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Original Research

Intravenous maintenance fluid tonicity and hyponatremia after major surgery- a cohort study

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ABSTRACT

Background: Intravenous maintenance fluid (IMF) tonicity and composition influence plasma electrolyte balance.
Objective: To determine if hypotonic IMF therapy contributes to post-surgical hyponatremia.
Setting: Single-center tertiary institution.
Participants: Adults who underwent major surgery and received peri-surgical IMF, with exclusive administration of hypotonic pre-mixed 0.33% saline, 5% dextrose and potassium chloride (DK0.33%S), or isotonic 0.9% saline with or without 5% dextrose (NS/DNS).
Outcomes and measures: We examined post-surgical hyponatremia, hypokalemia and acute kidney injury (AKI), associated with use of either IMF.
Results: We studied 659 patients, of whom 161 patients (24%) developed post-surgical hyponatremia. DK0.33%S (versus NS/DNS) IMF was administered in 52% of patients who developed hyponatremia, compared to 38% of patients with stable natremia ($p = 0.001$). More patients with hyponatremia underwent gastrointestinal-hepatobiliary or abdominal (GI/HBS/Abd) surgery versus other surgical-sites ($p = 0.001$). Hypokalemia developed in 1% versus 10% of patients who received DK0.33%S and NS/DNS IMF respectively ($p < 0.001$), with corresponding AKI rates of 3% versus 7% ($p = 0.02$). On multivariate analysis, adjusted for timing of biochemistry post-surgery, IMF infusion rate and volume; independent factors associated with post-surgical hyponatremia included DK0.33%S administration, GI/HBS/Abd surgery (versus other sites), and post-surgical AKI ($p < 0.05$). Subgroup analysis by surgical sites showed that association of DK0.33%S administration with hyponatremia was most evident in GI/HBS/Abd surgery.
Conclusions: Administration of DK0.33%S IMF, compared with NS/DNS, is associated with post-surgical hyponatremia in adults after major surgery, but with less hypokalemia. The higher rate of AKI observed with NS/DNS IMF requires further evaluation.

1. Introduction

Sodium is a major cation found within the extracellular fluid and plays a critical role in fluid balance and neurological stimulation. Sodium and water homeostasis are tightly controlled by anti-diuretic hormone (vasopressin), the renin-angiotensin-aldosterone system, and natriuretic peptides. On regulating the body's retention of water, vasopressin acts on the renal collecting ducts to increase water reabsorption, physiologically decreasing the concentration of sodium. Vasopressin secretion is increased by volume depletion, edematous states, or by stress, pain and surgery [1].

Patients undergoing major surgery are at risk of impaired free water excretion and consequent hyponatremia. Post-surgical hyponatremia is common and occurs in more than 25% of patients who have undergone major surgery [2,3]. This is especially so for abdominal surgeries where patients are fasted as part of their post-surgical care, and plasma tonicity is controlled primarily by vasopressin [4]. (See Fig. 2). Hyponatremia may lead to adverse consequences including metabolic

