Evaluation of urinary chloride dipsticks for the rapid estimation of hydration status in patients receiving artificial nutrition: Feasibility study

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Abstract

Background and aims: The home parenteral nutrition population (HPN) face many challenges, especially with respect to fluid balance management. A low urinary sodium concentration of <20 mmol/L is commonly used as an indicator of dehydration that requires clinical assessment in these patients. The Quantab titrator dipstick measures chloride concentration of a solution and correlates with sodium concentration. We assessed whether it would be feasible to use the Quantab dipstick in the HPN population and explored relationships between Quantab dipstick estimated chloride concentration and quality of life (QOL).

Methods: Patients on HPN were asked to collect urine samples at 5 specific times points (day 0,7,14, 21 and 28) to send to the laboratory for formal electrolyte analysis. The participant and a member of laboratory staff tested these samples with the Quantab dipstick to estimate urinary chloride concentration. Participants were instructed to complete a QOL questionnaire at each of the 5 time-points in addition to a baseline demographic questionnaire and an end-of-study questionnaire. Six participants completed an interview at the end of the study period. The

relationship between participant-derived and laboratory-derived data was assessed using rank correlation coefficients. QOL assessment was correlated with urine dipstick measurements. Results: 10 patients on HPN completed the study. Data on chloride concentration as estimated by the dipstick (assessed by participants and by the laboratory) and sodium concentration from the laboratory were available for 47 urine samples. There was a positive relationship between participant dipstick estimated chloride concentration and laboratory sodium (Kendall's τ=0.45; P<0.001; Spearman's r_s=0.58 P<0.001; 47 pairs). There was a strong correlation between chloride concentrations estimated by dipstick in the laboratory and by participants (Kendall 0.58 p<0.001, Spearman's 0.69 p<0.001; 47 pairs). In exploratory analyses, there was no relationship between QOL and dipstick estimated chloride concentration. Participants had no issues collecting urine samples but some difficulties were reported with determining the dipstick reading. Conclusions: Patients on HPN are able to collect urine specimens, complete QOL questionnaires, and are capable of using the Quantab dipstick to estimate urinary chloride concentration. The Quantab dipstick correlates with laboratory measured sodium and chloride concentrations. Further work is required to fully establish whether this point-of-care test could be used to guide fluid balance management in the HPN population.

Key words

Urinary sodium

Urinary chloride

Home parenteral nutrition

Dehydration

Introduction

Patients with intestinal failure (IF) have insufficient bowel length or function to maintain their fluid, electrolyte or protein-energy balance and are dependent on long term intravenous support at home with parenteral nutrition (PN). As such, patients with IF are at high risk of dehydration and consequent electrolyte abnormalities, with the potential for progression to renal dysfunction and its associated morbidity and mortality [1]. Risk of dehydration may be related to reliance on TPN, as reflected in the number of days per week infusions are required, as well as underlying diagnosis. Home parenteral nutrition (HPN) can have a negative impact on quality of life (QOL) but it can be difficult to distinguish the effects from the underlying illness or the PN regime and its associated complications [2], such as dehydration. Conversely, despite the restrictions imposed by HPN, some patients find it enhances their daily living compared to their time of ill-health prior to commencing HPN [3]. National guidance recommends spot testing of urinary sodium concentration as a measure of dehydration [4], with a sodium concentration of less than 20 mmol/L an indication for clinical assessment. Due to the relatively small numbers and complex multidisciplinary needs of this patient group, IF and PN services are centralised to approximately 50 centres in the UK [5], leading to a wide geographical spread of the HPN population. Urinary sodium measurement can only be performed in a laboratory and the inherent time and effort required for patients to submit urine samples for analysis can lead to delays in treatment decisions and monitoring of treatment effects. A rapid, accurate and simple point-of-care test would be useful in the HPN population to facilitate regular assessment of hydration status. This could ultimately improve their care by reducing delays in clinical decision making, enhancing patient autonomy and potentially improving quality of life.

Urinary chloride concentration may be a suitable indicator of urinary sodium concentration as they are highly correlated. The Quantab dipstick rapidly measures the chloride concentration of a solution and studies have shown that Quantab dipstick chloride measurements correlate highly with urinary sodium concentration assessed in the laboratory [6-9]. In a recent study by Hamilton et al a value of <4.3 on the scale printed on the Quantab dipstick (equivalent to 24mmol/L of chloride) had a negative predictive value of 94% for low sodium in samples from patients from a

variety of medical specialities that had been sent for urinary sodium assays [10]. However, that study included few patients with IF and focussed on inpatients with suspected dehydration, rather than patients living at home on PN.

In this study our aim was to assess the feasibility of estimating urinary chloride concentration with the Quantab dipstick in the HPN population. We also wanted to explore the relationship between urinary chloride and QOL. The results will help inform the design of an appropriately powered study examining the effect of home hydration monitoring using Quantab dipsticks in patients living at home on HPN.

Materials and Methods

Patient and public involvement (PPI)

Two PPI meetings were held during the planning stages of the study to discuss patient experience of managing hydration status, introduce the concept of the dipstick and to review the study materials and protocol. The design of the protocol and study materials were refined based on these discussions.

Participant selection

Participants were recruited from University Hospitals Bristol and Weston NHS Foundation Trust (UHBW). UHBW is a regional centre for managing patients with intestinal failure on HPN. The nutrition team at UHBW is responsible for overseeing the care of more than 50 patients who receive HPN or fluids. In this study the aim was to recruit 20 patients. The intention had been to also assess the correlation between urinary electrolytes and clinical assessment of dehydration among inpatients on TPN. However, this was obscured by too few patients being dehydrated.

