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Original article

Hyponatraemia in a Lao paediatric intensive care unit: Prevalence, associations and intravenous fluid use.

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Abstract

Aim

Hyponatraemia is a common and potentially deadly complication affecting hospitalised children worldwide. Hypotonic intravenous fluids can be a significant exacerbating factor. Exclusive use of isotonic fluids, coupled with rigorous blood monitoring, have proven effective in reducing hyponatraemia in developed settings. In developing countries, where hyponatraemia is often more common and severe, different factors may contribute to its incidence and detection. We aimed to determine the prevalence and disease associations of hyponatraemia and describe the intravenous maintenance fluid prescribing practices in a Lao paediatric intensive care unit.

Methods

We conducted a cross-sectional study of 164 children aged one month to 15 years admitted to intensive care at a tertiary centre in Lao PDR and recorded their serum sodium and clinical data at admission and on two subsequent days.

Results

Hyponatraemia was detected in 41% (67/164, CI 34-48%) of children, the majority of which was mild (34%, 56/164) and present at admission (35%, 55/158). Hyponatraemia was more common in malnourished children (OR 2.3, p=0.012) and females (OR 1.9, p=0.045). Hyponatraemia correlated with death or expected death after discharge (OR 2.2, p=0.015). Eighty-eight percent received maintenance intravenous fluids, with 67% of those receiving a hypotonic solution. Electrolyte testing was only performed in 20% (9/46) of patients outside the study protocol.

Conclusion

Hyponatraemia is highly prevalent in critically ill children in Lao PDR, as is the continued use of hypotonic intravenous fluids. With financial and practical barriers to safely detecting and monitoring electrolyte disorders in this setting, this local audit can help promote testing and has already encouraged changes to fluid prescribing.

What is already known on this topic

Hyponatraemia is potentially deadly complication of many illnesses and appears to be more common and severe in less developed countries.

Hypotonic intravenous fluids can be a significant exacerbating factor.

Exclusive use of isotonic fluids, coupled with rigorous blood monitoring, have proven safe and effective in reducing the burden of hyponatraemia.

What this paper adds

Hyponatraemia is extremely common in this Lao intensive care unit, where most of the burden of disease had previously gone unrecognised, due to the cost, practicalities and cultural views of blood testing.

Hypotonic solutions are still being used as first-line maintenance fluids in this setting.

Hyponatraemia was significantly associated with malnutrition in this population.

Keywords (MeSH)

Hyponatremia; Laos; Intensive Care Units, Pediatric; Pediatrics; Fluid Therapy; Water-Electrolyte Balance

Disclosure of interest

The authors report no conflicts of interest.

Datasets

Available for audit at Open Science Framework:
https://osf.io/mpn6k/?view_only=d102fdb44926443b9d52ef9fd43c5414

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Ethics

The study was conducted following approval from both the University of Melbourne Human Research Ethics Committee (ID: 1545095) and the Lao National Ethics Committee for Health Research.

Introduction

Hyponatraemia, generally defined as a serum sodium concentration less than 135 mmol/L, is the most prevalent electrolyte disorder in hospitalised children[1, 2]. Hyponatraemia may be detected at presentation in a wide variety of childhood illnesses, frequently infections of the respiratory, neurological or gastrointestinal systems[3, 4]. It is most often due to an increase in antidiuretic hormone and subsequent water retention in the kidneys[5, 6]. Hyponatraemia with onset during hospitalisation is, by comparison, less prevalent but more often severe[7-9]. It is frequently caused or exacerbated by medical intervention, particularly post-operatively or with the administration of intravenous fluid[5, 9, 10]. The prevalence of hyponatraemia varies widely, with rates generally higher in surgical and intensive care patients, where iatrogenic factors are more ubiquitous[11, 12].

Hyponatraemia leads to osmotic fluid shifts in the body and causes harm predominantly through cerebral oedema[5]. This is more dangerous in children than adults, due to anatomical vulnerability and limited cellular adaptability[13]. Sodium levels less than 128 mmol/L have been associated with an attributable mortality of over 8% in children, with the majority of deaths subsequently found to be iatrogenic in origin[14, 15]. Hyponatraemia carries other morbidity and economic costs, from chronic complications, prolonged hospital stays and increased readmission rates[16-21].

