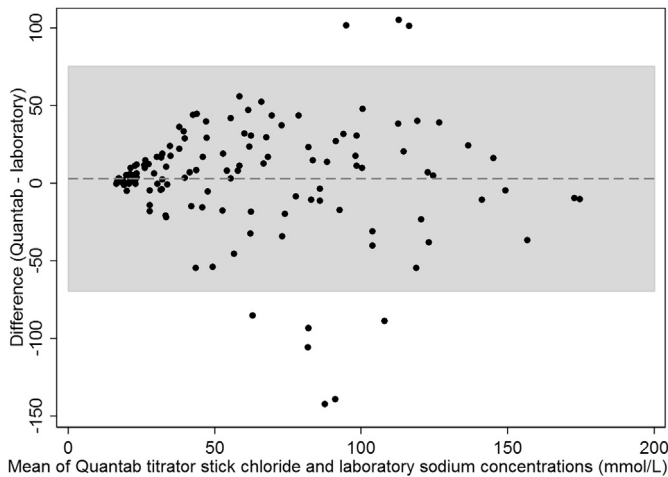[b] Concentration ≤20 mmol/L.

Fig. 2. Limits of agreement plot of converted Quantab titrator stick Chloride and laboratory assessed Sodium concentrations.

from women (59%) and from people who were older (median age = 60.5 years, IQR = 28–74 years) than the overall study sample. In this subset, the proportion of samples which were classified as biochemically dehydrated was slightly lower compared with the overall study sample (19% vs 23%, Table 1). The correlation between laboratory measured chloride and the converted Quantab titrator stick chloride results was r = 0.77. The mean difference between these two methods was 3.2 mmol/L (95% limits of agreement = −51.7–58.1 mmol/L) with the Quantab measured chloride being higher.

Using the optimal Quantab titrator stick cut-off of <4.3 units, the PPV and NPV varied from 32.2% to 97.7% respectively for a dehydration prevalence of 10%, to 81.0% and 82.4% respectively for a dehydration prevalence of 50% (Table 2). We repeated the above analysis on the sub-group of people under the age of 16 years, and the optimal Quantab titrator stick cut-off was <4.2 units.

4. Discussion

This study provides evidence that the Quantab titrator stick may be a useful clinical decision making tool to identify people who may be at risk of (biochemical) dehydration. Applying a threshold of <4.3 for the Quantab titrator sticks resulted in only six percent of negative results being incorrect. However, while the correlation between the Quantab titrator stick results and both laboratory measurements was high, it was poorer than expected.

Previous studies have shown that the Quantab titrator stick chloride measure correlates highly with sodium in urine (r > 0.95) [5–8]. In our study, we found a much lower correlation (r = 0.62),

Table 2
Variation in Quantab titrator stick PPV and NPV (cut-off = <4.3 units), by dehydration prevalence.

Prevalence of dehydration	PPV[a]	NPV[b]
10%	32.2%	97.7%
20%	51.6%	94.9%
30%	64.7%	91.6%
40%	74.0%	87.5%
50%	81.0%	82.4%

[a] PPV = Positive predictive value, i.e. the proportion of positive Quantab test stick results which are 'true positives'.
[b] NPV = Negative predictive value, the proportion of negative Quantab test stick results which are 'true negatives'.

although there was a higher correlation for chloride (r = 0.77). The reasons for this are unclear and would require further study to elucidate. A partial explanation may be that many of the previous studies have been conducted in healthy volunteers who were being assessed for salt intake, and were therefore different from our population who were being tested for renal excretion of sodium and chloride.

One previous study in 100 Emergency Department patients reported that the Quantab titrator stick had a maximal specificity of 100% and sensitivity of 93% for detecting dehydration, compared with 81% and 83% respectively for our optimal cut-off [12]. The same specification for dehydration was used as in our study (<20 mmol/L of chloride), and they had a similar proportion of people who were dehydrated (27% vs. 23% in their study and in ours, respectively). However, there were no data on diagnosis for those patients, therefore it is possible that differences in study populations contributed to differences in specificity and sensitivity.

The main strengths of this study are that the test was performed on samples from patients rather than asymptomatic volunteers and that the person reading the stick results was blind to the laboratory results. The main weakness of the study is that we did not collect information relating to other relevant clinical factors (for example intravenous fluid use, diuretic use, renal function, metabolic/endocrine disorders). This meant we were unable to determine the extent to which deviations from normal physiological function affected the validity of the sticks, particularly the correlation between urinary chloride and sodium concentrations. However, despite this, we found the same optimal cut-off point using urinary chloride concentration to specify dehydration as we found for urinary sodium, which suggests that any imbalance between urinary sodium and chloride concentrations in our population did not affect our main results. A further weakness was that the sticks were read by a single observer, however this is unlikely to have affected our findings as a previous study showed that inter-rater variability for this test was negligible [5]. Finally, this study was performed in one centre which serves a large paediatric and intestinal failure population, who provided the majority of samples. As such, it may not be possible to extrapolate the findings to other indications, particularly those in which dehydration is more or less prevalent than this population.

