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Clinical and Biochemical Parameters Changes after Using 0.9% Normal Saline as Maintenance Intravenous Fluid in Non-Critically Ill Children: An Experience from a Tertiary Care Hospital

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Abstract

Background and Aim: Recent recommendations are to use isotonic fluid as maintenance intravenous fluid (mIVF) in children. The most commonly prescribed fluid is 0.9% NS (normal saline) but there are concerns about hypernatremia, fluid overload and hyperchloremic metabolic acidosis leading to increased morbidity and even mortality mainly due to its adverse effects on kidneys. Most of the available literature is in the adult population. There is still not enough evidence to approve or disapprove 0.9% NS as a safe mIVF in children. This study was conducted to assess the clinical and biochemical effects of 0.9% sodium chloride as an isotonic mIVF in the general non-critically ill pediatric patients.

Methods: This observational study was conducted on admitted children requiring mIVF for a minimum 24 hours. Changes in the blood pressure (BP) and biochemical parameters like serum sodium (S Na), serum chloride (S Cl) and bicarbonate were evaluated and the incidence of hypo/hypernatremia, hyperchloremia and metabolic acidosis was calculated at 24 and 48 hours from baseline.

Results: Two hundred and fifty children were analyzed. The mean age of the patients was 3.79±3.2 years with majority (43.6%) in the age group 2 months- 1 year. There was no significant change in BP at any time point. The mean serum chloride level was 103.81±4.717, 104.5±4.581, and 105.28±4.545 at baseline, 24 hours and 48 hours respectively with a significant rise at 48 hours of mIVF (p-value< 0.001) and among 3 time points (p-value<0.01]. There was a significant decrease in the bicarbonate level at 48 hours from baseline (p<0.05).

Conclusion: According to the results, 0.9% NS as mIVF in non-critically ill pediatric patients causes a significant increase in the serum chloride level leading to hyperchloremia and metabolic acidosis.

Keywords: Normal saline; Maintenance intravenous fluids; Children; Hyperchloremic metabolic acidosis.

Conflict of interest: The authors declare no conflict of interest.
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Introduction

Maintenance intravenous fluids (mIVF) are required in hospitalized children unable to accept orally due to medical or surgical conditions. Routine mIVF in the pediatric population were traditionally hypotonic (fluid sodium 30-77 mEq/L) based on the Holliday-Segar formula (1). However, after reports of hospital acquired hyponatremia associated with hypotonic fluids (2-5), many studies including meta-analyses and systematic reviews have compared isotonic (sodium 131-154 mEq/L) with hypotonic fluids, which all found that isotonic fluids

were a better and more physiological choice (6-14). Increased AVP secretion in response to various non–osmotic stimuli like pain, fever, anxiety, stress, etc. (medical as well as surgical cases) reduces the ability to excrete free water, predisposing the children to hospital-acquired hyponatremia and a subsequent increase in morbidity and even mortality. As a result, recent clinical practice guidelines recommend the use of isotonic fluid as mIVF in pediatric patients and the most commonly recommended isotonic fluid is 0.9% sodium chloride solution (NS) (15, 16). Although the risk of iatrogenic hyponatremia is reduced with the use of 0.9% NS, there are concerns about hypernatremia, fluid overload and hyperchloremic metabolic acidosis. Hyperchloremic metabolic acidosis (HCMA) with use of NS was first recognized in 1923. Since then, studies have reported this adverse effect mainly in adult subjects (17-21) resulting in renal injury more so in patients requiring large volumes of resuscitation fluids (22). There is still not enough evidence to approve or disapprove 0.9% NS as a safe mIVF in hospitalized non-critically ill pediatric patients. Therefore, this study was conducted to assess the clinical and biochemical effects of 0.9% sodium chloride as an isotonic mIVF in the general non-critically ill pediatric patients.