Much of the burden of hyponatraemia has proved reducible in developed countries with prevention and early detection[22]. Meta-analyses have recently shown the exclusive use of isotonic maintenance fluids to safely and substantially decrease the incidence of hyponatraemia[23-25]. This is overturning decades of hypotonic fluid prescribing, based on physiological studies from the 1950s[26]. Excessive fluid administration can also cause hyponatraemia, and there is now support for the use of restricted maintenance volumes in children at risk of raised antidiuretic hormone levels[22, 27-30]. Regular testing of serum sodium concentration in those at risk remains essential for rapid detection of abnormalities and monitoring of treatment[22]. Despite the proven benefit of these interventions, implementation has repeatedly been found suboptimal, with inadequate monitoring and the continued use of hypotonic fluids and excessive volumes[31-35].

Data from low resource settings is limited, but hyponatraemia appears generally more common and more often severe[3, 9, 16, 36]. Although mostly associated with the same illnesses as in developed countries, endemic tropical infections and nutritional diseases are also important causes[37-40]. The iatrogenic contribution is likely high, with uptake of evidence-based fluid prescribing slow, and sodium monitoring practices inconsistent[9].

Little is known about the prevalence, associations or preventative practices around hyponatraemia in Lao PDR (Laos). Laos is a landlocked country of around 6.9 million, with high levels of poverty and ill health[41]. Cost and distance remain major barriers to accessing healthcare, with a user-pays system, largely poor, rural population, long distances and poor roads[42, 43]. Sodium testing is often not available in this context, and when it is, it can be financially prohibitive for families. Resulting under-recognition of hyponatraemia provides little motivation among health workers to change fluid prescribing or blood monitoring practices.

The primary aim of this study was to understand the epidemiology of hyponatraemia in a Paediatric Intensive Care Unit (PICU) in Laos, including its prevalence and disease associations, and to describe the current practice of prescribing maintenance intravenous fluids.

Methods and materials

We conducted a prospective, cross-sectional study, supplemented by a retrospective audit of medical records, performed in the PICU of a tertiary referral centre in Vientiane, Laos. All patients aged one month to 15 years admitted to PICU from January 1 to December 31 2016 were eligible for recruitment. Recruitment was carried out by a Lao resident doctor on admission with written consent obtained from a parent or guardian following a discussion and provision of a plain language statement. Translation services were carried out by the Lao co-investigators or an independent, medically trained translator.

De-identified information was collected onto paper case-record forms, including age, gender, admission pathway and pre-hospital treatment. A clinical dataset and sodium measurement were obtained where possible at three time points; at the time of admission, and on the fol-

lowing two mornings. More frequent or prolonged data collection was not feasible due to organisational constraints. Clinical data included the type and rate of intravenous fluid administration, conscious state (AVPU), presence of peripheral oedema, occurrence of seizures, medications and body weight. Electrolytes were tested on a HUMAN HumaLyte Plus 3 automated analyser which was calibrated daily. Results were made available to both the study and clinical teams once reported. On discharge from PICU a final dataset was recorded, including the diagnoses, clinical outcome, and length of admission. If electrolytes were tested by the clinical team outside of the planned testing, the result and an accompanying clinical dataset were also documented.

Hyponatraemia was defined as a sodium level of less than 135mmol/L and was further classified into mild (130.0 to 134.9mmol/L), moderate (125.0 to 129.9mmol/L) and severe (less than 125.0mmol/L). Malnutrition was defined as a body weight less than the third percentile on the appropriate World Health Organisation growth chart. Diagnoses were coded into organ system(s) affected, whether an infectious aetiology was suspected and whether surgery was required.

Retrospective audit

A retrospective audit was conducted to document the baseline rate of electrolyte testing in the unit, and identify possible biases in recruitment. The medical records of eligible children admitted to the study unit during the first five months of data collection, but not recruited into the study were examined. Age, intravenous fluid prescription, sodium measurements, discharge diagnoses, length of stay and clinical outcome were collected on to a paper form.

