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Normal saline and acute kidney injury in hospitalized patients; more precaution to be taken

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ABSTRACT

Introduction: Potential nephrotoxic agents are not well recognized and are being used irrespective of patients' vulnerability.**Objectives:** We aimed to evaluate the relationship between the prevalence of exposure to normal saline and the risk of hospital acquired acute kidney injury (HA-AKI).**Patients and Methods:** A retrospective case-control study of a total of 424 hospitalized patients was done. The frequency of exposure to the individual intravenous fluids and their risk of HA-AKI were calculated as odds ratios with 95% confidence interval (CI).**Results:** Of 424 total sampled hospitalized patients, post-admission normal saline exposure was found in 37.6% in which 22.6% had the development of HA-AKI and 15% did not develop AKI. The risk of HA-AKI was significantly higher in patients who received normal saline and lower in patients who received 5% dextrose water (ORs; 1.92, 95% CI; 1.28, 2.85; $P=0.001$ and ORs; 0.48, 95% CI; 0.24, 0.95, $P=0.02$, respectively).**Conclusion:** Exposure to normal saline was considerably high among hospitalized patients and was associated with a higher risk of AKI. Post-admission administration of high sodium and chloride containing intravenous fluid should be limited in patients who are vulnerable to develop AKI.

Implication for health policy/practice/research/medical education:

Our study results show that the risk of hospital acquired acute kidney injury (HA-AKI) is higher among patients who received normal saline as fluid therapy or volume replacement. Restriction of normal saline will be potentially beneficial in the prevention of HA-AKI.

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Introduction

Many therapeutic agents are associated with kidney injury (1). Singh et al demonstrated that nephrotoxin related acute kidney injury (AKI) was the commonest cause of hospital acquired (HA) AKI on the medical wards whereas sepsis was the leading cause of HA-AKI in ICU and surgical wards (2). HA-AKI was defined as the development of AKI any time after 48 h of hospitalization, in a patient who was admitted with normal renal function (3). Various definitions of acute kidney injury were used in the past but currently, AKI is diagnosed as an acute rise in serum creatinine levels of 0.3 mg (26.5 $\mu\text{mol/L}$) in 48 hours and/or rise of serum creatinine > 1.5 times the baseline in seven days and/or a decline in urine output < 0.5 ml/kg/hr over 6 hours (3-5). The Kidney Disease: Improving Global Outcomes (KDIGO) staging for AKI

is the most recognized classification of AKI severity at present. It contains 3 stages and defines stage 1 as serum creatinine 1.5-1.9 times the baseline, stage 2 as serum creatinine 2.0-2.9 times the baseline and stage 3 when the rise is ≥ 3 times from the baseline (5). Hanna et al raised a serious concern on potential nephrotoxic agents in their report based on the US FDA Adverse Event Reporting System (FAERS) database in which the adverse renal effects of potential nephrotoxins were far more commonly reported than those of known nephrotoxins (64.8% versus 16.5%) (6). Studies by Joannidis et al (7) and Bennett and Porter (8) showed that use of large amounts of normal saline 500 ml to 2L/24 hours was possibly nephrotoxic and recommended to limit its use. Volume expansion with intravenous fluid was considered as a part of the management in sepsis but we were not sure whether

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liberal use of intravenous fluids particularly 0.9% normal saline to the Afro-Caribbean population was helpful or harmful to the kidneys.

Objectives

We hypothesized that use of normal saline might not have been well recognized widely as a potential nephrotoxin in our hospital setting. We conducted this study to provide the frequency of exposure to the normal saline and other kinds of intravenous fluid as well as the association between risk of AKI and the exposure to intravenous fluids.

Patients and Methods

Study design

This is a retrospective case-control, hospital-based study of in-patients of the university hospital of the West Indies, Jamaica. The participants were cases with HA-AKI and patients without AKI who were admitted between July 1, 2016 and June 30, 2018. Patients who had deterioration of renal function during their admission were selected as HA-AKI group by using KDIGO diagnostic criteria for AKI. The control group was generated by operator-based stratification of patients without AKI. These patients were randomly selected, and the total number of participants equaled the number of HA-AKI patients. Medication records of both groups were reviewed. Participants with doubtful diagnoses were excluded.