Methods

This observational study was conducted at a tertiary care hospital in New Delhi, India from September 2018 to March 2020. All patients aged 2 months to 12 years requiring mIVF were screened for inclusion and detailed clinical evaluation was done after obtaining informed written consent from the caretaker/guardian. The study was approved by the Institutional Ethics Committee (IEC/2018/09). The children with baseline hyponatremia (serum sodium <135 mEq/L), hypernatremia (serum sodium >145 mEq/L), metabolic acidosis (pH≤7.31 and serum bicarbonate ≤22mEq/L), dehydration, shock, acute or chronic liver failure, congestive heart failure, acute or chronic renal failure, nephrotic syndrome, diabetes insipidus or diabetes mellitus, critically ill children requiring mechanical ventilation or PICU care, children taking both oral and intravenous fluids (partial IVF on admission), and children taking drugs like furosemide, hydrochlorothiazide, vasopressin, or desmopressin were excluded from study. Blood pressure was measured for all of the patients using an automatic digital blood pressure monitor and categorized as per AAP recommendations (23). Two milliliters of venous blood was drawn for baseline investigations (T0) like serum sodium, potassium, chloride, blood urea, serum creatinine and 0.2-0.3 ml blood was collected for venous blood gas (VBG).

Serum electrolytes were analyzed with direct potentiometry using the Backman AU680 analyzer and VBG was done using the ABL800 FLEX blood gas analyzer. The enrolled children received 0.9% NS with 5% dextrose and potassium at a concentration of 20 mEq/L given at the standard calculated rate (1). Repeat blood samples were collected at 24 and 48 hours. The primary outcome measures were changes in serum sodium, chloride and bicarbonate levels from baseline to 24 and 48 hours after starting mIVF and the objective of the study was to determine the incidence of hyperchloremia (serum chloride > 110mEq/L) and metabolic acidosis (pH <7.31 with serum bicarbonate level < 22 mEq/L). Other objectives were to determine the incidence of hypertension, hyponatremia (serum sodium <135 mEq/L), and hypernatremia (serum sodium >145 mEq/L). The sample size was calculated using studies conducted by Wilkes et al (18), which reported an incidence of 67% for hyperchloremic metabolic acidosis in the saline group, and McNab et al (10), which reported an incidence of 4% for hypernatremia with isotonic fluid. The minimum required sample size was 236 subjects with a margin of error of 6% and a level of significance of 5%. A total of 250 subjects were selected to reduce the margin of error using the following formula:

$N \geq ((i(1-i))/(ME/z_{\alpha})^2$

Where Z_{α} is the value of Z at two-sided alpha error of 5%, ME is the margin of error and i is the incidence rate.

Statistical analysis: All data was entered into a Microsoft EXCEL master chart. Categorical variables are presented as number and percentage (%) and continuous variables are presented as mean ± SD and median. Quantitative variables were compared using unpaired t test/Mann–Whitney test (when the data sets were not normally distributed) between the two groups and ANOVA/Kruskal–Wallis test (for non-parametric data) was used for comparison between more than two groups. Qualitative variables were evaluated using Chi-square test/Fisher's exact test. A p value was

considered statistically significant if it was <0.05. Statistical Package for Social Sciences (SPSS) version 21.0 was used for Statistical analysis.

Results

A total of 1920 patients were screened for inclusion of whom 1440 were excluded due to various reasons (Figure 1).