Analysis and Statistical considerations

Data was coded and transcribed into an EpiData database then analysed using SPSS software. Numerical variables are described using appropriate measures of central tendency. Prevalences of hyponatraemia are reported with 95% confidence intervals, calculated using the Wilson score interval. Binary categorical variables are described using percentages and absolute numbers positive for that variable. Due to a range of clinical and study factors, most patients

did not have a complete dataset. This includes patients discharged or dying prior to collecting all three days of data, along with data-points being missed due to the significant organisational barriers to undertaking research in this context (language barriers, large number of rotating doctors working in the study unit, etc). Denominators therefore reflect the number of valid data-points for that variable.

Bivariate comparison was made using Pearson's Chi-squared test for categorical variables, with the strength of association described as an odds ratio (OR) and 95% confidence interval (CI) where $p < 0.1$. Comparison of non-parametric variables between groups was made using the Mann-Whitney U test.

Results

A total of 164 children were recruited to the study, with the baseline demographics, disease characteristics and outcomes outlined in table 1. Table 1 also shows the number of sodium tests performed both according to and outside of the study protocol.

The total prevalence of hyponatraemia detected in this cohort was 41% (67/164, CI 34-48%). Mild hyponatraemia was detected in 34% (54/164, CI 27-42%), moderate in 4.9% (8/164, CI 2.5-9.3%) and severe in 1.8% (3/164, CI 0.6-5.2%). Hyponatraemia was present in 35% at presentation (55/158, CI 28-43%), while 18% of children were found to have developed new or worsening hyponatraemia while in hospital (21/114, CI 12-27%). Hypernatraemia was detected in 12% of children (19/164).

Hyponatraemia was more common in malnourished children (OR 2.3, p=0.012) and in females (OR 1.9, p=0.045), but was not associated with disease in any specific body system (Table 2). Hyponatraemia at any stage of admission was correlated with death or expected death after discharge (OR 2.2, p=0.015) but not with increased in-hospital mortality (24% vs 17%, p=0.25) or length of stay (3 vs 3 days median, p=0.29).

Fluid prescribing practices in the unit are outlined in table 3. No significant associations were established between pre-hospital intravenous fluid use and hyponatraemia at presentation

(p=0.25 for any fluid, p=0.24 for hypotonic fluid), nor in-hospital intravenous fluid and hyponatraemia developing or worsening in hospital (p=0.32 for any fluid, p=0.23 for hypotonic fluid). No significant associations were found between intravenous fluid rate and hyponatraemia, with no decrease in in-hospital hyponatraemia for those prescribed restricted volumes (p=0.31).

Audit

46 children eligible for the study were admitted to the unit but not recruited in the first five months. Electrolyte testing was performed at some point in 20% of them (9/46). This included eight children being tested at presentation and one later in their stay. No child was tested more than once. There were significant differences between the study and audit populations in median age (12 vs 24 months, p=0.023), rates of infectious (85% vs 69%, p=0.016) and gastrointestinal disease (9.1% vs 22%, p=0.020), in hospital usage of intravenous fluids (88% vs 41%, p<0.001), and median length of stay (3 vs 1 days, p=0.001). There were no differences in other disease categories, rates of malnutrition, multi-system disease, prehospital intravenous fluid use, poor outcomes or death.

Discussion

This study in a low resource paediatric intensive care unit demonstrates a high prevalence of serum sodium abnormalities, well above those seen in developed settings and approaching some of the highest reported anywhere in the literature for a non-disease specific population[1, 3, 9, 44, 45]. Only a small proportion of the hyponatraemia documented was of moderate degree or worse, the range known to cause clinical encephalopathy[14, 46]. Hyponatraemia detected at the time of admission was more common than that developing in hospital, similar to findings in other studies[8, 9]. However, our study likely under-reported the prevalence of hyponatraemia developing in hospital for two reasons; sodium measurements in the study protocol being missed, and cases developing after the third day of admission. A previous study found that only two thirds of hospital-acquired hyponatraemia occurred in the first 48 hours of admission, suggesting that more cases may have been identified had more prolonged and consistent monitoring been feasible[9].