At the baseline, medication records of study participants who had AKI or did not have AKI throughout the admission period were retrieved. For patients who were prescribed intravenous fluid infusion, types of fluid used, amounts and duration of therapy were recorded. Participants were in-patients of medicine wards, surgery wards, obstetrics and gynaecology wards and intensive care units. All patient-data were coded and kept anonymous.

Data collection

The parameters were collected by trained recruiters such as research nurses and graduate students. The diagnosis of HA-AKI and its staging were confirmed by certified nephrologists. The patient's age, gender, baseline serum creatinine, peak serum creatinine, urine output per hour if known, timeline between changes of serum creatinine and medications, type and amount of intravenous fluid given were included in the data collection. The recruiters also collected independent variables which involved background medical illnesses, previous medication exposure and admitting diagnoses.

Participants in both groups were over 16 years old with no previous history of end-stage kidney disease. Key distinguishing features between the two groups were whether absolute serum creatinine rise in 48 hours was $>26.5 \mu\text{mol/L}$ (0.3 mg/dL) or urine output was $<0.5 \text{ ml/kg/h}$ for more than 6 hours or not. Key exclusion criteria were age younger than 16 years, patients with known

chronic kidney disease, abnormal renal function on arrival to the hospital and duration of hospital stay less than 48 hours.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. The ethics committee of the University of the West Indies, Mona approved this study. The institutional ethical committee at the University of the West Indies approved all study protocols (ECP 251, 15/16). Accordingly, written informed consent was taken from all participants before any intervention.

Statistical analysis

Descriptive analysis was used to identify differences in baseline characteristics between HA-AKI and control groups. Correlations of exposure to intravenous fluid, different types of intravenous fluids and the development of HA-AKI were analysed by the Pearson chi-square test. We estimated the risk of the development of HA-AKI in association with individual type of intravenous fluid by using Kendall rank correlation coefficient or phi test, as appropriate. The adjusted odds ratios (ORs) of individual type of intravenous fluid exposed to the HA-AKI and control groups were analysed by using the Cochran–Mantel–Haenszel statistics with the estimated test common odds ratio of 1. The data on correlation between the two tested populations (AKI and without AKI) were applied by means of 95% confidence interval (CI). Patient demographic characteristics as continuous numerical variables were expressed as counts and percentages or mean with standard deviations. Covariates included were age, gender, baseline serum creatinine, peak serum creatinine, urine output, medication exposed and admitting diagnoses. Categorical variables were expressed as number and proportion, as appropriate. A P value <0.05 was considered statistically significant. All statistical analysis was done by using IBM SPSS version 22 and Graph pad prism version 8.4.3.

Results

Baseline characteristics of the 424 participants are shown in [Table 1](#). There were 424 total participants in whom 212 patients had confirmed diagnosis of HA-AKI and 212 randomly selected patients had no evidence of AKI. All participants were admitted to the university hospital of the West Indies, Jamaica between July 1, 2016 and June 30, 2018. Each patient had available baseline serum creatinine and repeated serum creatinine results for two or more times within 7 days from the initial baseline test. All HA-AKI patients had significant serum creatinine changes of either absolute serum creatinine rise $>26.5 \mu\text{mol/L}$ (0.3 mg/dL) or serum creatinine rise > 1.5 times from the baseline and 76 (35.8%) of them had documented oliguria of $<0.5 \text{ ml/Kg/ hour}$ for more than 6 hours. Of 424 patients, 200 (47.2%) were male and 224 (52.8%) were female. HA-AKI

Table 1. Baseline characteristics of identified HA-AKI patients versus randomly selected non-AKI patients admitted to university hospital of the West Indies between 2016-2018