Eligibility criteria

To be eligible for recruitment potential participants required: a diagnosis of IF, to be established on a PN/fluid regime, aged 18-65 years old and have capacity to give informed consent. Exclusion criteria included: patients receiving haemodialysis or diuretics given their potential impact on urinary electrolytes, and being over the age of 65 due to impaired renal concentrating mechanisms.

Participant recruitment

Potential participants who met the inclusion criteria were sent a letter inviting them to participate in the study. Those who expressed interest were sent a Patient Information Sheet (PIS) and seen in a designated clinic where informed written consent was obtained.

Baseline measures

At the initial clinic visit each participant's medical background, drug history and PN/fluid prescription were confirmed and their body mass index (BMI) in kg/m^2 was calculated from clinical measures of height and weight. Serum creatinine within three months of commencement of the study was recorded. Other baseline demographic data were obtained using a self-reported questionnaire that asked participants to select the most appropriate option for ethnicity, marital status, education level, employment status, alcohol intake and smoking status.

The Quantab titrator dipstick

The use of the Quantab titrator dipstick (HACH Lange) has been described in detail in a previous study [9]. In summary, the Quantab dipstick is 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. When placed in a sample of solution a colour change occurs in approximately 10 minutes which can be quantified with the printed graduation on the dipstick which corresponds to a chloride ion concentration in mg/L. There are two types of Quantab dipsticks available: the 'low

range' Quantab dipstick covers a chloride ion concentration range of 27-624 mg (0.76-17.88 mmol/L) and the 'high range' dipstick covers a range of 298-6525 mg/L (8.4-184 mmol/L). The low range dipstick was used in the present study.

Participant testing

We wished to assess the acceptability of collecting and testing urine samples with the Quantab titrator dipstick by the HPN population and whether these measurements could estimate urinary chloride concentration. Participants were instructed to collect a urine sample in a plain universal container, dipstick test the urine with the Quantab dipstick, and send the urine sample to the laboratory at UHBW at the following time-points – day 0, 7, 14, 21 and 28. Repeated samples were obtained from each participant, rather than using a single sample from a larger pool of patients, as there are relatively small numbers of patients on HPN. A table to record dipstick results was provided. Participants were asked to collect a sample before midday if possible, but not to use urine from the first void of the day. In addition, if the participant planned to administer additional intravenous (IV) fluids beyond that of their normal prescription they were instructed to collect, dipstick test and send a urine sample to the laboratory before and after the extra IV fluids. Participants were instructed not to change their normal management based on the urine dipstick result.

Laboratory testing

The UHBW laboratory uses the Cobas 8000 analyser (Roche, West Sussex, UK) for electrolyte measurement of a solution, as previously described [9]. All urine samples received in the laboratory were analysed for chloride, sodium, potassium, creatinine and urea. Laboratory Quantab dipstick measurements were performed to assess inter-rater reliability. Prior to automated analysis, an aliquot of urine was separated into a test tube for dipstick analysis using the Quantab dipstick. A single investigator (KS) blinded to the biochemical assay result read all

dipsticks in this study. All dipsticks were read at 20 minutes when the reaction would be complete, as the participants were instructed to do.

Quality of life assessment

We wanted to assess the acceptability of completing QOL assessment questionnaires and explore whether there was a relationship between QOL and biochemical signs of dehydration. On days 0, 7, 14, 21 and 28 participants were asked to complete a Home Parenteral Nutrition Quality of Life (HPN-QOL) questionnaire. This questionnaire has 48 items and was developed and tested in patients on long-term HPN [11]. Response to the question 'During the past week, how has your quality of life been?' was used in analyses. In addition, if the participant administered additional IV fluids beyond that of their normal prescription, they were asked to rate how they felt before and after the extra fluid using a five-point scale depicted by sad to happy faces.

Participant feedback and interviews

All participants were asked to complete a questionnaire at the end of the study period asking about their experience performing the urine testing, whether they perceived any relationship between sense of hydration and sense of well-being, and whether they would be prepared to use the dipsticks to guide management in the future. During the designated clinic for consent, all participants were asked whether they would participate in an interview after the study. If they agreed, written consent was gained. After the study, six participants were chosen to participate in a face-to-face, semi-structured interview where their experience on HPN and the study were explored further. The selection of the six participants to invite for interview was guided by sex, age, underlying diagnosis, length of time on HPN and participant availability.

The interviews were conducted by SJ and were audio recorded on an encrypted digital recorder and transcribed verbatim using a University of Bristol approved transcription service. An inductive thematic analysis was undertaken by SJ and an experienced qualitative researcher (AS). The transcripts were read for familiarisation with the data and a coding framework was developed

following the procedure outlined by Braun and Clarke, (2006) [12]. Both analysts coded the transcripts independently and then met to discuss any discrepancies in coding until consensus was reached. Once a definitive coding frame was developed all transcripts were stored and coded in NVivo 11. Once all transcripts were coded the following themes were identified: self-efficacy, utility and perceived benefit of dipstick, acceptability of home testing and wellbeing and acceptability of study reporting materials.

Statistical analysis

The laboratory analyser had a lower limit of 20 mmol/L for sodium and chloride, therefore any sample with a sodium or chloride concentration of less than 20 mmol/L were arbitrarily assigned the value of 0 mmol/L; these were highlighted in Figures 2-3. Dipstick values were converted to concentration of chloride according to the manufacturer's instructions. Any dipstick values converted to chloride concentration below the valid detection level of the dipstick (0.76 mmol/L) were arbitrarily assigned a value of 0 mmol/L, and those above the valid detection level of the dipstick (17.88 mmol/L) assigned a value of 20 mmol/L.