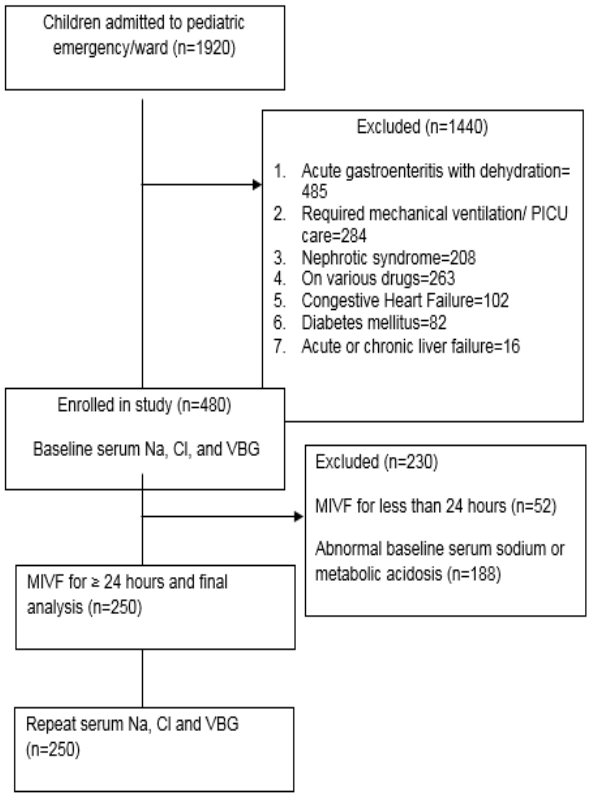

Figure 1. Flowchart of study plan

Blood samples were collected from the remaining 480 patients for baseline serum electrolytes and VBG. Of 480 subjects, 230 were further excluded due to abnormal serum sodium levels (<135 mEq/L or >145 mEq/L) or metabolic acidosis at baseline or not requiring fluids for 24 hours or more. Finally, 250 patients with a mean age of 3.79±3.2 years were analyzed. The majority (43.6%) of the participants were in the age group 2 months to 1 year old. There was a slight female preponderance (51.6%). Baseline clinical and biochemical parameters are presented in Table 1.

Table 1. Baseline clinical and biochemical parameters of the study population

Baseline parameter	Mean±SD
Age (years)	3.79±3.2
2 month- 11 months	109 (43.6%)
12 months- 5 years	72 (28.8%)
5 years- 12 years	69 (27.6%)
Male	121 (48.4%)
Female	129 (51.6%)
Blood pressures (mmHg)	
Systolic blood pressure	94.83±11.62
Diastolic blood pressure	54.85±10.53
Serum sodium level (mEq/L)	139.67±3.278
Serum chloride level (mEq/L)	103.81±4.717
Serum bicarbonate level (mEq/L)	23.455±1.218

As for the etiology, the majority of the admitted patients had pulmonary infection followed by seizure and CNS infections. A few of the patients had other causes (Figure 2). According to Table 2, no significant changes were observed in the mean blood pressure in the study subjects from baseline to 24 hours and 48 hours. There was no significant change in the mean serum sodium level at 24 hours compared to baseline (t value= -1.12, p-value- 0.26) but the change was significant at 48 hours (t value- = -2.38, p-value- 0.017). Overall, there were no significant changes among the three time points. The serum chloride and bicarbonate levels showed significant changes at 48 hours compared to baseline as well as among three time points ($p<0.001$ and < 0.01 each respectively). According to Figure 3, the mean serum chloride level was 103.81±4.717, 104.5±4.581, and 105.28±4.545 at baseline, 24 hours, and 48 hours respectively indicating a significant rise at 48 hours of mIVF (p-value< 0.001) and among three time points (p-value<0.01] .

