



Fluid Accumulation Dilemma in the Critically Ill Children, A Retrospective Study

Kritik Hasta Çocuklarda Sıvı Birikimi İkilemi, Retrospektif Bir Çalışma

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Abstract

Aim: Fluid accumulation occurs in pediatric patients in pediatric intensive care units (PICU). Medications administered in pediatric intensive care units can contribute to significant cumulative load in patients. In present study, we aimed to study fluid accumulation on patients without AKI and to determine contribution of medications over fluid intake.

Material and Method: In this study, 527 daily follow-up forms of 101 patients was investigated retrospectively.

Results: Total fluid load was found to be higher in patients with comorbidities, who underwent invasive mechanical ventilation, and who needed inotropes. While fluid load was higher in patients with sepsis than in other diagnostic groups, it was significantly lower in patients with multisystem inflammatory syndrome in children (MIS-C). While the median (IQR) of the cumulative fluid load was 11.6% (7.1-16.4) in the first 5 days, the median (IQR) reached 25.7% (14.65-34.1) on the 10th day. The cumulative fluid load increased as the patient's follow-up days increased. The median average daily fluid intake (IQR) from drugs alone was 14.48% (8.07-24.13). The contribution of drugs to the total fluid load increased as the age of patients decreased ($r: -0.164, p < 0.001$).

Conclusion: A cumulative fluid load occurs in PICU patients without AKI. Particularly in young children, the contribution of fluids given with drugs to the fluid load should be kept in mind. Clinicians should perform patient-specific fluid management by supporting fluid status assessments with objective criteria in order to get out of the fluid accumulation- fluid over load dilemma.

Keywords: Pediatric intensive care, fluid accumulation, fluid load, medication

Öz

Amaç: Çocuk yoğun bakım ünitelerinde (ÇYBÜ) hastalarda sıvı birikimi meydana gelmektedir. Çocuk yoğun bakım ünitelerinde uygulanan ilaçlar, hastalarda önemli kümülatif sıvı yüküne katkıda bulunabilir. Bu çalışmada akut böbrek yetmezliği (AKI) olmayan hastalarda sıvı birikimini araştırmayı ve ilaçların sıvı alımına katkısını belirlemeyi amaçladık.

Gereç ve Yöntem: Bu çalışmada 101 hastaya ait 527 adet günlük takip formu geriye dönük olarak incelendi.

Bulgular: Komorbiditesi olan, invaziv mekanik ventilasyon uygulanan ve inotrop ihtiyacı olan hastalarda toplam sıvı yükü daha yüksek bulundu. Sepsisli hastalarda sıvı yükü diğer tanı gruplarına göre daha yüksek iken, çocuklarda multisistem inflamatuvar sendromlu hastalarda (MIS-C) anlamlı olarak daha düşüktü. Kümülatif sıvı yükü medyan (IQR) ilk 5 günde %11,6 (7,1-16,4) iken 10. günde medyan (IQR) %25,7'ye (14,65-34,1) ulaştı. Hastanın takip günleri arttıkça kümülatif sıvı yükü arttı. Tek başına ilaçlardan ortalama günlük sıvı alımı (IQR) %14,48 (8,07-24,13) idi. İlaçların toplam sıvı yüküne katkısı hastaların yaşı azaldıkça arttı ($r: -0,164, p < 0,001$).

Sonuç: AKI'si olmayan ÇYBÜ hastalarında kümülatif sıvı yükü oluşur. Özellikle küçük çocuklarda ilaçla birlikte verilen sıvıların sıvı yüküne katkısı akılda tutulmalıdır. Klinisyenler sıvı birikimi-sıvı aşırı yüklenmesi ikileminden kurtulmak için sıvı durum değerlendirmelerini objektif kriterlerle destekleyerek hastaya özel sıvı yönetimi yapmalıdır.