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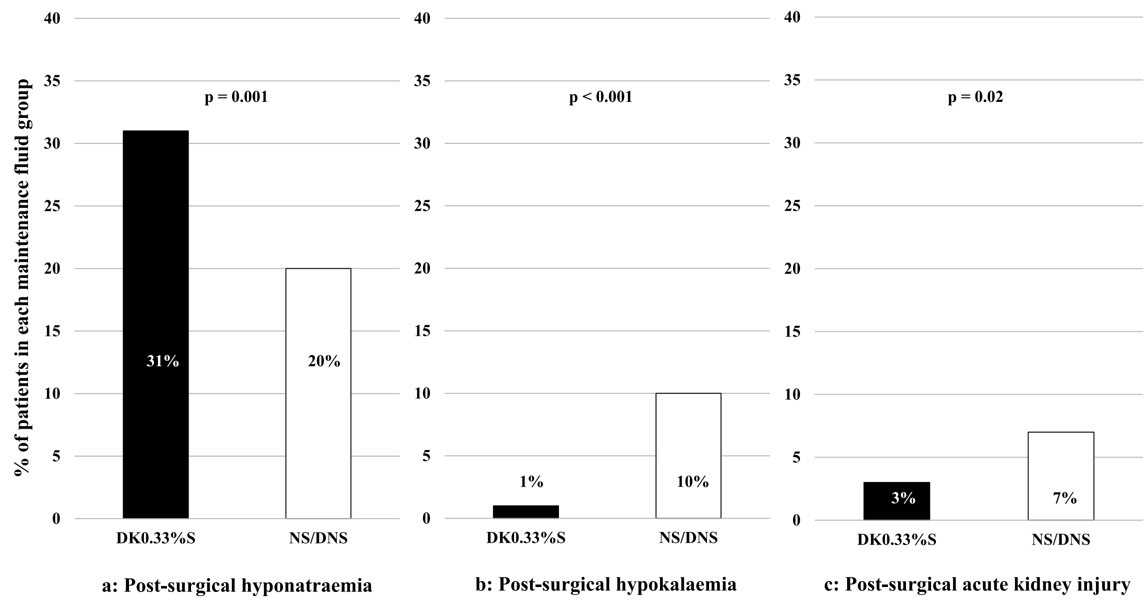

Fig. 1. Study outcomes in patients receiving 0.33% saline (pre-mixed with 5% dextrose and potassium) (■) or 0.9% saline (with or without 5% dextrose) (□).

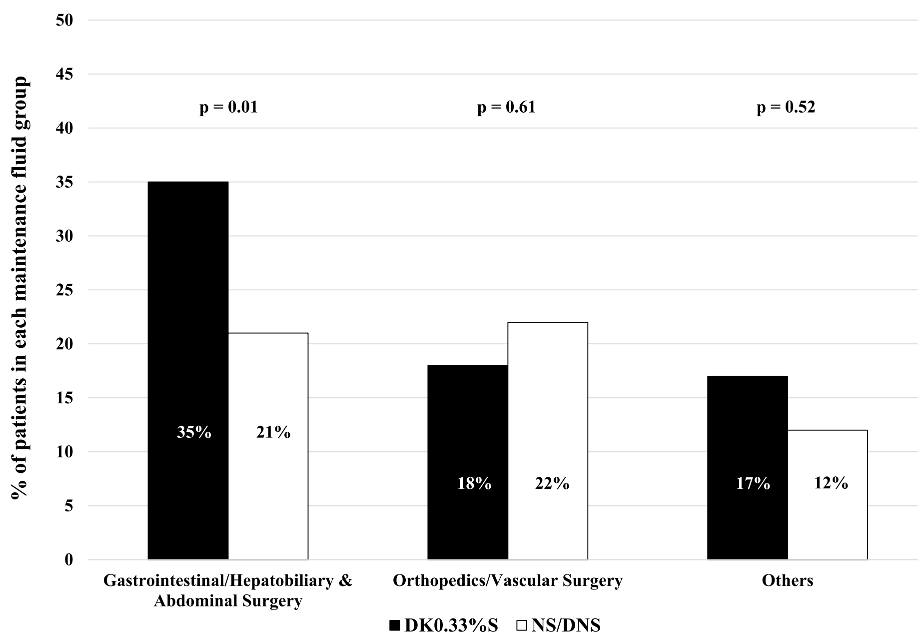

Fig. 2. Post-surgical hyponatraemia in patients from different surgical cohorts, receiving 0.33% saline (pre-mixed with 5% dextrose and potassium) (■) or 0.9% saline (with or without 5% dextrose) (□).

encephalopathy and brain injury. Such electrolyte abnormality may be worsened by administration of hypotonic intravenous fluids [1,5]. The prevailing practice to administer hypotonic maintenance fluids is based on the original proposal by Holliday and Segar in 1957, whereby physiologic caloric and electrolyte requirements were calculated by weight, producing an 'ideal', hypotonic, solution [6]. Such an approach to maintenance fluid therapy may not apply universally to hospitalised patients who might have unique nutritional requirements. Accordingly, numerous studies have suggested an association of hospital-associated hyponatremia with hypotonic maintenance fluid therapy [7,8].