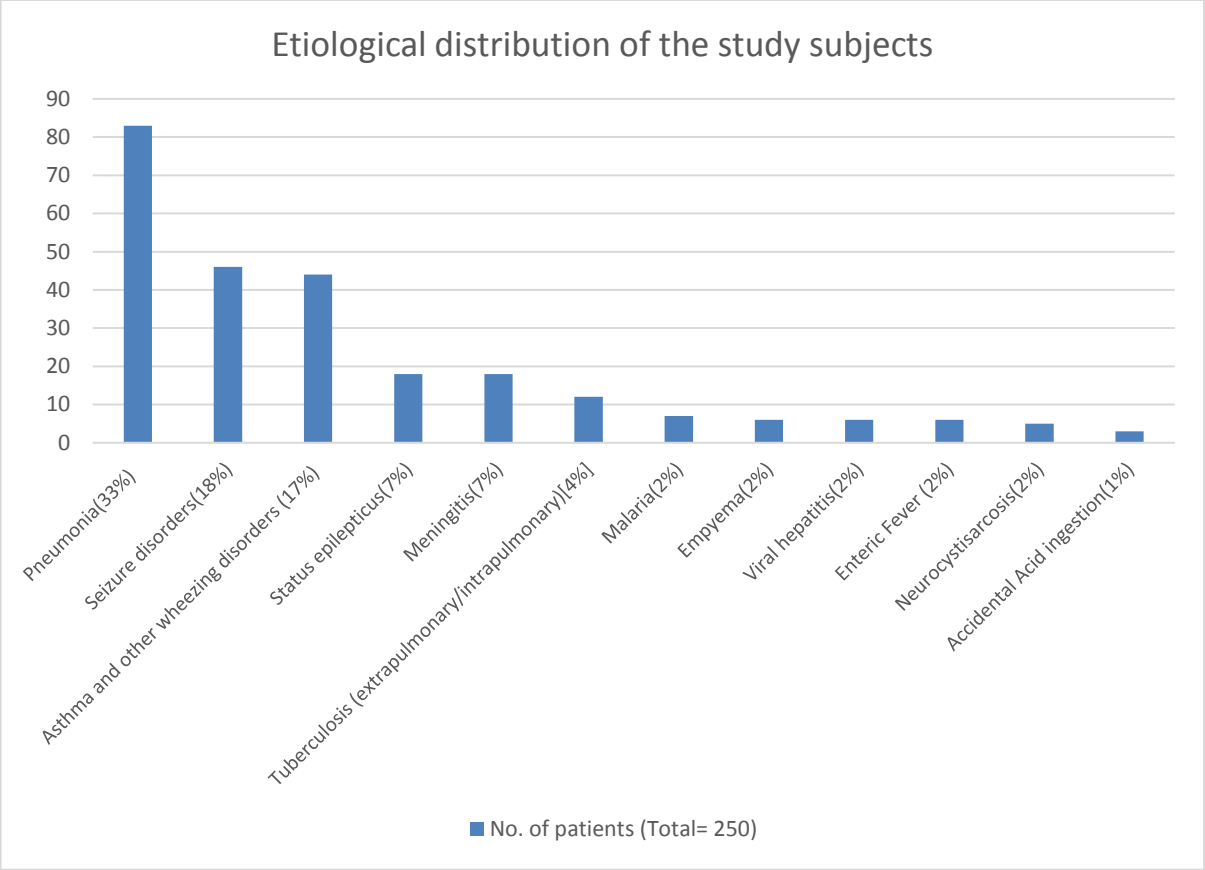

Figure 2. Etiological distribution of the study subjects

The mean serum bicarbonate level was 23.455±1.218, 23.21±1.191 and 23.08±1.162 at baseline, 24 hours and at 48 hours with a significant decrease at 24 hours and 48 hours compared to baseline (baseline -24 hours, p-value= 0.02; baseline - 48 hours, p-value< 0.001) also among three time points (p-value<0.01) (Figure 4). According to Table 3, the incidence of hyponatremia was 2% (5/250) at 24 hours and 0.8% (2/250) at 48 hours and the incidence of hypernatremia was 2.4% (6/250) and 2.8% (7/250) at 24 and 48 hours, respectively (p=0.25 and 0.07). The incidence of hyperchloremia was 4.8% (12), 7.2% (18) and 9.6% (24) at baseline, 24 hours and 48 hours respectively with a significant rise from baseline to 48 hours (p=0.03). However, there was no significance hyperchloremia at 24 hours compared to (p=0.25). 24 and 48 hours respectively with a significant difference (p<0.01). Similarly, the number of subjects with low bicarbonate levels were 22, 33, and 46 at baseline, 24 and 48 hours respectively with a significant difference (p<0.01) at 48 hours, but not at 24 hours, from the baseline. According to Table 4, the percentage of patients with metabolic acidosis (pH<7.31 with a serum bicarbonate level <22 mEq/L) increased from 0 at baseline to 1.6% (4) and 3.6% (9) at24 and 48 hours respectively indicating a statistically significant difference (p<0.01).