Anahtar Kelimeler: Çocuk yoğun bakım, sıvı birikimi, sıvı yükü, ilaç



INTRODUCTION

Intravenous fluid treatment is important in critically ill children management. In pediatric intensive care units, the amount of fluid taken by the patient is routinely recorded. Based on these records, daily or cumulative fluid balance can be calculated.^[1] Fluid balance helps the clinician in fluid resuscitation and diuretic therapy management. Cumulative fluid accumulation occurs in almost every child admitted to the intensive care unit. In the large retrospective evaluation of Alobadii et al., it was shown that in the first few days of admission to the intensive care unit, there was a 10% cumulative fluid load in 32.7% of patients and 15% in 15.8% of patients.^[2] Studies examining the effects of fluid load on outcome in critically ill children are mostly studies evaluating fluid load before renal replacement therapy in patients with acute kidney injury (AKI) or undergoing cardiac surgery, and it has been shown that mortality increases with increased fluid load.^[1,3,4]

Fluid and drug treatments in children are regulated by dosing schemes according to body weight or body surface area. In the pediatric intensive care units, care is given to a group between the ages of 1 month and 18 whose body weight and body surface area are highly variable. Despite these variable sizes of the patients, drugs are prepared with fixed preparation methods or used in constant concentration. There is only one study in the literature examining the contribution of drugs to total fluid balance. Furman et al. showed that the fluid administered with drugs can contribute 19-39% to positive fluid balance in patients undergoing prospective observational mechanical ventilation.^[5] According to the best knowledge of the author, there is no study examining the contribution of drugs to fluid load in other patient groups. In this study, we aimed to retrospectively determine the fluid accumulation and the contribution of the drugs used to fluid intake in all patients admitted to the pediatric intensive care unit for any reason.

MATERIAL AND METHOD

We conducted this retrospective cohort study in January 2022 for 30-day period at the PICUs of Ankara City Hospital, Turkey. The study was approved by the local ethic committee (Approval No.: E2-21-733). All patients between the ages of 1 month and 18 who were admitted to the pediatric intensive care unit for any reason and stayed for at least 24 hours were included in the study. Demographic data of the patients such as age, gender, hospitalization diagnosis, comorbidity, PRISM scores and laboratory values of the patients were recorded from the hospital operating system. In our unit, total inputs (all given such as intravenous fluids, nutrition, drugs, blood products) and total losses (urine amount, if any, coming from drainage tubes, watery stool) are recorded in daily follow-up forms. Data on total fluid intake, total fluid output, total fluid intake from drug administration alone, and diuretic, inotropic use, and ventilation modality were recorded from daily follow-up forms for each patient. Daily and total fluid load was calculated as: %GFO = (fluid intake (L)–total output (L)) /

baseline body weight (kg) x 100. At the same time, cumulative fluid accumulation was calculated for each day. The creatinine levels at the time of admission to the intensive care unit and the serum creatinine level that can be reached before admission were recorded. AKI was defined based on the Kidney Disease Relief Global Outcomes Criteria (KDIGO) using serum creatinine. Urine output over 2000 ml/body surface area/day was considered as polyuria. Body surface area was calculated according to the patient's weight (body surface area= (4x body weight (kg) +7/ 90+ body weight (kg)).

Statistical Analyses

Statistical analyses were performed by using SPSS version 25.0 program. The conformity of the variables to the normal distribution was examined by histogram graphics and the Kolmogorov-Smirnov test. While descriptive analyzes were presented, mean, standard deviation, median, and IQR values were used. Categorical variables were compared with the Pearson Chi-Square Test. The Mann Whitney U Test was used when evaluating non-normally distributed (nonparametric) variables between two groups, and the Kruskal Wallis Test was used when evaluating between more than two groups. Spearman Correlation Test was used in the analysis of the measurement data with each other. Cases with a P-value below 0.05 were considered as statistically significant results.

RESULTS

In the study, 527 daily follow-up forms of 101 patients were analyzed retrospectively. 55 (54.5%) patients were male. The median (IQR) age was 31 (8-128) months. Pneumonia (34.65%) and bronchiolitis (20.8%) were the most common reasons for hospitalization. There was an accompanying comorbidity in 48.5% of the patients. Neurological (26.7%) comorbidity and malignancy (7.9%) were the most common comorbidities. The patients were followed up for a mean of 5.2 (±5.75) days. The median follow-up period (IQR) of the patients who died was 10 (5-26) days and was significantly higher than the survivors 3(2-5) (p=0.002). Invasive mechanical ventilation was applied to 45 (44.5%) patients and non-invasive mechanical ventilation was applied to 29 (28.7%) patients. 29 (28.7%) patients used inotrope/ diuretic during their hospitalization. None of the patients received renal replacement therapy (RRT). The mortality was 6.9% (n:7). Basal creatinine value was 0.36 (±0.2) mg/dL. None of the patients had AKI at the time of admission. Demographic data of the patients are presented in **Table 1**. There were 64 (63.37%) patients with total fluid balance <10%, 17 (16.83%) patients with 10%-20%, 7 (6.93%) patients with 20%-30%, and 13 (12.87%) patients with >30%. There were 11 (10.89%) patients with total fluid balance negative. The mean total fluid balance was 12.84% (± 18.94, min:-16.85, max 83.20). The median daily fluid intake (IQR) from drugs alone was 14.48% (8.07-24.13). As the age of the patient decreased, the contribution of drugs to the total fluid load increased (r:-0.164, p< 0.001). Medication percentage and cumulative fluid load values according to follow-up days are given in **Table 2**.