General characteristics	HA-AKI	Controls	Total
Number of patients (%)	212 (50)	212 (50)	424 (100)
Age, year, mean \pm SD	62.7 \pm 18.6	58.3 \pm 19.2	60.5 \pm 19
Gender			
Male	91 (21.4)	109 (25.8)	200 (47.2)
Female	121 (28.6)	103 (24.2)	242 (52.8)
SCr on admission, μ mol/L, mean \pm SD	72.6 \pm 18.3	71.9 \pm 16.9	72.25 \pm 17.6
Systolic BP, mm Hg, mean \pm SD	132 \pm 21	129 \pm 18	130 \pm 20
Diastolic BP, mm Hg, mean \pm SD	79 \pm 12	77 \pm 11	78 \pm 12
Duration of iv fluid therapy in days	2.6 \pm 1.4	2.5 \pm 1.7	2.5 \pm 1.6
Amount of iv fluid in average in L/day	1.5 \pm 0.8	1.5 \pm 0.9	1.5 \pm 0.9
Primary diagnoses, No. (%)			
Medical	88 (20.7)	88 (20.7)	176 (41.4)
Urological	34 (8.0)	34 (8.0)	68 (16.0)
General surgical	35 (8.2)	34 (8.0)	69 (16.2)
Neurosurgical	19 (4.4)	20 (4.7)	39 (9.1)
Orthopedic	22 (5.1)	21 (4.9)	43 (9.9)
Gynaecological	14 (3.3)	15 (3.5)	29 (6.8)
Pre-admission medications, No. (%)			
ACEI/ARBs	45 (10.6)	51 (12.0)	96 (22.6)
Metformin	15 (3.5)	22 (5.1)	37 (8.6)
Diuretics	43 (10.1)	42 (9.9)	85 (20.0)
β -blockers	33 (7.7)	36 (8.4)	69 (16.2)
Insulin	12 (2.8)	11 (2.5)	33 (7.7)
CCB	39 (9.1)	41 (9.6)	80 (18.8)
Cytotoxic agents	6 (1.4)	3 (0.7)	9 (2.1)
Corticosteroids	13 (3.1)	11 (2.5)	33 (7.7)
Pre-admission morbidity, No. (%)			
Hypertension	80 (18.8)	89 (20.9)	169 (39.8)
Diabetes	44 (10.3)	39 (9.1)	83 (19.5)
Malignancies	12 (2.8)	8 (1.8)	20 (4.7)

ACEI, Angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; SD, standard deviation; CCB, calcium channel blockers; SCr, serum creatinine.

was found in 91 (21.4%) males and 121 (28.5%) females. Among the patients without HA-AKI, 109 (25.7%) were males and 103 (24.2%) were females (Figure 1). The mean \pm SD age of HA-AKI and control groups were 62.7 \pm 18.6 and 58.3 \pm 19.2 years, respectively.

On the view of primary diagnoses, 41.5% (n=176) had primary medical problems, 16.0% (n=68) had primary urological problems, 16.2% (n=69) had primary general surgical problems, 9.1% (n=39) had primary neurosurgical problems, 10.1% (n=43) had primary orthopedic problems and 6.8% (n=29) had primary gynecological problems. The development of HA-AKI was found in 20.7% (n=88) of medical, 8.0% (n=34) of urosurgical, 8.2% (n=35) of general surgical, 4.4% (n=19) of neurosurgical, 5.1% (n=22) of orthopedic and 3.3% (n=14) of gynecological patients (Figure 1).

Frequencies of exposure to intravenous fluid therapy

Of 424 total patients, 71.2% (n=302) received intravenous fluid therapy of one or more types for minimum of 500 ml. In the HA-AKI group, 36.5% (n=155) were exposed to intravenous fluid therapy whilst in the no-AKI group, 34.6% (n=147) were exposed after admission. The average length of iv fluid therapy for all those who received it was 2.5 \pm 1.6 days in which the average length of intravenous fluid therapy in the HA-AKI group was 2.6 \pm 1.4 days and 2.5 \pm 1.7 days in the no-AKI group. The average amount of intravenous fluid HA-AKI patients was exposed to per day was 1.5 \pm 0.8 L and for patients without AKI was 1.5 \pm 0.9 L. Some of these patients were exposed to more than one type of iv (intravenous fluid) fluid. The types of intravenous fluid given to these patients were 0.9% normal saline 37.6% (n=160), Ringer's lactate 13.2% (n=56),

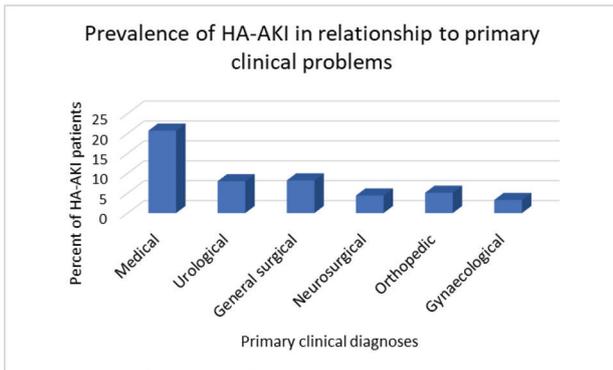


Figure 1. Relationship between prevalence of HA-AKI at university hospital of the West Indies and the primary clinical diagnoses