Because of results below or above the limits of assay or dipstick measurement, relationships between them were described using rank correlation coefficients (Spearman and Kendalls tau), assigning results below or above the limits to the (equal) lowest or (equal) highest ranks respectively.

Demographics of completers and non-completers were compared with the non-parametric Mann-Whitney U-tests (continuous variables) and Fishers Exact tests (categorical variables).

Ethics approval

This study was reviewed and approved by the South West-Frenchay Research Ethics Committee (reference number 17/SW/0175).

Results

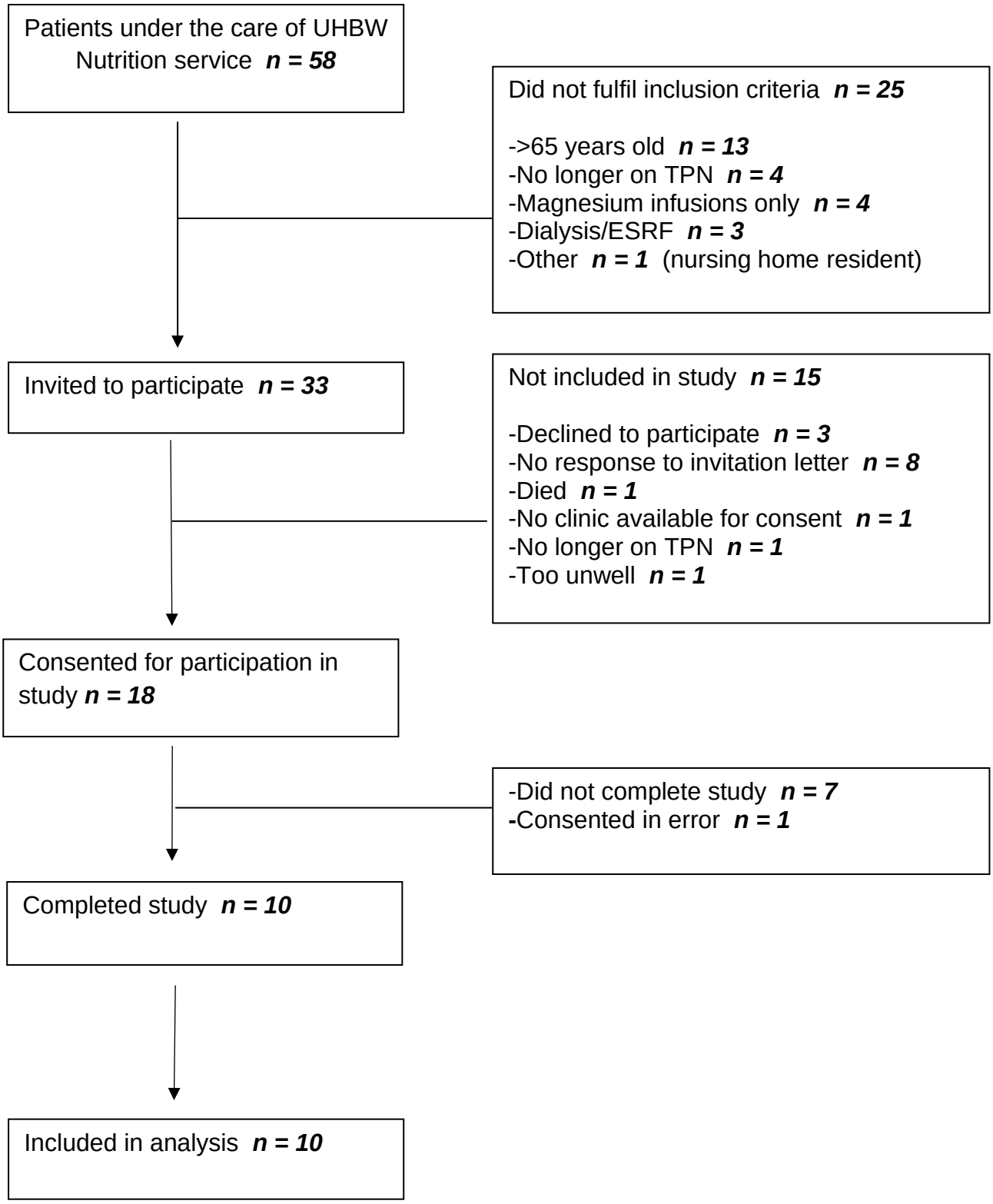
Patient and public involvement, recruitment and demographics

Four patients receiving HPN attended the first PPI group. They discussed a number of aspects of life on PN and that assessing the presence and severity of dehydration was guesswork. They relied on a variety of methods to assess dehydration such as volume and colour of urine, heart rate, dry mouth, dizziness on standing and confusion. They had different strategies for self-management when they felt dehydrated including drinking water, drinking electrolyte solution, and using extra IV fluids. During a 'crisis' period they would contact the Nutrition team at the hospital more frequently. The group unanimously felt that more guidance would be helpful and an objective measure of hydration status would be useful alongside the subjective methods they currently use. The group felt the Quantab dipsticks would be helpful if they could detect dehydration early so they could act before they become symptomatic.

At the time of recruitment (October 2017) the Nutrition team at University Hospitals Bristol and Weston NHS Foundation Trust managed 58 patients with intestinal failure on a home parenteral nutrition or fluid regime. Based on a review of their medical records, 33 were considered eligible for recruitment and were invited to participate in the study (**figure 1**). Written informed consent was obtained from 18, of which 10 completed the study and were included in the analysis. Eight patients who consented did not complete the study (seven were lost to follow up and one was no longer on TPN and had been consented in error).