In this study, we aim to examine the incidence of hyponatremia in adults following major surgery, particularly in relation to the maintenance fluid tonicity and surgery types. We hypothesize that the predominant use of hypotonic intravenous fluid maintenance peri-surgery is associated with higher risk of post-surgical hyponatremia.

2. Methods

2.1. Study design and setting

We performed a retrospective observational study of adult patients in a tertiary, 1200-bedder institution who underwent major surgery from March 2012 to September 2013. The study design and data reporting were performed in accordance to the STROCSS guideline for cohort studies [28]. We used prospectively maintained electronic health records, including an electronic inpatient medication record (eIMR) system, to identify patients who were administered maintenance intravenous fluids of interest; this data was cross-checked with electronic surgical records during the same period.

2.2. Participants

All patients aged > 18 years who had undergone major surgery and received peri-surgical intravenous maintenance fluid therapy with either pre-mixed 0.33% saline, 5% dextrose and potassium chloride at 20 mEq/L (DK0.33%S), or 0.9% saline with or without 5% dextrose (NS or DNS), were reviewed for inclusion. We included only the first surgery for all unique patients during the study period. The exclusion criteria were i) patients who received a combination of two or more fluids of interest for intravenous maintenance; ii) patients who received one or more boluses of NS for fluid resuscitation; iii) neurosurgical patients who might have received hypertonic or isotonic maintenance fluid preferentially, due to the nature of their condition [4,9]; and iv) patients with end-stage kidney disease or who received dialysis at baseline. Patients included in the study had their post-surgical routine biochemistry and outcomes during the index hospitalization examined.

2.3. Maintenance intravenous fluids

DK0.33%S is the hypotonic fluid of interest, comprising of sodium at 56 mEq/L, potassium at 20 mEq/L, chloride at 76 mEq/L and dextrose at 5 g/dL. It has a tonicity of 152 mEq/L. This is compared to isotonic (308 mEq/L) NS, which comprises sodium and chloride at 154 mEq/L and DNS, which is NS with 5 g/dL of dextrose. As a quality measure, our institution does not advise the routine addition of concentrated potassium solution to intravenous fluids (outside of emergency or critical care setting), due to the risk of error in dilution or misadministration [10]. The duration and infusion rate of maintenance fluid received peri-surgery were routinely recorded in the eIMR system.

2.4. Major surgery and patient cohort

Details of each surgery (e.g. type and duration) were recorded prospectively in electronic surgical records. In this study, the complexity of surgery was inferred from the Table of Surgical Procedures provided by regulatory authorities. It ranges from 1 A to 7C, categorized by their complexity, with 7C defining complex operations such as a Whipple's procedure [11]. We defined major surgery as those classified as Table 3A or higher, and included patients undergoing both elective and emergency procedures. We stratified patients based on the anatomical location of surgery (Supplementary Table 1).

2.5. Peri-surgery biochemistry

Pre- and post-surgical biochemistry were retrospectively collected. These included serum sodium, potassium, and creatinine levels. Serum creatinine was measured using Advia 2400 (Siemens, Munich, Germany) using the enzymatic creatinine method traceable to isotope-dilution mass spectrometry (IDMS). Baseline estimated glomerular filtration rate (eGFR) was calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) Study equation [12].

2.6. Baseline demographics

Patient profiles were indexed at time of hospitalization. Age, gender, and length-of-stay were obtained from the electronic health records. Comorbidities including diabetes mellitus, hypertension, ischemic heart disease and malignancy were determined retrospectively. Chronic kidney disease (CKD) was defined as baseline (pre-surgery) eGFR $< 60\,mL/min/1.73\,m^2$.

2.7. Outcomes

Our primary outcome measure was new-onset post-surgical hyponatremia. This was defined as (i) post-surgical serum sodium < 135 mmol/L with pre-surgical sodium ≥ 135 mmol/L; or (ii) post-surgical serum sodium < 130 mmol/L with pre-surgical sodium between 130 and < 135 mmol/L; or (iii) a decrease in serum sodium of > 5 mmol/L from pre-surgical sodium of < 130 mmol/L.