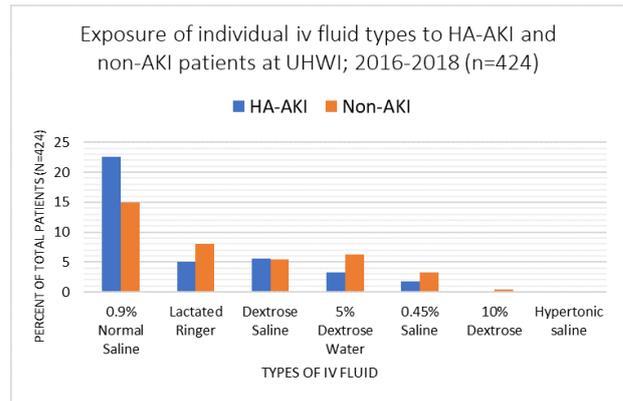


Figure 2. Correlation between exposure of different iv fluid types and HA-AKI at University Hospital of the West Indies, Jamaica (2016-2018)

dextrose saline 11% (n=47), 5% dextrose water 9.6% (n=41), 0.45% saline 5.1% (n=22), 10% and dextrose 0.7% (n=3) (Figure 2). None of the study population received Hartmann’s solution or hypertonic saline >500 mL. The detailed stratification on the exposure to individual intravenous fluid was collectively shown in Table 2.

Frequency of exposure to individual intravenous fluid types and the risk of HA-AKI

Overall, 22.6% of patients in HA-AKI group were exposed to 0.9% normal saline. Compared to that, 15% of non-AKI patients were exposed to 0.9% normal saline. The association between the exposure of 0.9% normal saline and the development of AKI was found to be statistically significant (ORs; 1.92; 95% CI; 1.28, 2.85, P=0.001). The exposure to lactated ringer was 5.1% for the HA-AKI group and 8% for the non-AKI group. No significant association between use of lactated ringer and HA-AKI was found (ORs; 0.6; 95% CI; 0.34, 1.07, P=0.08). Similarly, no statistically significant finding was observed among the patients who were exposed to dextrose saline to which 5.6% of HA-AKI patients and 5.4% of non-AKI patients were exposed (ORs; 1.04; 95%CI; 0.57, 1.92, P=0.5). Analysis of 5% dextrose exposure showed that its exposure was 3.3% in HA-AKI patients and 6.3% in non-AKI patients. Comparison between HA-AKI and controls demonstrated a significant lower risk with HA-AKI to the

exposure of 5% dextrose water (ORs; 0.48; 95% CI; 0.24, 0.95, P=0.02).

With regards to 0.45% saline exposure, 1.8% of HA-AKI group and 3.3% of non-AKI group received it. The association of 0.45% saline exposure to HA-AKI was insignificant (ORs; 0.55; 95% CI; 0.22, 1.35, P=0.19). Use of 10% dextrose was found to be very limited. There was no difference between the exposure of 10% dextrose and the development of HA-AKI (OR; 0.45; 95% CI; 0.04, 5.5, P=0.5).

The correlation between the risk of HA-AKI and exposure to individual intravenous fluids is shown in Figure 3.

In the entire study group, overall prevalence of sepsis was 40% (P=171) in which 21.2% was found in the HA-AKI group and 19.1% was found in the non-AKI group. Average length of intravenous fluid therapy in this subgroup with sepsis was 3.1 ± 1.6 days for the HA-AKI group and 2.9 ± 1.4 days for the non-AKI group.