Table 1. Demographic data of the patients

		n	%
Gender	Female	46	(45.54)
	Male	55	(54.46)
Diagnosis	Pneumonia	35	(34.65)
	Bronchiolitis	21	(20.79)
	Post-op	9	(8.91)
	Status epilepticus	10	(9.90)
	Sepsis	4	(3.96)
	Trauma	10	(9.90)
	Mis-c	7	(6.93)
	Other diagnosis	5	(4.95)
	None	52	(51.49)
	Neurological	27	(26.73)
Comorbidity	Malignancy	8	(7.92)
	Congenital heart	6	(5.94)
	Respiratory (BPD, CF)	4	(3.96)
	Metabolic disease	4	(3.96)
Tracheostomy	No	90	(89.11)
	Yes	11	(10.89)
Mortality	No	94	(93.07)
	Yes	7	(6.93)
	<%10	64	(63.37)
Total fluid balance %	%10-%20	17	(16.83)
	%20-%30	7	(6.93)
	>%30	13	(12.87)
Diuretic	No	72	(71.29)
	Yes	29	(28.71)
Inotrope	No	72	(71.29)
	Yes	29	(28.71)
Mechanical ventilation	None	27	(26.73)
	Invasive	45	(44.55)
	Non-invasive	29	(28.71)

Table 2. Medication and cumulative fluid load values according to the follow-up days of the patients.

	n	Medication % Median (P25-P75)	Fluid Load Median (P25-P75)	Cumulative fluid load Median (P25-P75)
1. day	101	14.32 (8.59-24.34)	2.12 (0.78-4.52)	2.2 (0.9-4.8)
2. days	82	11.92 (7.14-20.09)	2.12 (0.29-3.85)	4.1 (1.9-7.7)
3. days	59	16.64 (7.57-29.07)	1.97 (-0.01-4.88)	7 (3.4-13.4)
4. days	47	19.26 (9.48-31.46)	1.83 (0.32-3.52)	10.6 (4.1-16.3)
5. days	34	15.18 (13.25-23.75)	1.6 (0.2-3.6)	11.6 (7.1-16.4)
6. days	28	16.59 (12.48-22.85)	2.88 (0.77-3.76)	15.3 (10.65-20.6)
7. days	22	19.28 (7.04-26.82)	1.99 (0.13-3.84)	17.7 (12-23.4)
8. days	19	17.26 (7.82-26.76)	1.32 (0.36-3.71)	22.5 (15.7-29.1)
9. days	18	14.43 (6.63-24.62)	1.89 (0.3-3.13)	24.1 (16.8-31.4)
10. days	16	8.3 (6.62-20.75)	2.15 (1.18-5.92)	25.7 (14.65-34.1)
11. days	12	18.02 (11.37-25.9)	1.99 (0.22-4.77)	26.95 (16.4-36.3)
12. days	11	8.9 (6.18-23.59)	2.8 (1.23-5.27)	29.6 (22.7-45.8)
13. days	10	13.68 (7.62-33)	3.61 (3.37-4.61)	35.6 (30.2-52.5)
14. days	10	15.88 (7.12-28.1)	4.12 (1.67-4.68)	40.05 (31.4-54.2)
15. days	6	13.53 (7.98-29.48)	4.52 (3.25-5.12)	41.25 (34.7-48.4)
16. days	6	13.61 (7.86-17.02)	4.42 (1.24-5.96)	46.7 (34.4-54.8)
17. days	5	15.46 (8.71-18.04)	2.01 (1.41-2.51)	51.7 (47.4-56.2)
18. days	5	13.78 (8.97-14.12)	1.57 (1.21-2.44)	52.7 (49.8-57.8)
19. days	5	11.21 (10.12-15.71)	2.3 (0.83-2.6)	53.5 (52.4-60.1)
20. days	5	6.52 (6.52-9.01)	2.94 (0.96-3.3)	55.7 (52.9-66.7)
21. days	5	8.07 (8.05-8.72)	1.58 (1.22-4.46)	60.2 (54.1-68.3)