Our secondary outcomes included: new-onset post-surgical hypokalemia, defined as post-surgical serum potassium level < 3.5 mmol/L with pre-surgical levels ≥ 3.5 mmol/L; post-surgical acute kidney injury (AKI), defined as a relative increase of post-surgical serum creatinine levels ≥ 1.5 times above pre-surgical levels [13].

2.8. Bias

To address the issue of bias with regard to fluid prescription practice patterns among different surgical types, preferred selection of hypotonic or isotonic fluid therapy, and confounding effect of fluid infusion volume or timing of biochemistry, we have described the primary outcome stratified by various confounding patient and surgical variables and performed sensitivity analyses and multivariate analyses as detailed below.

2.9. Quantitative variables

We described the incidence of post-surgical hyponatremia and made univariate comparisons of study variables between hyponatremic and non-hyponatremic patients. Next, we compared the outcomes of interest between patients with exclusive administration of DK0.33%S and NS/DNS maintenance fluid therapy, and specifically, that of post-surgical hyponatremia versus type of maintenance fluid therapy by surgical sites.

2.10. Statistical methods

Parametric variables were presented as mean (± standard deviation); non-parametric variables in median (interquartile range). Differences were compared using Students' t-test and Wilcoxon rank-sum tests, respectively. Categorical variables were presented as frequency (percentage) and compared using Chi-square or Fisher-exact test, where appropriate.

Next, we performed sensitivity analyses by examining the incidence of hyponatremia with use of hypotonic versus isotonic fluid maintenance in patients stratified by age, comorbidities, CKD, surgery types and duration, surgical complexity, AKI, and fluid infusion rates. Finally, we performed multivariate logistic regression to identify independent variables associated with post-surgical hyponatremia. Covariates for the multivariate model were selected based on (i) study intention, i.e. hypotonic (versus isotonic) fluid maintenance; followed by (ii) clinically plausible variables that may influence post-surgical natremia, including age, key comorbidities including CKD, abdominal surgery, emergent surgery and surgery duration, AKI; and (iii) fluid infusion rate and cumulative volume, as well as timing of biochemistry tests performed post-surgery. A two-sided $p < 0.05$ was taken as measure of statistical significance. Goodness-of-fit for the final logistic regression model was assessed with the Hosmer-Lemeshow test. Analysis was performed using STATA® SE version 13.0 (Lakeway Drive, College Station, Texas, USA).

3. Results

3.1. Participants

We studied 659 patients. 317 patients (48%) underwent gastrointestinal/hepatobiliary or major abdominal surgery (including 16 patients who underwent nephrectomy) (see Supplementary Table 1). 272 patients (41%) received DK0.33%S as maintenance therapy, with the remaining patients receiving NS/DNS maintenance. Their baseline profile is shown in Table 1. Post-surgical serum biochemistry was performed at median 26 (14–60) hours after surgery, with patients

Table 1
Baseline patient profile.