Baseline characteristics of the participants are shown in **Table 1.** Of the 10 participants that completed the study the median age was 45 (range 27-64) and seven were female. Seven participants were receiving daily TPN, and three were receiving TPN three, four and five days per week respectively. The median duration of time on TPN was 32.5 months (range 3-204). Four participants had Crohn's disease, three had short bowel syndrome from a variety of causes, one had malabsorption, and two had a motility disorder. There were no differences between the 10 participants that completed the study and those who did not (**supplementary table 1**).

Figure 1 *Recruitment diagram*



UHBW: University Hospitals Bristol and Weston NHS Foundation Trust , TPN: Total parenteral nutrition, ESRF: end-stage renal failure

Table 1 *Baseline clinical and demographic data of participants who completed study (n=10)*

	Number
Gender	
Male	3
Female	7
Age (years)	
18-29	1
30-39	4
40-49	0
50-59	4
60-65	1
Diagnosis	
Crohn's	4
Short bowel syndrome	3
Malabsorption	1
Other	2
BMI (kg/m^2)	
<18	1
18-24.9	7
25.29.9	2
≥30	0
Creatinine (μmol/L)	
<60	5
60-79	1
80-99	1
100-119	3
≥120	0
Days per week on TPN	
1-2	0
3-4	2

5-6	1
7	7
Duration on TPN	
<1 year	3
1-2 years	1
2-5 years	2
5-10 years	0
>10 years	2
Information not available	2
Ethnicity	
Caucasian	8
Non-Caucasian	2
Educational status	
No formal qualification	1
GCSE	4
A-level/equivalent	1
Degree	2
Information not available	2
Current smoker	
Yes	0
No	10
Frequency of alcohol intake	
Never	3
Monthly or less	2
2-4 times per month	2
2-3 times per week	1
4+ times per week	2

TPN: total parenteral nutrition, BMI: body mass index

Supplementary table 1 *Descriptive statistics comparing the completers of the study and those lost to follow up.*

	Completers (n = 10) Median (range) or N	**Lost to follow up (n = 7)** Median (range) or N	**Comparison[1]**
Age	45 (27-64)	45 (27-57)	P=0.88
Gender	7 female; 3 male	5 female; 2 male	P>0.99[2]
Days per week on TPN:	7 (3-7)	7 (3-7)	P=0.56
Duration (months) on TPN	32.5 (3-204)	36 (8-84)	P=0.49
Distance from UHBW (miles)	13.35 (1-62.5)	10.1 (4.3-23.7)	P>0.99
Diagnosis Crohn's Short bowel syndrome Malabsorption Other	 4 3 1 2	 2 3 0 2	P>0.99

[1] all significance tests are two-tailed' Mann-Whitney U test unless otherwise indicated

[2] Fisher's Exact test

TPN: total parenteral nutrition, UHBW: University Hospitals Bristol and Weston NHS Foundation Trust

Sample collection and baseline data

Eight participants had complete data, i.e., they completed the five dipstick measurements at the specified time-points, returned the urine samples to the laboratory for formal analysis and dipstick testing, and completed the questionnaires (baseline demographic questionnaire, post-study feedback questionnaire, and HPN-QOL questionnaire). Two participants sent urine samples to the lab for testing but did not return any self-reported data (questionnaires or participant dipstick readings) so it was not possible to compare their measurements with laboratory measurements. Four participants collectively administered a total of ten additional infusions of intravenous fluids during the study period and performed extra urine dipstick testing. Laboratory dipstick readings and formal electrolyte analysis were available for nine of these infusions, but self-reported data (questionnaire data and dipstick readings) were only available for four of the infusions.

In total 65 urine samples were received in the laboratory, for which laboratory dipstick estimates of chloride concentration and laboratory measures of sodium, chloride, potassium, urea and creatinine were available. Results from dipstick tests conducted by participants were available for 49 samples, although one dipstick reading was excluded as it was not a reading that could be converted to a chloride concentration using the printed scale. In addition, laboratory data was not available for one sample, which resulted in paired data (i.e., data from participant and laboratory) available for 47 samples. In relation to timing of sample collection, 32 samples were obtained before midday, 14 after midday, and time of day was unknown for 19 samples.

There were 27 laboratory and 16 participant dipstick readings (includes 10 pairs) that were above the valid range of the dipstick for conversion to chloride concentration, and one paired laboratory and participant dipstick reading below the valid range. The median laboratory measured sodium concentration was 38.0 mmol/L (interquartile range (IQR) <20-66 mmol/L). 17 / 65 (26%) samples had a laboratory sodium concentration <20 mmol/L and were therefore considered to be biochemically dehydrated. The median laboratory measured chloride concentration was 76.8 mmol/L (IQR 24.1-109.3 mmol/L). 15 / 65 (23%) samples had a laboratory chloride concentration <20 mmol/L.

Inter-rater reliability

There was a strong correlation between chloride concentrations measured by dipstick in the laboratory and by participants (Kendall's τ=0.58 p<0.001, Spearman's 0.69 p<0.001; 47 pairs) (**figure 2**).