Although the results of this study are encouraging, further work is needed to establish the usefulness and cost-effectiveness of Quantab titrator sticks in people at risk of dehydration. Firstly, it is important to understand why the correlation between the Quantab sticks and laboratory measurements was worse in our study than in previous studies, and whether we can address this issue to reduce false positive results. Urine samples in our study were from a variety of different patient groups. A next step would be to test the validity of these sticks in a single relevant population at risk of dehydration and who could potentially benefit from these tests, such as people with intestinal failure and on parenteral nutrition. A prospective study would allow the collection of information on potentially relevant clinical factors, which would enable a more detailed exploration of the utility of the sticks. In addition, factors such as intra-individual variability in the stick readings could be elucidated. Finally, further work to look at associations between biochemical measures of dehydration and clinical outcomes is needed.

5. Conclusions

In this study, we present a quick and convenient method of estimating urinary sodium at the bedside. The Quantab titrator stick is rapid and may be a useful clinical decision making tool in people at risk of dehydration. The current clinical cut-off point for

biochemical dehydration (urinary sodium concentration <20 mmol/L) equated to a result of <4.3 on the Quantab scale in this study population. It is possible that people on, for example home parenteral nutrition who are dependent on a static prescription to remain hydrated, may be able to use these sticks to self-screen for risk of dehydration, but further work is needed to fully elucidate their clinical potential.

Ethics approval and consent to participate

This study was reviewed by the University Hospitals Bristol NHS ethics committee and judged not to need full ethical approval.

Funding source

This study was supported by the UK National Institute for Health Research Biomedical Research Unit in Nutrition, Diet and Lifestyle at University Hospitals Bristol NHS Foundation Trust and the University of Bristol. The funder had no involvement in the study design; collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the article for publication.

Statement of authorship

F.H. contributed to the study design, data collection and drafting of the paper; C.P. contributed to the data analysis, interpretation of data and drafting of the paper; A.N. contributed to the interpretation of data and revisions of the paper; K.S. contributed to the data collection and revisions of the paper; C.A. contributed to the interpretation of data and revisions of the paper; A.D. contributed to the study design, data collection and drafting of the paper; G.S.R. contributed to the study design and revisions of the paper; J.T.P. contributed to the study design, data collection and drafting of the paper. All authors read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflicts of interest.

List of abbreviations

HPN   Home parenteral nutrition.
NPV   Negative predictive value.
PPV   Positive predictive value.

References

[1] Nightingale J, Woodward JM. Guidelines for management of patients with a short bowel. Gut 2006;55:iv1–12. https://doi.org/10.1136/gut.2006.091108.
[2] Schrier RW. Diagnostic value of urinary sodium, chloride, urea, and flow. J Am Soc Nephrol 2011;22:1610–3. https://doi.org/10.1681/ASN.2010121289.
[3] Van Dam RM, Hunter D. Biochemical indicators of dietary intake. In: Willett W, editor. Nutr. Epidemiol. New York, NY: Oxford University Press; 2013.
[4] Van Gossum A, Cabre E, Hébuterne X, Jeppesen P, Krznaric Z, Messing B, et al. ESPEN guidelines on parenteral nutrition: gastroenterology. Clin Nutr 2009;28:415–27. https://doi.org/10.1016/j.clnu.2009.04.022.
[5] Sloan PJ, Beevers G, Baxter FE. The Quantab strip in the measurement of urinary chloride and sodium concentrations. Clin Chem 1984;30:1705–7.
[6] Jeffery RW, Mullenbach VA, Bjornson-Benson WM, Prineas RJ, Forster JL, Schlundt DG. Home testing of urine chloride to estimate dietary sodium intake: evaluation of feasibility and accuracy. Addict Behav 1987;12:17–21. https://doi.org/10.1016/0306-4603(87)90004-9.
[7] Luft FC, Fineberg NS, Sloan RS. Overnight urine collections to estimate sodium intake. Hypertension 1982;4:494–8. https://doi.org/10.1161/01.HYP.4.4.494.
[8] Minetti EE, Airaghi C, Cozzi MG, Guidi E. Urinary salt titrator stick: a useful and quick estimate of dietary sodium intake? J Hum Hypertens 1992;6:287–9.
[9] Liu X. Classification accuracy and cut point selection. Stat Med 2012;31: 2676–86. https://doi.org/10.1002/sim.4509.
[10] Mander A. BATPLOT: stata module to produce Bland-Altman plots accounting for trend. 2012.
[11] Clayton C. CUTPT: stata module for empirical estimation of cutpoint for a diagnostic test. 2013.
[12] Sherman RA, Faustino EF. Bedside urinary chloride measurement: assessment in the acute setting. Am J Emerg Med 1987;5:52–3.