Variables	All patients		Post-op hyponatremia		Stable natremia		p-value
	n = 659		n = 161		n = 498		
Age, mean (SD), years	60	(17)	62	(17)	60	(18)	0.24
Male, No. (%)	371	(56)	100	(62)	271	(54)	0.09
Diabetes mellitus, No. (%)	193	(29)	55	(34)	138	(28)	0.12
Hypertension, No. (%)	342	(52)	91	(57)	251	(50)	0.18
Ischemic heart disease, No. (%)	98	(15)	25	(16)	73	(15)	0.79
Chronic kidney disease, No. (%)	110	(17)	30	(19)	80	(16)	0.45
Malignancy, No. (%)	210	(32)	59	(37)	151	(30)	0.13
Gastrointestinal/hepatobiliary/abdominal surgery, No. (%)	317	(48)	96	(60)	221	(44)	0.001
Peripheral (orthopedic or vascular) surgery, No. (%)	248	(38)	52	(32)	196	(39)	0.11
Cardiothoracic surgery, No. (%)	34	(5)	4	(2)	30	(6)	0.08
Other urological (ureteric, bladder, prostate) surgery, No. (%)	22	(3)	2	(1)	20	(4)	0.09
Head & neck, breast, skin surgery, No. (%)	38	(6)	7	(4)	31	(6)	0.37
Admission till surgery, median (IQR), days	1.5	(1–4)	1.5	(1–5)	1.5	(1–4)	0.57
Surgery duration, median (IQR), hrs	3.6	(2.5–5.3)	3.7	(2.5–5.4)	3.5	(2.5–5.3)	0.82
Emergency (vs elective) surgery, No. (%)	195	(30)	48	(30)	147	(30)	0.94
Surgical classification table 5A and above, No. (%)	391	(59)	95	(59)	296	(59)	0.92
Hypotonic (vs isotonic) IMF therapy, No. (%)	272	(41)	84	(52)	188	(38)	0.001
Dextrose-containing IMF therapy, No. (%)	467	(71)	123	(76)	344	(69)	0.08
Cumulative IMF therapy volume, median (IQR), L	5.0	(3.6–7.8)	5.4	(3.7–9.2)	4.9	(3.6–7.3)	0.08
Total IMF infusion hours, median (IQR), hrs	85	(63–112)	90	(64–129)	84	(63–110)	0.06
IMF infusion rate, median (IQR), mL/hr	63	(43–83)	63	(52–83)	63	(42–83)	0.29
Timing performed before surgery, median (IQR), hrs	42	(15–160)	34	(15–116)	43	(15–164)	0.23
Pre-surgical serum sodium, median (IQR), mmol/L	139	(137–141)	138	(137–140)	140	(137–142)	< 0.0001
Timing performed after surgery, median (IQR), hrs	26	(14–60)	41	(17–85)	22	(13–52)	< 0.0001
Post-surgical serum sodium, median (IQR), mmol/L	136	(134–139)	133	(131–134)	138	(136–139)	< 0.0001
Hospital length of stay, median (IQR), days	9	(6–17)	10	(7–19)	8	(5–17)	0.006

LEGEND: hrs: hours; IQR: interquartile range; IMF: intravenous maintenance fluid; L: liters; labs: laboratory tests; No.: number; vs: versus; SD: standard deviation.

having a median hospital length-of-stay of 9 (6–17) days. Data was complete for every variable of interest, except for post-surgical serum potassium. Eight patients (3%) of 272 patients who received DK0.33%S and 6 patients (2%) of 387 patients who received NS/DNS, had invalid post-surgical potassium results.

3.2. Outcomes

161 patients (24%) developed post-surgical hyponatremia. Comparing 161 patients with hyponatremia and 498 patients with stable natremia, DK0.33%S was administered in 84 patients (52%) versus 188 patients (38%), respectively (p = 0.001). Additionally, more patients who developed hyponatremia had undergone gastrointestinal-hepatobiliary or abdominal surgery (p = 0.001), with trend for higher cumulative maintenance fluid volume (p = 0.08). Patients who developed post-surgical hyponatremia had longer length-of-stay (p = 0.006) (see Table 1 and Fig. 1a).

Thirty-three of 659 patients (5%) developed post-surgical AKI; 40

Table 2
Maintenance fluid therapy and post-operative hyponatremia - sensitivity analyses.