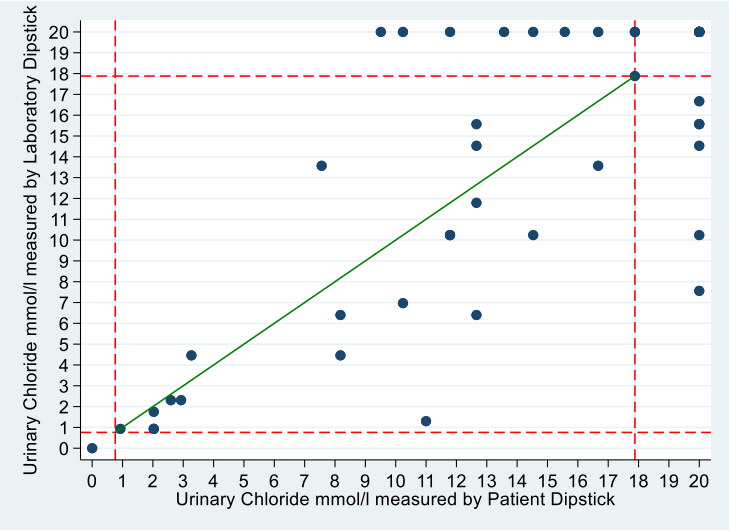
Relationship between sodium and chloride

There was a positive correlation between laboratory measured chloride and laboratory measured sodium (Kendall's τ=0.37; P<0.001; Spearman's r_s=0.47 P<0.001; n=65 samples) (**figure 3**)**.** In addition, there were positive correlations between chloride estimated by participant dipstick and laboratory measured sodium (Kendall's τ=0.45; P<0.001; Spearman's r_s=0.58 P<0.001; n=47 samples), and between chloride estimated by laboratory dipstick and laboratory measured sodium (Kendall's τ=0.24; P=0.011; Spearman's r_s=0.31 P=0.012; n=65 samples) concentrations.

Relationship between dipstick chloride and laboratory chloride

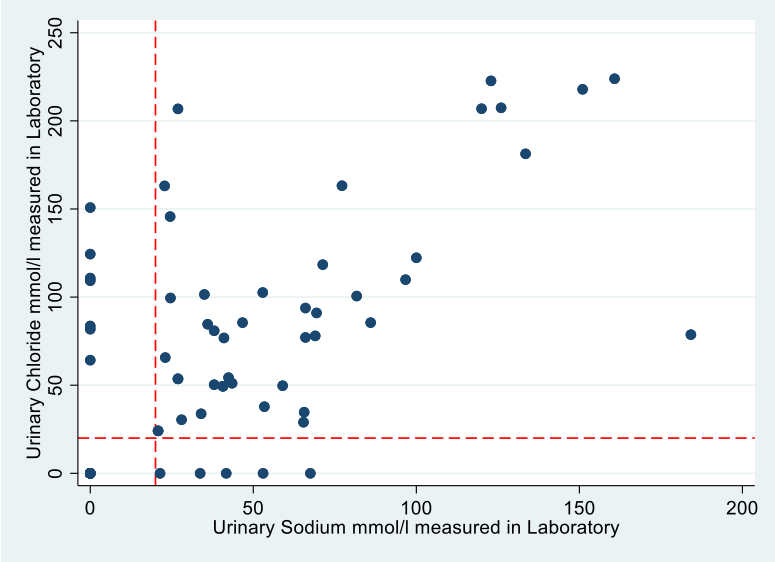
There were positive correlations between the concentration of chloride estimated using the dipstick and using the 'Cobas analyser'; participant dipstick and laboratory chloride: Kendall's τ=0.49; P<0.001; n=47 samples; Spearman's r_s=0.63 P<0.001, and laboratory dipstick and laboratory chloride: Kendall's τ=0.41; P<0.001; Spearman's r_s=0.54 P<0.001; n=65 samples.

Figure 2 *Relationship between laboratory and participant assessed urinary chloride as estimated by the Quantab dipstick.*



The red dotted lines inidicate the limits of measurement for the valid range of the dipstick with converted concentrations of >17.88 mmol/L arbitrarily assigned a value of 20 mmol/L, and <0.76 mmol/L arbitrarily assigned a value of 0 mmol/L. The green line shown would be the line of 'perfect agreement'

Figure 3 *Relationship between urinary sodium and urinary chloride concentration measured in the laboratory with the 'Cobas analyser'.*



The red dotted lines indicate the limit of laboratory measurement (20 mmol/L) with any value below this arbitrarily assigned a value of 0 mmol/L

Quality of life and dipstick measured urinary chloride concentration

Data on QOL at each of the five time-points were available for eight participants. ***Table 2*** displays the QOL score and urinary chloride concentration as estimated by the participants' Quantab dipstick at the five time-points. Quality of life ratings were not correlated with participant dipstick estimated chloride concentration (Kendall's τ=0.01; P=0.95; Spearman's r_s=-0.0002; P>0.99 respectively). This analysis pools all results and does not take into account correlated results from the same individual, but visual inspection of individual participant data in table 2 did not suggest strong within-subject relationships between QOL and dipstick estimated chloride concentration.

Table 2 *Quality of life (QOL) and chloride concentration as estimated by patient Quantab dipstick for the eight participants with available QOL and dipstick data.*

Time-point	**Day 0**		**Day 7**		**Day 14**		**Day 21**		**Day 28**	
Participant	QOL score	Quantab dipstick converted to chloride concentration (mmol/L)	QOL score	Quantab dipstick converted to chloride concentration (mmol/L)	QOL score	Quantab dipstick converted to chloride concentration (mmol/L)	QOL score	Quantab dipstick converted to chloride concentration (mmol/L)	QOL score	Quantab dipstick converted to chloride concentration (mmol/L)
1	6	8.18	6	>17.88	5	2.93	4	12.66	4	14.53
3	4	2.59	4	8.18	7	17.88	6	12.66	6	17.88
4	7	2.03	7	11.79	5	N/A	6	2.03	1	<0.76
5	7	>17.88	7	>17.88	4	>17.88	8	>17.88	5	>17.88
6	7	>17.88	4	15.57	6	17.88	7	11.79	5	14.53
8	4	9.51	8	16.67	5	10.24	5	12.66	6	13.57
10	0	>17.88	0	>17.88	0	>17.88	0	>17.88	0	>17.88
11	8	16.67	10	>17.88	7	11	9	7.56	8	>17.88

QOL graded on a scale from 0 (very bad) to 10 (very good)

Acceptability of the data collection protocol

Findings from the interviews and data from the post-study questionnaire (**table 3)** indicated that participants had no substantial issues collecting urine specimens. Questionnaire responses showed that half of the participants reported problems using the dipsticks. The two highlighted issues were uncertainty as to when to read the results from the dipstick, and some difficulties defining the top of the peak from which the reading against the graded scale is made.