Many patients in this study had multi-system disease and there were few post-operative admissions. This reflects the prevalence of comorbidity and low capacity for surgical procedures in Laos[41]. The association of malnutrition with hyponatraemia has had minimal emphasis elsewhere in the literature and is a particularly relevant risk factor in Laos given its prevalence[37, 47]. The association with female gender is also novel, though it is likely an aberrant finding. Female sex hormones have previously been associated with an increased risk of encephalopathy but not hyponatraemia itself, and regardless, almost all patients in our study were prepubertal[5, 6]. The correlation of hyponatraemia with poor clinical outcomes cannot be used to assign causation, as hyponatraemia is more likely to occur in sicker patients in the first place. We also were unable to accurately record the duration of hyponatraemia or nadir in serum sodium, both of which would have been important in associating outcomes. These limitations on study data also reflect the limitations on care in the setting.

There was much variation in the local prescribing of maintenance intravenous fluids, suggesting no adherence to standardised guidelines. The preference for hypotonic fluids indicates that the recent evidence on fluid choice had yet to be adopted locally[48, 49]. The high rate of prescribing less that full maintenance fluid rates was more likely due to doctors factoring in oral fluid intake and the volume of intravenous medications, rather than as a specific measure to prevent hyponatraemia in those at risk of raised ADH. The most commonly used clinical guidelines in the hospital were the WHO Pocketbook of Hospital Care for Children, one of the few guidelines translated into Lao language[50]. In the second edition which was current during the study period, these guidelines included half-normal saline with dextrose as a recommended general purpose maintenance fluid. McNab et al showed that a switch to the exclusive use of isotonic solutions could halve the rate of hyponatraemia, without any increase in adverse effects[25]. This is cost neutral and could significantly reduce the high prevalence of hyponatraemia demonstrated. Discussions on updating Lao guidelines to recommend isotonic fluid for maintenance requirements were occurring around the time this study was conducted, but a lack of data on hyponatraemia in the local setting was limiting the impetus to change.

During the study period, electrolyte testing was performed infrequently in non-recruited patients. A previous audit in the unit found hyponatraemia was only recognised in around 6% of

admissions (Vongxay, unpublished), well below the 41% found in this study. The low rate of testing is a combination of lack of clinical suspicion by staff and parental refusal of blood testing for financial or cultural reasons. Other practicalities influencing laboratory testing included the considerable time taken to receive results (generally longer than five hours) and the greater expense of after-hours testing. The cost of electrolyte testing is significant, at approximately four Australian dollars per occasion. This is more than the daily income for 30% of the Lao population[51] and accumulates with repeated monitoring. However, the frequency of hyponatraemia both on admission and developing in hospital is demonstrably high and hyponatraemia may be assymptomatic until brain swelling is severe. With knowledge of their local data, medical staff are in a better place to advocate not just for initial testing but also ongoing monitoring in those at risk, acknowledging the financial burden for patients, but understanding its importance to reduce preventable morbidity.

Although this study is a simple audit and may not add significantly to international knowledge regarding hyponatraemia in children, the power of local data has been in its ability to subsequently advocate for change. This has now occurred both in terms of guideline content, with new fluid prescribing guidelines in place as of 2018, and clinical awareness of the risk of hyponatraemia. Further actions are required to overcome the financial constraints and laboratory support needed to achieve ideal electrolyte monitoring in this setting, and to help staff prioritise testing appropriately.

Study limitations

Our study likely suffered from an element of selection bias, particularly during the early stages. The audit performed after the first five months of data collection revealed that just half of eligible cases were being recruited, with multiple differences between groups that could have inflated the prevalence of hyponatraemia, particularly the higher rates of infectious disease and intravenous fluid usage in the study. Poor recruitment was due to a combination of missed opportunities and parental refusal of consent. Cases where consent was refused were unlikely to be biased, but those where recruitment was forgotten or not attempted may have been influenced by clinical factors. Recruitment rates increased substantially in the later study period and may have reduced these biases. The baseline rate of electrolyte testing could also be in-

fluenced by enrolment bias, but was more likely inflated by the extra attention electrolyte disorders were receiving during the study.

Conclusion

Hyponatraemia is highly prevalent in critically ill children in Laos, and was associated with malnutrition and poor clinical outcomes. Hypotonic maintenance intravenous fluid prescribing and outdated guidelines likely contribute to the problem. Inadequate electrolyte monitoring, due to financial and practical barriers, contributes to lack of awareness of hyponatraemia, as well deficits in clinical care. Simple local studies of the prevalence of conditions like hyponatraemia in low resource settings have the power to create impetus for improvement.