Type of intravenous fluid used and the severity of HA-AKI

Of 212 patients with confirmed HA-AKI in this study, 73.1% (n=155) received intravenous fluid therapy. Analysis on these HA-AKI patients who received intravenous fluid therapy showed that 58.7% had stage 1,

Table 2. Association between iv fluid therapy, individual type of iv fluid and HA-AKI at university hospital of the West Indies (2016-2018)

Type of iv fluid	HA-AKI	Controls	Total	ORs (95% CI)	P value
Exposure to iv fluid	155 (36.5)	147 (34.6)	302 (71.2)	1.2 (0.78, 1.3)	0.39
0.9% Normal saline	96 (22.6)	64 (15.0)	160 (37.6)	1.92 (1.28,2.85)	0.001
Lactated Ringer	22 (5.1)	34 (8.0)	56 (13.2)	0.6 (0.34,1.07)	0.08
Dextrose saline	24 (5.6)	23 (5.4)	47 (11.0)	1.04 (0.57, 1.92)	0.5
5% Dextrose	14 (3.3)	27 (6.3)	41 (9.6)	0.48 (0.24,0.95)	0.02
0.45% saline	8 (1.8)	14 (3.3)	22 (5.1)	0.55 (0.22,1.35)	0.19
10% Dextrose	1 (0.2)	2 (0.4)	3 (0.7)	0.49 (0.04,5.5)	0.5
Hypertonic saline	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA

HA-AKI, Hospital Acquired Acute Kidney Injury; UHWI, University Hospital of the West Indies; ORs, Odds ratios; CI, confidence interval.

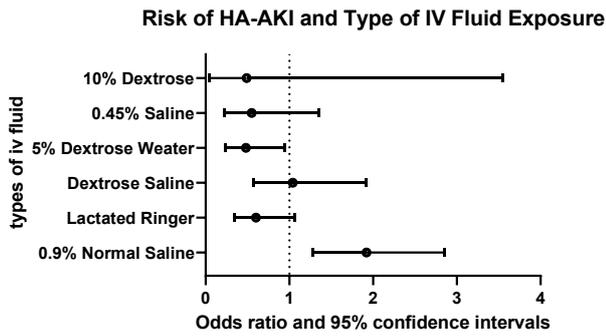


Figure 3. Risk of HA-AKI in association with the exposure of individual intravenous (iv) fluids at the University Hospital of the West Indies, Jamaica; 2016-2018.

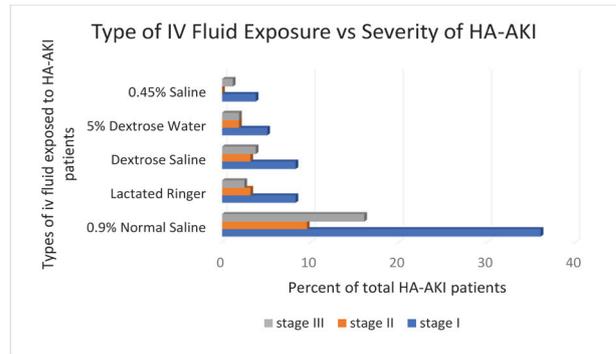


Figure 4. Correlation between the exposure of individual iv fluids and the different stages of AKI at the University Hospital of the West Indies, Jamaica; 2016-2018.

17.4% had stage 2 and 23.8% had stage 3 AKIs. Further stratification on individual type of intravenous fluid demonstrated that 61.9% of them received 0.9% normal saline in which 36.1% had stage 1, 9.6% had stage 2 and 16.1% had stage 3 AKIs, 14.1% received lactated ringer in which 8.3% had stage 1, 3.2% had stage 2 and 2.5% stage 3 AKIs, 15.4% were exposed to dextrose saline in which 8.3% had stage 1, 3.2% had stage 2 and 3.8% had stage 3 AKIs, 9% received 5% dextrose water in which 5.1% had stage 1, 1.9% had stage 2 and stage 3 each, 5.1% received 0.45% saline in which 3.8% developed stage 1 and 1.2% had stage 3 AKIs (Table 3, Figure 4).

Discussion

Our analysis underscores that the risk of AKI is considerably high in patients who receive normal saline after admission and the risk is lower in patients who receive sodium chloride free 5% dextrose water. The non-physiologic composition of sodium and chloride in the normal saline (10% higher sodium and 50% higher chloride than in human serum) has been explored for decades (9). In 2009, Juan Li et al proved that even a small rise in serum sodium (>5 mmol/L) could significantly suppress the action of endothelial nitric oxide synthases (eNOS) (10). More studies, thereafter, found sodium related endothelial dysfunction (11,12).

High serum sodium could initiate the development of glomerular hypertension as it can increase the vasoconstriction of glomerular arterioles and may

consequently affect the glomerular filtration rate.