Table 3 *Summary of responses to the end-of-study questionnaire*

Question from end-of-study questionnaire	**No**	**Yes**	**Not sure**
Did you have any problems collecting urine specimens?	8	0	0
Did you have any problems using the dipstick?	4	4	0
Did you find the instructions easy to follow?	0	8	0
In the future would you be prepared to make a decision about administering yourself fluids based on the urine dipstick result?	0	7	1

In the interviews, participants indicated that it can be problematic getting urine samples to their GP to be sent to the laboratory for the Nutrition team to review.

> *'…but obviously when I'm hooked up to my drip stand and everything, it can be quite difficult sometimes for me just to get in my car and go down to my doctors surgery and drop it in'.* (123, Female, short bowel syndrome)

Feedback from the initial PPI groups and also from post-study interviews indicated that participants liked the idea of the immediate feedback the dipstick result could provide, and the potential for enhancing their autonomy and aiding self-management of their condition.

> '…*but I think it is quite good to have something that you can do as a patient just to help you make those decisions. You are given that decision making power of, do you need to have some fluid or not, and you have got your fluid at home. I think having something extra to help you make that decision is good.' (*122, Female, Crohn's disease)

> *'I find that when you've got something like this, having your own control over something is really important. And, if you are told that you can work within these parameters, I think it's really important that you can make some decisions about yourself*' (121, Female, Crohn's disease)

Participants said that they would trust the result of the dipstick but would want to know how sensitive and specific the test is, how frequently to use it and when to use it. Participants indicated they would be prepared to use the dipsticks in the future to guide fluid management but they would want clear guidance and action points on the utility of the dipstick.

> '*I think so. If it gives you an added bit of information to how you are feeling. I am reluctant to use fluids but then, if there was something else that added – partly that is just because I don't like to use it if I have to. Actually, if I had something that was confirming that actually, maybe I am a bit dry, it probably would be beneficial. With a dipstick, it would make me more likely to*. (122, Female, Crohn's disease)

Sensitivity and specificity of the dipstick for identifying biochemical dehydration

It was not possible to establish an optimal cut-off point on the dipstick to identify a low urinary sodium (<20 mmol/L) concentration as the 'low range' Quantab dipstick was used, for which the upper valid range of the dipstick converts to a chloride concentration of 17.88 mmo/l. Of the 47 samples with both laboratory sodium concentration and participant dipstick reading, 31 had a laboratory assessed sodium concentration ≥ 20 mmol/L. Of these, 14 had a dipstick reading (converted to chloride concentration) above 17.88mmol/L. Sixteen of the 47 samples had a laboratory assessed sodium concentration < 20 mmol/L. Two of these had a dipstick reading (converted to chloride concentration) above 17.88mmol/L, and 14 had a dipstick reading (converted to chloride concentration) of ≤ 16.67 mmol/L. This corresponds to a sensitivity for dehydration (i.e., the ability to correctly identify those with a urinary sodium concentration < 20 mmol/L) of 87.5%. Seventeen of the 31 participants with a laboratory assessed urinary sodium concentration ≥ 20 mmol/L had a dipstick reading (converted to chloride concentration) of >16.67mmol/L. This corresponds to a specificity for dehydration (i.e., the ability to correctly identify those with a urinary sodium concentration ≥ 20 mmol/L) of 54.8%.

Relationship between administration of additional intravenous fluids, quality of life and urinary chloride concentration

Overall, only four participants administered extra fluid infusions during the study period. Data on the feelings score, dipstick measurements and laboratory measurements before and after additional infusions are shown in Table 4. The administration of extra intravenous fluids did not have a consistent effect on the sense of wellbeing in the participant, on dipstick readings or on laboratory measurements.

Table 4 *Summary of feelings score, laboratory and participant dipstick readings, and laboratory measures of sodium and chloride concentrations*

Participant	Infusion	Feelings score (1-5)		Laboratory dipstick value (converted to chloride concentration (mmol/L))		Participant dipstick value (converted to chloride concentration (mmol/L))		Laboratory measured chloride (mmol/L)		Laboratory measured sodium (mmol/L)	
		Pre-fluids	Post-fluids	Pre-fluids	Post-fluids	Pre-fluids	Post-fluids	Pre-fluids	Post-fluids	Pre-fluids	Post-fluids
1	1 2 3	2 3 2	4 4 3	1.75 16.67 0.93	6.97 15.57 4.46	2.03 >17.88 0.93	10.24 >17.88 3.27	<20 85.5 <20	29 109.9 <20	33.7 86 21.4	65.4 96.7 41.7
4	1 2	3 1	3 1	10.24 No result	6.4 No result	11.79 No result	12.66 2.03	<20 No result	<20 No result	<20 No result	<20 No result
7	1	No result	No result	4.91	6.97	No result	No result	118.4	163.2	71.3	77.2
12	1 2 3 4	No result No result No result No result	No result No result No result No result	1.52 >17.88> 17.88 >17.88	>17.88 14.53 >17.88>17.88	No result No result No result No result	No result No result No result No result	53.6 91 51.1 223.39	100.6 24.1 85.5 49.4	26.9 69.4 43.5 160.8	81.7 20.8 46.7 40.7

Discussion

This feasibility study demonstrates that patients on HPN face challenges when managing their hydration status and would value objective support. They are willing to collect urine samples, complete quality of life (QOL) questionnaires, and are capable of using the Quantab dipstick to estimate urinary chloride concentration. This study begins to address a major concern in the HPN population – dehydration. It is a real-world study showing that patients with IF can and will utilise a urine dipstick to test their urine for chloride concentration. It also shows the frequency of supplemental fluids in a single centre patient population, although this is based on a small sample size.