% of subcohort with new-onset hyponatremia		Hypotonic fluid maintenance		Isotonic fluid maintenance		p-value
AGE	> 60 years	45/141	(32)	48/230	(21)	0.02
	≤60 years	39/131	(30)	29/157	(18)	0.03
DM	Diabetics	24/62	(39)	31/131	(24)	0.03
	Non-diabetics	60/210	(29)	46/256	(18)	0.007
Hypertension	Hypertensives	49/129	(38)	42/213	(20)	< 0.001
	Non-hypertensives	35/143	(24)	35/174	(20)	0.35
IHD	Underlying IHD	11/25	(44)	14/73	(19)	0.01
	No IHD	73/247	(30)	63/314	(20)	0.009
CKD	eGFR < 60 ml/min/1.73m^2	15/33	(45)	15/77	(19)	0.005
	eGFR ≥ 60 ml/min/1.73m^2	69/239	(29)	62/310	(20)	0.02
Cancer	Underlying cancer	38/115	(33)	21/95	(22)	0.08
	No cancer	46/157	(29)	56/292	(19)	0.02
Surgery	Gastrointestinal/hepatobiliary/abdominal types	73/209	(35)	23/108	(21)	0.01
	Other surgery types	11/63	(17)	54/279	(19)	0.73
Acuity	Emergency surgery	29/92	(32)	19/103	(18)	0.03
	Elective surgery	55/180	(31)	58/284	(20)	0.01
Duration	Surgery hours > 3 h	54/179	(30)	46/219	(21)	0.04
	Surgery hours ≤ 3 h	30/93	(32)	31/168	(18)	0.01
Complexity	Table 5A and above	50/153	(33)	45/238	(19)	0.002
	Below table 5A	34/119	(29)	32/149	(21)	0.18
Infusion rate	Maintenance infusion > 83 mL/h (> 2 L/day)	35/112	(31)	9/56	(16)	0.04
	Maintenance infusion ≤ 83 mL/h	49/160	(31)	68/331	(21)	0.01
AKI	Post-op AKI	4/7	(57)	10/26	(38)	0.42
	No post-op AKI	80/265	(30)	67/361	(19)	0.001

LEGEND: AKI: acute kidney injury; CKD: chronic kidney disease; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate by 4-variable Modification of Diet in Renal Disease equation; hrs: hours.

Table 3
Multivariate analysis for independent factors associated with hyponatremia.

Final model variables	Odds ratio	95% confidence interval		p-value
ALL patients (n = 659)				
Hypotonic fluid maintenance (vs isotonic)	1.67	(1.08 -	2.57)	0.02
GI/HBS/Abdominal surgery (vs others)	1.68	(1.09 -	2.58)	0.02
Post-op AKI (vs no AKI)	2.53	(1.20 -	5.29)	0.01
Diabetes mellitus (vs none)	1.46	(0.98 -	2.18)	0.06
Higher cumulative infusion volume (L)	1.02	(0.98 -	1.07)	0.27
Higher maintenance fluid infusion rate (mL/hr)	1.00	(0.99 -	1.01)	0.43
Increasing hours that biochemistry was performed post-surgery	1.004	(1.001 -	1.01)	0.007
(Hosmer-Lemeshow test, p = 0.82)				
ONLY GI/HBS/Abdominal surgeries (n = 317)				
Hypotonic fluid maintenance (vs isotonic)	2.09	(1.15 -	3.81)	0.02
Post-op AKI (vs no AKI)	2.36	(0.73 -	7.65)	0.15
Diabetes mellitus (vs none)	1.16	(0.64 -	2.08)	0.63
Higher cumulative infusion volume (L)	1.10	(1.00 -	1.20)	0.05
Higher maintenance fluid infusion rate (mL/hr)	0.99	(0.97 -	1.00)	0.11
Increasing hours that biochemistry was performed post-surgery	1.01	(1.004 -	1.02)	0.002
(Hosmer-Lemeshow test, p = 0.59)				
NON-GI/HBS/Abdominal surgeries (n = 342)				
Hypotonic fluid maintenance (vs isotonic)	0.88	(0.41 -	1.87)	0.74
Post-op AKI (vs no AKI)	3.10	(1.16 -	8.28)	0.02
Diabetes mellitus (vs none)	1.71	(0.97 -	3.00)	0.06
Higher cumulative infusion volume (L)	0.99	(0.94 -	1.05)	0.81
Higher maintenance fluid infusion rate (mL/hr)	1.01	(0.99 -	1.02)	0.35
Increasing hours that biochemistry was performed post-surgery	1.00	(1.00 -	1.01)	0.10
(Hosmer-Lemeshow test, p = 0.19)				

LEGEND: AKI: acute kidney injury; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; HBS: hepatobiliary system; vs: versus.
Other factors considered but not included in final model selection: Older age, hypertension (vs none), ischemic heart disease (vs none), cancer (vs none), baseline eGFR $< 60\,ml/min/1.73\,m^2$ (vs higher), longer surgery duration (hrs), emergency (vs elective) surgery.