In comparisons, total fluid balance did not change with age (p=0.71) and gender (p=0.60). Total fluid balance was found to be higher in patients with accompanying comorbidities (p=0.037), undergoing invasive mechanical ventilation (p<0.001) and in need of inotropes (p=0.001). Total fluid balance was high in patients with sepsis (p=0.002) and those with a fluid balance above 30% were significantly higher when compared to other diagnostic groups (p=0.001). Fluid load in hospitalized patients with the diagnosis of pneumonia and bronchiolitis was not different from other diagnostic groups (p=0.196, p=0.192, respectively). Total fluid balance was significantly lower in patients diagnosed with MIS-C (p=0.039). The rate of negative fluid balance was higher in patients with MIS-C (p=0.005). The rate of those with total fluid balance between 20% and 30% in inotropic patients was higher than in those who did not receive inotropics (p=0.001). The rate of total fluid balance >30% in patients with invasive mechanical ventilation was higher than those with and without non-invasive mechanical ventilation (p<0.001).

The rate of patients with total fluid balance >30% was higher in patients who resulted in mortality (p=0.025). When the correlation between total fluid balance and weight, age and day of follow-up was examined, total fluid balance increased as the follow-up days increased (r:0.629, p<0.001). There was no correlation between the patient's weight, age, and basal creatinine values and total fluid balance (Table 3). While the median daily fluid load (IQR) was 0.4% (-0.8-2.2) in polyuric patients, it was 3% (1.6-4.9) in non-polyuric patients, and it was statistically significantly higher (p<0.001).

Table 3. The correlation between total fluid balance and weight, age, follow-up day

		Weight	Age (Month)	Follow-up day
Total fluid balance	r	-0.082	-0.037	0.629
	p	0.414	0.712	<0.001
Spearman Correlation Test				

DISCUSSION

In our retrospective cohort study, we aimed to determine the level of fluid accumulation and to determine the contribution of drugs to this in patients who were admitted to the intensive care unit for any reason and did not have AKI. According to our results, total fluid accumulation was found to be higher in our patients with accompanying comorbidities, undergoing invasive mechanical ventilation, and in need of inotropes. While fluid balance was higher in our patients with sepsis than in other diagnostic groups, fluid balance was significantly lower in patients with MIS-C and even negative fluid balance was present. The cumulative fluid accumulation of our patients was higher comparing to the literature.^[2] The median cumulative fluid load was 11.6% in the first 5 days was increasing to 25.7% on the 10th day. Similar to the literature,^[2] the cumulative fluid load of the patients was increasing as the follow-up days increased.

One of the most important weapons of critical care clinicians is intravenous fluid therapy. However, this treatment is a two-edged sword. While early targeted therapy is life-saving in cases such as sepsis and shock, there are studies showing that fluid overload increases mortality and morbidity.^[3,6-10] Studies showing that mortality increases with fluid load are studies investigating the effect of fluid load on survival at the beginning of renal replacement therapy, which is generally applied for acute kidney injury in pediatric intensive care units.^[1,3,11] However, AKI develops at a rate of 20-30% in patients hospitalized in the pediatric intensive care unit.^[12] Goldstein et al. showed that fluid load above 20% at the beginning of renal replacement therapy in 116 pediatric intensive care patients increased mortality. However, that study was not randomized to expose patients to different fluid loads, and more than half (59.2%) of patients required RRT because of sepsis and cardiogenic shock.^[13] In our study, the rate of patients with a cumulative fluid load >30% was higher in patients who died. RRT was not applied in these patients. The follow-up period of the patients who died was long. The longer the follow-up period, the more fluid accumulation in the patients was an expected result. In the patients who died, the death of the patient was expected due to comorbidities such as terminal stage malignancy. Therefore, it cannot be said that there is a relationship between cumulative fluid accumulation and mortality, even if the cumulative fluid accumulation is statistically higher in the deceased. A certain amount of fluid load occurs in all children admitted to the intensive care unit. Fluid load can be calculated based on the intake and output records recorded by the nurses and changes in body weight. Perren et al. prospectively studied changes in cumulative fluid balance and body weight in 147 adult intensive care unit patients. They found the correlation between cumulative fluid balance and body weight measurements to be weak.^[14] Selewski et al. showed that the weight-based calculated fluid load definition used at the beginning of the RRT is useful.^[15] There isn't any standard definition of fluid load in current literature, and there is no guideline to manage it.^[1,16] In the literature, prevention of fluid accumulation in children has been associated with better survival,^[17,18] and increased fluid load with increased mortality.^[11,19] The first-line therapy to increase output in fluid management is diuretics. We found that only 28% of the patients used diuretics. In addition to the risks of diuretics such as electrolyte disorders and ototoxicity, it has been shown that they do not prevent the formation of AKI in adult patients and are associated with increased mortality rates.^[16,20] In this study, we found that almost all of the patients had fluid accumulation exceeding 10% in the first few days of hospitalization, and a cumulative fluid accumulation of more than 50% when the hospitalization period exceeded 15 days. In the literature, fluid load over 10-20% in intensive care units was associated with increased mortality, but it should be kept in mind that recommendations come from studies conducted with patients with AKI.^[11,13,19]