The HPN population are a complex set of patients with variable underlying pathology and fluid balance issues, and one-off measurement of urinary electrolytes may not be the best way to assess fluid balance status. We did not differentiate patients based on underlying diagnosis or days per week on TPN, but these factors affect a patient's reliance on TPN and therefore their reactions to feelings of thirst. A larger study would allow these factors to be assessed.

Previous studies in healthy volunteers have shown that Quantab dipstick chloride measurement correlates highly with urinary sodium [6-8]. Although our findings are not directly comparable given that we did not assess correlations, but instead used a non-parametric measure of relationships between the ranked data, we nevertheless showed a similar relationship between Quantab dipstick chloride concentration and laboratory measured sodium. The relationship was stronger with laboratory measured urinary chloride than sodium, but this is not surprising given that the dipstick is intended to measure chloride. Qualitative data demonstrated that it is acceptable for the HPN population to test their urine. When testing inter-rate reliability, a strength of the study is that a single technician performed all laboratory dipstick readings and was blinded to formal laboratory results and participant dipstick results. However, some participants experienced difficulties with interpreting the dipstick reading which may have affected associations with laboratory measurements. Future studies could provide additional pictures of examples of dipstick readings to minimise such difficulties.

Specificity of the dipstick for detecting biochemical dehydration was lower than the sensitivity (55% vs. 87.5%). This was in part due to the suboptimal association between urinary sodium and chloride. In addition, use of the low-range dipstick made it difficult to compare the dipstick and laboratory measurements due to many samples being out of the dipstick valid range. This also prevented the identification of an optimal cut-off to identify patients with low urinary sodium.

Other possible causes of the discordance between urinary sodium and chloride could be medications. One patient was taking 7mg prednisolone daily adrenal replacement and one was prescribed 4g sodium bicarbonate daily, both of which may affect chloride excretion. The laboratory measured urinary sodium and chloride correlated well in the patient taking prednisolone

which suggests that low-dose prednisolone in this context has little mineralocorticoid activity. However the urinary chloride was significantly higher than the urinary sodium in the patient receiving sodium bicarbonate. It may be that the anion bicarbonate cross reacted with the dipstick. We had insufficient patient numbers to subdivide by residual anatomy or underlying pathology which could also impact on gastrointestinal electrolyte losses and affect urinary electrolyte secretion.

There are no published data on use of supplemental IV fluids by HPN patients. In an effort to make a clinical correlation with dipstick readings we collected symptom and dipstick response to supplemental IV fluids. However, during the study only four participants administered a total of ten additional IV infusions. As such, we were unable to fully explore effects of supplemental fluids on subjective well-being and whether it varied with biochemical dehydration according to dipstick chloride concentration. Future work with larger sample sizes could address whether supplemental fluids improve QOL and whether their provision can ultimately be guided by the dipstick.

In addition, in order to determine which electrolyte correlated best with clinical assessment of dehydration, we planned to assess inpatients clinically, together with their urinary electrolytes. However too few patients were dehydrated to draw any meaningful conclusions.
A dedicated study is required to describe the relationship between different urinary electrolytes and how that relates to clinical state, and particularly which electrolytes best correlate with fluid requirement. Such a study will need to fluid and electrolyte deplete subjects while monitoring acid-base balance, extracellular fluid volume, arterial filling and monitor gastrointestinal losses. Urinary electrolyte response to fluid filling may prove to be a useful diagnostic tool.
Other bodily fluids could potentially be used to assess hydration status. One study has demonstrated that salivary osmolality could be used to detect dehydration [13]. This may be a promising alternative as it would perhaps be considered more socially acceptable to collect, and subject to fewer neuro-hormonal influences than renal excretion mechanisms.

One of the main weaknesses of this study is that the low-range Quantab dipstick was used. It has a valid upper value of 17.88 mmol/L chloride which is below the concentration of interest (20 mmol/L). In addition, participant numbers were small for addressing some of our aims; for example, only four participants administered extra IV fluids, and participant data was not available for all urine samples received in the laboratory. However, this was a feasibility study and not powered to perform meaningful statistical analysis. With respect to data analysis, the Bland-Altman test would be the preferred method to assess the agreement between the dipstick- and laboratory-derived measurements, but due to missing data this was not possible. Instead we reported rank correlation coefficients. Another weakness is that recruitment was lower than the target, and, despite no reported difficulties in obtaining urine samples and completing QOL assessments, a large proportion of those consented were lost to follow up. There were no differences in participant characteristics between completers and non-completers, but it is possible that completers were more self-motivated and likely to want to use a point-of-care test to guide their management than non-completers, which could have biased the results. For example, they may have taken more time and care in performing the dipstick testing and providing end-of-study feedback.