(6%) patients developed hypokalemia. Comparing 272 patients who received DK0.33%S and 387 patients who received NS/DNS, 7 patients (3%) and 26 patients (7%) developed AKI, respectively (p = 0.02); correspondingly, 3 patients (1%) and 37 patients (10%) developed hypokalemia ($p < 0.001$).

3.3. Sensitivity analyses for post-surgical hyponatremia

The study cohort was stratified by demographics, comorbidities, and surgical variables. The increased risk of post-surgical hyponatremia seen with DK0.33%S was significant in patients with hypertension, gastrointestinal-hepatobiliary or abdominal surgery (versus other surgical sites, Fig. 1b–d), and higher surgical complexity. (See Table 2).

3.4. Multivariate analysis (Table 3)

The independent factors associated with post-surgical hyponatremia included patients who had undergone any gastrointestinal-hepatobiliary or abdominal surgery (p = 0.02), patients who received DK0.33%S maintenance (p = 0.02), and patients who acquired post-surgical AKI (p = 0.01). In the subgroup analysis, administration of DK0.33%S was independently associated with post-surgical hyponatremia only in patients undergoing gastrointestinal-hepatobiliary or abdominal surgery (p = 0.02), but not other surgery types (p = 0.74).

4. Discussion

4.1. Key results

In our observational cohort study of adult patients on maintenance intravenous fluid therapy peri-surgery, we found that the exclusive use of hypotonic fluid maintenance was independently associated with post-surgical hyponatremia, and hyponatremia in turn was associated with longer hospital stay. The risk of hyponatremia with hypotonic fluid therapy was most evident in patients with gastrointestinal-hepatobiliary or abdominal surgery, higher surgical complexity, and those with hypertension. Other independent factors associated with post-surgical hyponatremia included gastrointestinal-hepatobiliary or abdominal surgery and post-surgical AKI. We observed however, higher incidence of post-surgical AKI and hypokalemia, in patients who received exclusive NS/DNS versus DK0.33%S as maintenance fluid therapy.

4.2. Interpretation

The risk of hyponatremia following hypotonic maintenance fluid use has been consistently reported in the pediatric population [14,15]. However, there is no consensus in adults. Following general anesthesia and in the post-surgical state, hyponatremia is commonly attributed to two main factors: the infusion of excessive amounts of electrolyte-free water, and vasopressin release in response to stressors and plasma volume loss during surgery [16–18]. It is possible that further infusion of hypotonic fluid worsens the risk of post-surgical hyponatremia and this should be considered when prescribing maintenance fluids. In that regard, the British consensus guidelines on intravenous fluid therapy for adult surgical patients, published in 2011, advises caution about excessive administration of hypotonic intravenous fluids and risk of hyponatremia especially in the elderly [19]. Likewise, in 2013, the National Institute for Health and Care Excellence recommended maintenance fluids containing daily key physiological electrolyte requirement, adjusted for body weight (which produces a hypotonic composition), but cautioned against hyponatremic risk with high daily infusion volumes (guideline 1.4.4)[20]. An evidence-based approach to achieve the right balance between appropriate fluid tonicity/composition and therapy-related complications is desirable.

Post-operative hyponatremia was more marked in patients undergoing major abdominal surgery including gastrointestinal-hepatobiliary surgery. We suggest that this could relate to longer fasting periods following abdominal surgery that renders the patients' plasma electrolyte balance more dependent on the maintenance intravenous fluid composition. Alteration in bowel movement post-operatively might also contribute to extra-renal loss of sodium through gastrointestinal fluids.

The hyponatremia risk with hypotonic fluids was also more evident in patients with hypertension, which might relate to baseline thiazides or renin-angiotensin-aldosterone system blockade for blood pressure control [21,22], but we lack medication details to support this hypothesis. A maintenance fluid tonicity higher than that of DK0.33%S used in our study, may be desirable to reduce the hyponatremic tendency in similar surgical patients.