Indeed, normal saline is not isotonic because its sodium and chloride concentrations are higher than plasma sodium and chloride concentrations. When normal saline was compared to balance crystalloids (13), more edema was observed in the normal saline group as a result of slow renal chloride excretion (14). Several recent randomized trials have shown that normal saline infusion, even as low as 500 mL/24 hours in a few studies, was related to higher prevalence of adverse outcomes compared to Plasma-Lyte, Lactated Ringer and Hartmann’s solution (13-17).

Normal saline has significantly high acidic mean pH of 5.4. The excessive use of normal saline of more than 1 L per 24-hour after arrival to the emergency department has been recognized as a major contributor for the development of acidosis in traumatized patients in shock (18).

In the first human randomized controlled double blinded trial by Chowdhury et al comparing rapid infusion of normal saline and lactated ringer, the development of sustained hyperchloremia was significantly observed only in patients who received >2 L of normal saline over an hour but not in patients who received lactated ringer. The most alarming finding of that study was that the 0.9% normal saline decreased renal cortical perfusion and renal blood flow velocity (19).

Normal saline is physiologically thought to be harmful to the kidneys for its chloride component as well. Chloride, the most abundant extracellular anion which

Table 3. Association between type of iv fluid exposure and severity of AKI at UHWI

IV fluid exposure	Stage 1 AKI	Stage 2 AKI	Stage 3 AKI	Total
Overall iv fluid	91 (58.7)	27 (17.4)	37 (23.8)	155 (100)
0.9% Normal saline	56 (36.1)	15 (9.6)	25 (16.1)	96 (61.9)
Lactated Ringer	13 (8.3)	5 (3.2)	4 (2.5)	22 (14.1)
Dextrose saline	13 (8.3)	5 (3.2)	6 (3.8)	24 (15.4)
5% Dextrose	8 (5.1)	3 (1.9)	3 (1.9)	14 (9.0)
0.45% saline	6 (3.8)	0 (0)	2 (1.2)	8 (5.1)

Note. All data were expressed as No. (%). AKI, acute kidney injury; UHWI, University Hospital of the West Indies;

is significantly involved in the regulation of acid-base balance, serum osmolarity and fluid shift of the cells, also had proven adverse kidney outcomes (20). One study on critically ill adult patients done by Shaw et al demonstrated that chloride liberal fluid is associated with a higher prevalence of AKI stages 2 and 3 compared to the group which received chloride restricted fluid (14).

Recently published SALT-ED and SMART studies showed a lower incidence of major adverse kidney events in 30 days (MAKE30) in the non-ICU hospitalized patients who received balanced fluid compared to the patients who received normal saline more than 500 mL on admission (14.3% versus 15.4% and 4.7% versus 5.6% respectively (21,22).

Our study demonstrated the likelihood of AKI secondary to the exposure to normal saline which contains higher sodium and chloride contents than plasma. We also observed that giving 5% dextrose water which is free of sodium and chloride had a lesser risk of AKI. However, 5% dextrose water is relatively hypotonic, and it will not be choice of fluid for diabetic population. This is the first study in the Caribbean region which demonstrated the relationship between iv fluid exposure and the risk of AKI.

Conclusion

Exposure to normal saline was found to be associated with HA-AKI whereas, use of sodium chloride free, 5% dextrose water, was found to have lesser occurrence of HA-AKI. Use of normal saline should be restricted to reduce the incidence of HA-AKI especially among the people who are vulnerable to develop acute kidney injury.

Limitations of the study

Our study has some limitations particularly on case selection as most participants were of Afro-Caribbean decent, who had been well recognized as a vulnerable population for AKI (4). It was also a single centre study at a tertiary institution in Jamaica which may not represent the entire country of Jamaica in terms of patient distribution and facilities available for patient care. Amount of different types of fluid utilized for different patients might not be accurate as intravenous infusion had to be interrupted on some occasion before completion of the entire bag. Additionally, many patients received more than one type of intravenous fluid which created some difficulties in accurate analysis. Consequently, we were unable to correlate the amount of individual types of fluid exposed to the patients and the severity of AKI. As the matter of fact, further multi-centre studies on different races with a higher number of participants need to be carried out.

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Authors' contribution

KK Hoe was the principal investigator of the study. KK Hoe, S Rowe-Gardner, Y Dawkins and TH Hoe were included in preparing the concept and design. S Rowe-Gardner and TH Hoe revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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Availability of data and materials

The datasets in this study from the corresponding authors can be available upon reasonable request.

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