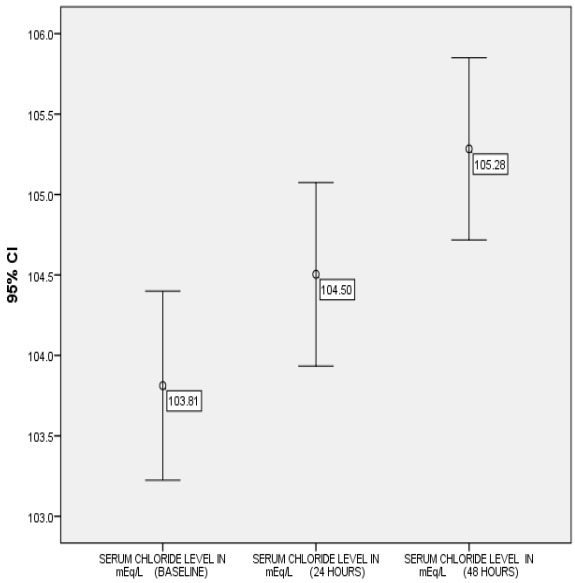

Figure 3. Change of serum chloride level in study subjects at 24 hours and 48 hours from baseline.

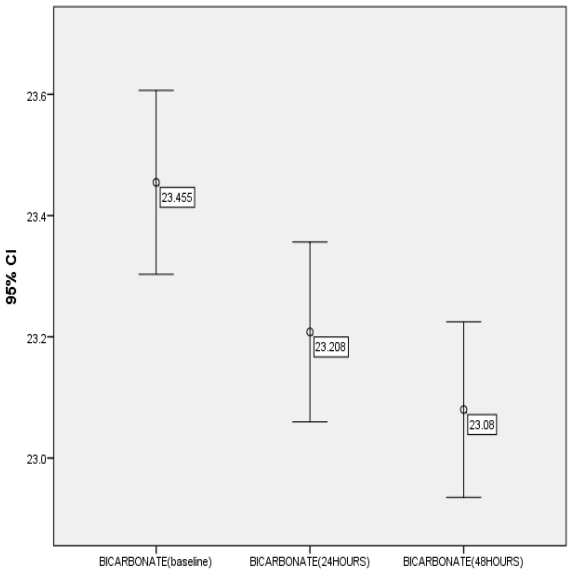

Figure 4. Change of serum bicarbonate level in study subjects at 24 hours and 48 hours from baseline.

Table 2. Changes of biochemical parameters from the baseline to 24 and 48 hours

	Baseline	24 hours	48 hours	Baseline vs. 24 hours* p-value	Baseline vs. 48 hours* p-value	Among 3 points of time p-value#
Systolic blood pressure(mmHg)	94.83±11.62	95.10±11.37	95.48±11.35	-	-	0.81
Diastolic blood pressure(mmHg)	54.85±10.53	55.45±10.02	55.63±10.49	-	-	0.67
Serum Sodium(mEq/L)	139.67±3.278	140.00±3.284	140.36±3.198	0.26	**0.017**	0.06
Serum Chloride(mEq/L)	103.81±4.717	104.5±4.581	105.28±4.545	0.097	**< 0.001**	**<0.01**
Serum Bicarbonate(mEq/L)	23.455±1.218	23.21±1.191	23.08±1.162	**0.02**	**<0.001**	**<0.01**

* T test applied; # ANOVA test applied; p-values in the bold type are statistically significant

Table 3. Incidence of hyponatremia, hypernatremia, hyperchloremia and low bicarbonate level at baseline, 24 and 48 hours.