We do not have a fluid management protocol in our unit. Since the study was planned retrospectively, we do not know the clinicians' decision mechanisms in fluid management. Evaluating fluid status in the critically ill may be more complex than expected. Therefore, it may be beneficial to support the cumulative fluid load and weight-based fluid load calculations with objective criteria such as examination of cardiac, lung, and vascular flow models by bedside ultrasound.^[21,22]

In our study, we observed that RRT was not applied to any patient since urine output did not decrease even though the cumulative fluid loads were high. There are clearer recommendations for RRT in patients with AKI in the literature. Whereas, there is no clear recommendation for the application of RRT in patients without AKI and with urine output.^[1,16,23,24] Is renal replacement therapy required in patients with high cumulative fluid load but without AKI and with urine output in the pediatric intensive care unit? If necessary, what should be the timing? Randomized controlled studies are needed to answer these questions and develop guidelines based on objective criteria.

In addition, fluid management in intensive care units should not be perceived only as an effort to remove fluid. It is also important to optimize the fluids that patients are taking. While calculating the total daily intake, intravenous fluids, enteral nutrition solutions and intakes as well as fluids administered with drugs should not be ignored. In this study, the contribution of fluids taken with drugs to the total fluid load increased as the age decreased, but the contribution of drugs to the total fluid load was lower than the literature. There is only one study in the literature investigating the contribution of drugs to fluid load. It should be noted that only patients who underwent mechanical ventilation were included in this study by Fuhman et al.^[5]

Drugs used in standard concentrations such as IVIG increase the amount of drugs that patients take with the drugs and the total amount of fluid they take if care is not taken. In our clinic, IVIG is administered at a dose of 2 g/kg according to our MIS-C treatment protocol.^[25] However, the cumulative fluid load was significantly lower in patients diagnosed with MIS-C who received high-volume IVIG and multiple drugs. The reason for this may be the echocardiographic demonstration of fluid overload findings and our application of limited fluid and early diuretic therapy based on this.

Limitations

This is a retrospective single-center study. We could not evaluate the clinicians' fluid management decision mechanisms and the physical examination findings of the patients during the study period.

CONCLUSION

Fluid load is inevitable in pediatric intensive care units. When calculating fluid load, clinicians should not ignore the fluids they take with drugs as the age of the patient gets

younger. There is a need for guidelines for the definition and management of fluid load in patients with high cumulative fluid load but not AKI in the pediatric intensive care unit. Randomized controlled studies should be conducted to develop guidelines based on objective criteria and to determine the indications for renal replacement therapy in these patients. There are lots of useful, noninvasive, and practical methods like the point of care ultrasonography for detecting FO in intensive care units. It is important that clinicians make their diagnoses based on objective criteria (cardiac, lung, and vascular flow models) and perform patient-specific fluid management in order to establish a common language in fluid status assessments.

ETHICAL DECLARATIONS

Ethics Committee Approval: The approval of the Ethics Committee of Ankara City Hospital (Approval No.: E2-21-733) was obtained for our study.

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The author has no conflicts of interest to declare.

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