Although a validated QOL questionnaire for HPN patients was used, responses to only one question was used in analyses which may not have been optimal for assessing QOL. Not all urine samples were obtained before midday as per instructions, and no information was obtained about the timing of urine samples in relation to PN infusions. Higher urinary chloride and sodium concentrations would be expected in the hour and days after PN infusions (not all patients have daily infusions). However, if a single point-of-care test is to be employed to determine hydration status on a day-to-day basis it would need to tolerate these fluctuations. Further work needs to be undertaken to define the optimal time at which patients should test their urine.

Future studies should use the high-range Quantab dipstick in the HPN population and identify a cut-off with a maximum sensitivity and specificity to identify those with urinary sodium concentration <20 mmol/L. As discussed, future studies need to be conducted in a clinical

context. In this study the low-range dipstick was effective at identifying those with a low urinary sodium, but two out of 16 would have been missed i.e. there would be a reading above the upper limit of the dipstick but with a laboratory sodium concentration <20 mmol/L. If acting on the dipstick results, these patients would potentially be falsely reassured and would not be prompted to contact the nutrition team for review of salt and fluid balance. There was a high false positive rate i.e. 17 out of 31 participants with laboratory urinary sodium concentration >20 mmol/L had a reading below the upper limit of the dipstick. Given that the upper limit of the dipstick corresponds to a chloride concentration of 17.88 mmol/L these participants would have been prompted to seek clinical assessment potentially unnecessarily. As well as being an inconvenience for the patient, this could have considerable cost implications. Future studies also therefore need to address cost-effectiveness. It is possible, however, that this false positive rate may be improved with the use of the high-range Quantab dipsticks.

Use of HPN is relatively rare, and collaboration with multiple intestinal failure units would allow for higher patient numbers to examine relationships between perceived dehydration, QOL, and changes in urinary electrolytes. It would also allow subgroup analysis according to underlying diagnosis, given the heterogeneous nature of the HPN group. For example, the presence of a high-output stoma is likely to have a significant impact on urinary electrolyte concentration owing to the high electrolyte concentration of the effluent.

Conclusions

This study has shown that patients on HPN are willing and able to test urine samples for chloride concentration using the Quantab dipstick. The ultimate goal is to determine whether this dipstick could be used by patients to screen for risk of dehydration, and this work is the first step in addressing this question. Further work needs to be performed to fully elucidate the potential of this point-of-care test in this patient group.

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Statement of authorship

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

Conflict of interest

JTP received financial support from Johnson & Johnson for an inflammatory bowel disease study. All other authors declare that they have no conflicts of interest.

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References

1. Lauverjat M, Hadj Aissa A, Vanhems P, Boulétreau P, Fouque D, Chambrier C. Chronic dehydration may impair renal function in patients with chronic intestinal failure on long-term parenteral nutrition. Clin Nutr. 2006 Feb;25(1):75-81. https://doi.org/10.1016/j.clnu.2005.09.010
2. Baxter JP, Fayers PM, McKinlay AW. A review of the quality of life of adult patients treated with long-term parenteral nutrition. Clinical nutrition (2006) 25, 543-553. https://doi.org/10.1016/j.clnu.2006.05.003
3. Tsang PY, Carey S. Impact of home parenteral nutrition on daily life: A qualitative study of eight patients: Qualitative nutrition and HPN. Nutrition & Dietetics 2013; 72(1):16-21. https://doi.org/10.1111/1747-0080.12091
4. Nightingale J, Woodward JM. Small Bowel and Nutrition Committee of the British Society of Gastroenterology. Guidelines for management of patients with a short bowel. Gut. 2006 Aug;55 Suppl 4:iv1-12. http://dx.doi.org/10.1136/gut.2006.091108
5. Home parenteral nutrition in the United Kingdom a position paper. Prepared by the British Association for Parenteral & Enteral Nutrition, 2003 Dr Barry JM Jones BSc MD FRCP, Home Parenteral Nutrition Officer, BAPEN.
6. Sloan PJ, Beevers G, Baxter FE. The Quantab strip in the measurement of urinary chloride and sodium concentrations. Clin Chem 1984;30:1705e7. https://doi.org/10.1093/clinchem/30.10.1705.
7. 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;12:17e21.https://doi.org/10.1016/0306-4603(87)90004-9. https://doi.org/10.1016/0306-4603(87)90004-9

8. Luft FC, Fineberg NS, Sloan RS. Overnight urine collections to estimate sodium intake. Hypertension 1982;4:494e8. https://doi.org/10.1161/01.HYP.4.4.494. https://doi.org/10.1161/01.HYP.4.4.494
9. 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;6:287e9.
10. Hamilton FW, Penfold CM, Ness AR, Stevenson KP, Atkinson C, Day AM, Sebepos-Rogers GM, Tyrrell-Price J. Can Quantab titrator sticks reliably predict urinary sodium? Clin Nutr ESPEN. 2018 Feb;23:217-221. https://doi.org/10.1016/j.clnesp.2017.09.011
11. Baxter JP, Fayers PM, McKinlay AW. The clinical and psychometric validation of a questionnaire to assess the quality of life of adult patients treated with long-term parenteral nutrition. JPEN J Parenter Enteral Nutr. 2010 Mar-Apr;34(2):131-42. https://doi.org/10.1177/0148607109348612
12. Braun, V. and Clarke, V. (2006) Using thematic analysis in psychology. Qualitative Research in Psychology, 3 (2). pp. 77-101.
13. Fortes MB, Owen JA, Raymond-Barker P, Bishop C, Elghenzai S, Oliver SJ and Walsh NP. Is this elderly patient dehydrated? Diagnostic accuracy of hydration assessment using physical signs, urine, and saliva markers. Journal of the American Medical Directors Association. 2015 16(3): 221 – 228. https://doi.org/10.1016/j.jamda.2014.09.012