The ideal maintenance fluid should be a balanced solution containing essential electrolytes such as potassium, and not solely sodium chloride [20,23]. Isotonic fluids like NS and DNS do not contain potassium and their exclusive administration may be associated with hypokalemia in surgical patients, especially with prolonged fasting. However, adding concentrated potassium chloride to NS/DNS risks misadministration [10], and renders the former hypertonic. Therefore, while maintenance with DK0.33%S might be associated with more hyponatremia, isotonic maintenance with NS/DNS is also not ideal [24]. Our finding of higher post-surgical AKI incidence in patients on NS/DNS versus DK0.33%S maintenance therapy raises concern about the association of high chloride content in isotonic saline preparations and AKI risk [25,26]. Hyperchloremia may induce renal vasoconstriction and reduce glomerular filtration rate [27]. Our patient numbers with AKI were small, fluid therapy groups were not randomized, and we did not examine serum chloride levels, which limits further conclusion about maintenance fluid composition and adverse renal outcomes.

4.3. Generalizability

Our study contributes to the very limited literature on peri-surgical maintenance fluid therapy in adult patients and provides data relevant to hospital-wide practice. Our findings suggest that the tonicity of DK0.33%S is too low and associated with hyponatremia, especially in those who undergo gastrointestinal-hepatobiliary or abdominal surgery. Routine isotonic preparations lack potassium, however, and contribute to hypokalemia. Pre-mixed solutions with adequate potassium but of higher tonicity than DK0.33%S may provide a more balanced option in similar patient scenarios. Our results are hypothesis-generating and provide the effect size for intervention trials on intravenous maintenance fluid therapy and its influence on both biochemical and clinical outcomes in adult surgical patients.

4.4. Limitations

Our study was not prospective or randomized. However, patients at risk of hyponatremia and hypokalemia should not have been preferentially administered with hypotonic solutions and non-potassium containing solutions respectively. We had also excluded patients who received NS for fluid resuscitation. These factors would have minimized various selection bias to the outcomes assessed in this study. The differences in timing of post-operative serum biochemistry could have influenced the detection of hyponatremia in patients, but the hyponatremic risk associated with hypotonic fluids remains strong following appropriate statistical adjustment in the multivariate model.

5. Conclusions

Appropriate maintenance fluid administration should be individualized for unique surgical types and patients at risk of various electrolyte imbalances. Our study has highlighted the high incidence of post-surgical hyponatremia, which is associated with DK0.33%S maintenance therapy, especially in patients who undergo gastro-intestinal, hepatobiliary or abdominal surgery. More balanced electrolyte solutions of a higher tonicity and containing adequate potassium to meet daily requirements, should be considered for clinical use, and routine isotonic preparations are not ideal. The biochemical and clinical outcomes with different pre-mixed solution tonicity administered peri-surgery, and the effects of hyperchloremia with higher sodium chloride content in fluids, should be explored in a randomized, prospective study.

Ethical approval

The Domain Specific Review Board of the National Healthcare Group Singapore approved the study (2013/01040) and waived the need for informed consent because it involved no intervention and data were anonymized and de-identified.

Sources of funding

This study was performed as part of our routine work. No funding was obtained. This study involved a retrospective design and was not pre-registered in an independent, institutional registry.

Author contribution

Study design and conception: Wei-Ying. JEN, Margaret. L. TENG, Wee-Chuan. HING, Shridhar. Ganpathi. IYER, Horng-Ruey. CHUA.

Data assembly: Wei-Ying. JEN, Margaret. L. TENG, Wee-Chuan. HING, Valerie. MA, Horng-Ruey. CHUA.

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Manuscript revision: Adeline. S. WINATA, Shridhar. Ganpathi. IYER, Horng-Ruey. CHUA.

Conflicts of interest

Nil conflict of interest.

Research registration number

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Guarantor

Horng-Ruey. CHUA.

Data statement

De-identified research data could be provided on request made to the corresponding author:

Provenance and peer review

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijsu.2019.04.019.

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