	Baseline	24 hours	48 hours	Baseline-24 Hours p –value	24-48 hours p –value	baseline -48 hours p –value
Incidence of hyponatremia	0	5 (2.1%)	2 (0.8%)	-	0.253	-
Incidence of hypernatremia	0	6 (2.4%)	7 (2.8%)	-	0.079	-
Incidence of hyperchloremia	12(4.8%)	18(7.2%)	24(9.4%)	0.258	0.333	0.038
Incidence of low bicarbonate level	22(8%)	23(9.2%)	46(18%)	0.87	0.002	0.003

Hyponatremia (<135 mEq/L); Hypernatremia (>145mEq/L); Hyperchloremia (>110mEq/L); Low bicarbonate level (<22mEq/L); Applying crosstab's chi square test.

Table 4. Incidence of metabolic acidosis at 24 and 48 hours from the baseline

Metabolic acidosis	PH<7.31 and serum bicarbonate level <22 mEq/L	PH≥7.31 and bicarbonate level ≥22mEq/L	P value
Baseline	0	250	Sig.
24 hours	4	246	Sig.
48 hours	9	241	Sig.

Discussion

The mean age of the study population was 3.79±3.2 years with a female preponderance (51.6%). The majority (43.6%, n=109) were in the age group 2 months to 11 months (Table 1). Pneumonia was the most common diagnosis (33%) followed by status epilepticus (18.4%) and wheezing episodes (17.6%) (Figure 2). Blood pressure (BP) did not show any significant change at 24 and 48 hours compared to baseline (Table 1). Most of the previous studies have reported effects on BP; however, some studies did not report hypertension (10, 24). Choong et al reported new-onset hypertension in 1.54% (2 of 130) of the children receiving hypotonic fluids compared to those receiving isotonic fluid (25). There was no significant change in the mean serum sodium (S Na) level at 24 hours while the change from baseline (139.6±3.2 mEq/L) to 48 hours (140.3±3.1mEq/L) hours (p=0.017) was significant (Table 2). At 24 hours, 2.1% (5) and at 48 hours 0.8% (2) developed hyponatremia whereas hypernatremia was detected in 2.4% (6) of the subjects at 24 hours and in 2.8% (7) of the participants at 48 hours (Table 3), but the difference was not statistically significant. Previous studies also reported a lower risk of hyponatremia and a non-significant risk of hypernatremia after administration of 0.9% sodium chloride as isotonic mIVF (9-14). Few studies found a significant change in S Na after administration of isotonic saline but mainly in critically ill patients in the intensive care setting requiring fluid boluses (22). Most of the conducted studies have compared isotonic fluids with hypotonic fluids. Saba et al randomized 16 children to 0.9% NS and 21 children to 0.45% NS maintenance IVF groups and observed the rate of change in S Na as the primary outcome. S Na was measured at baseline and repeated at 12 hours. The results showed significant changes in S Na in the 0.9% NS group (+3.0 mmol/L [IQR 0.5, 4.5]) compared to the 0.45% saline group (+1.0 mmol/L [IQR 0.0, 2.0]); however, the difference between the two groups was not statistically significant (26). In a similar study, Bagri et al found a higher S Na at 24 h in children receiving NS (138.3 ± 6.0 mEq/L) compared to N/2 saline (135.1 ± 4.4 mEq/L) (p value <0.01). However, there was neither any significant difference in serum sodium levels between the two groups nor any case of symptomatic hypo or hypernatremia at 48 h (27). Similarly, Kumar et al reported significant changes in the serum sodium level at 12 and 24 hours