Appendices

Abbreviations
AVPU - Alert, Verbal, Pain, Unconscious (conscious state rating scale)
CI - 95% Confidence Interval
NaCl - Sodium chloride
OR - Odds Ratio
PICU - Paediatric Intensive Care Unit
WHO - World Health Organisation

Geolocation
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Table 1: Baseline characteristics, sodium measurements and outcomes in children aged one month to 15 years old admitted to a Lao PICU between January 1 and December 31, 2016 (n=164).

Variable	Proportion of children in study (%)	n
Demographics		
Age 1 month to 1 year	50%	81
Age 1 to 5 years	24%	40
Age 5 to 10 years	12%	20
Age 10 to 15 years	14%	22
Female sex	49%	80
Disease characteristics and comorbidities		
Infectious illness	85%	139
Malnutrition‡	38%	62
Multi-system disease	29%	48
Post-operative admission	2.4%	4
Respiratory system disease	52%	86
Neurological system disease	29%	47
Cardiovascular system disease	21%	35
Gastrointestinal system disease	9.1%	15
Sodium measurements performed		
At the time of admission	96%	158
Day 1 post admission	76%	115
Day 2 post admission	35%	41
Additional testing outside of study protocol	12%	20
Outcome measures		
Poor outcome (death or discharge for palliation)	37%	60
Death in hospital	20%	32

† Proportions are calculated from the number of cases with valid data which is not always n=164. Percentages rounded to two significant figures.
‡ Malnutrition was defined as a body weight below the 3rd centile for adjusted age on the appropriate WHO growth chart.

Table 2: Associations between the presence of hyponatraemia and demographic, clinical and outcome measures in children aged one month to 15 years old admitted to a Lao PICU between January 1 and December 31, 2016 (n=164).

Variable	**Proportion of hyponatraemic children (n=67, [n])**		**Proportion of non-hyponatraemic children (n=97, [n])**		**OR**	**95%CI**	**p**
Demographics							
Female gender	58%	[39]	42%	[41]	1.9	1.0-3.6	0.045
Disease and comorbidities							
Infectious illness	91%	[61]	80%	[78]	2.5	0.93-6.6	0.063
Underlying malnutrition‡	49%	[33]	30%	[29]	2.3	1.2-4.3	0.012
Respiratory system disease	52%	[35]	53%	[51]	-	-	0.97
Cardiovascular system disease	21%	[14]	22%	[21]	-	-	0.91
Gastrointestinal system disease	6.0%	[4]	11%	[11]	-	-	0.24
Neurological system disease	36%	[24]	24%	[23]	1.8	0.91-3.6	0.092
Outcome measures							
Poor outcome (death or discharge for palliation)	48%	[32]	29%	[28]	2.2	1.2-4.3	0.015
Death in hospital	24%	[16]	17%	[16]	-	-	0.25

† Proportions are calculated from the number of cases with valid data in that field. Pearson's Chi squared test was used for comparison between proportions. 95% confidence interval (95%CI) and odds ratio (OR) only provided if $p < 0.1$. Numbers are rounded to two significant figures.
‡ Malnutrition was defined as a body weight below the 3rd centile for adjusted age on the appropriate WHO growth chart.

Table 3: Intravenous fluid prescribing practices in children aged one month to 15 years old admitted to a Lao PICU between January 1 and December 31, 2016.

Variable	**% of total patients (n=164)**	**% of maintenance fluid prescribing instances (n=198)**
Intravenous fluid received prior to admission		
Received any fluid	32%	-
Received a hypotonic solution‡	20%	-
Maintenance intravenous fluid prescribed during admission		
Received maintenance fluids	88%	-
Received a hypotonic maintenance solution‡	59%	-
Fluid choice:		
0.45% sodium chloride + 5% dextrose	-	41%
0.3% sodium chloride + 5% dextrose	-	15%
0.9% sodium chloride + 5% dextrose	-	14%
Ringer's lactate + 5% dextrose	-	12%
Others	-	19%
Fluid rate prescribed:	-	
Full maintenance rate	-	42%
50-85% of maintenance rate	-	53%

† Results rounded to two significant figures.
‡ Hypotonic solutions are defined as any with a sodium concentration of less that 120mmol/L.

Original article

Hyponatraemia in a Lao paediatric intensive care unit: Prevalence, associations and intravenous fluid use.

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