compared to baseline in the isotonic group (12 hours; p = 0.005, 24 hours; p < 0.001), however, there was no significant hypo or hypernatremia (28). In the present study, the mean serum chloride level was 103.81±4.7, 104.5±4.5, and 105.28±4.5 mEq/L at the baseline, 24 and 48 hours respectively (Table 2, Fig 3) with a significant rise in the incidence of hyperchloremia (serum chloride >110mEq/L) at 48 hours compared to baseline (p=0.038) (Table 3). The mean serum chloride level in hyperchloremic patients was 114.58±3.42, 114.06±3.13, and 113.92±3.16 at baseline, 24 and 48 hours respectively. Although serum chloride did not change significantly from baseline to 24 hours, its changes were significant at 48 hours from baseline as well as among three time points (p<0.01) (Table 2). There are previous reports of significant hyperchloremia following the administration of 0.9% NS in adult population (18-22), but there is paucity of data in pediatric patients**.** Lima MF et al (29) compared 0.9% saline and balanced crystalloid/plasmalyte-A in 49 pediatric patients undergoing neurosurgery receiving IVF in the perioperative period and found a significant increase in the serum chloride level from baseline in the 0.9% saline group [17/25 (68%) versus 2/24 (8%)] (P<0.01). Moreover, the incidence of hyperchloremic metabolic acidosis (serum chloride > 110 mEq/L plus > 50% decrease in the base excess) was higher in the saline group after surgery (6/25 (24%) vs. 0; P =0.022), which was similar to the results of the present study that found significantly little changes in the bicarbonate level at 24 hours and 48 hours after starting maintenance IVF compared to baseline (p<0.01) (Table 2, Fig 4). There was significant increase in the incidence of low bicarbonate levels at 48 hours (18%, n=46/250) compared to baseline (8%, n=22/250) (Table 3) (p<0.01). Bulfon AF et al conducted a retrospective study in 543 PICU patients <18 years of age who received 50% or more of their calculated total maintenance fluid requirements parenterally mostly in the form of 0.9% NS during the first 24 hours of admission. The results showed that the incidence of hyperchloremia (serum chloride >107mEq/L) and hyperchloremic metabolic acidosis (serum pH <7.35 and bicarbonate of <23mmol/L and/ or a base deficit of >5 mEq/L) was 94.9% (95% CI: 93.2–96.9) and 38.9% (95% CI: 34.6–43.2) respectively in the first 72 hours of admission, which was attributed to the combined effect of volumes of boluses and mIVF (30). There is evidence of increased hyperchloremia and hyperchloremic metabolic acidosis following the use of 0.9% NS as resuscitation fluid, which favors the use of balanced solution in the adult population (18, 20, 21, 31). Univariate analysis did not show any significant associations between age or sex and serum sodium or chloride level during mIVF infusion in the present study.

The most appropriate mIVF type in children is still debated. Although the most recommended and widely used isotonic mIVF fluid has been 0.9% NS, increased incidence of adverse effects like hyperchloremic metabolic acidosis cannot be ignored more so in centers with a large number of patients requiring mIVF with resource limited settings of patient monitoring. Hyperchloremia caused by 0.9% sodium chloride is attributed to a lower [Na+/Cl−] ratio in normal saline (1:1) as compared to plasma (1.38:1). Previous studies have reported significant mortality and morbidity due to hyperchloremia, primarily due to its effect on the kidneys (18-22, 29-32). Hyperchloremia may inhibit proximal tubular chloride reabsorption, which increases chloride delivery to the distal nephron and results in subsequent negative feedback to afferent renal vessels to limit the flow causing their vasoconstriction responsible for reduced renal perfusion leading to kidney injury and failure (32).

Balanced solutions, such as Plasmalyte-148 or Hartmann's may be a more appropriate choice for mIVF. Most important evidence comes from a recent study by McNab et al who observed a lower incidence of hyponatremia in the plasmalyte-148 group compared to the 0.45% sodium chloride group. However, they found no significant difference in the incidence of hypernatremia and hyperchloremia between the two groups (10).

A strength of this study was its large sample size of non-critically ill children admitted to general wards requiring mIVF and its main limitation was lack of a comparison group.

Conclusion

According to the results, 0.9% NS as mIVF does not cause any significant changes in serum sodium level in non-critically ill pediatric patients but leads to a significant increase in the serum chloride level resulting in hyperchloremia and metabolic acidosis.

Conflict of Interest
The author declares no conflicts of interest.

Financial Support
This research received no external funding.

Ethics
Institutional board ethics approval was taken for study (IEC/2018/09)

Authorship Declaration
All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Deepali malviya, Shobha Sharma, Anita Rani and Namita Srivastava. The first draft of the manuscript was written by Shobha Sharma and editing by Kanika Kapoor and Rani Gera. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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