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Fluid overload due to intravenous fluid therapy for vaso-occlusive crisis in sickle cell disease: incidence and risk factors

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Summary

Intravenous fluid therapy (IV-FT) is routinely used in the treatment of vaso-occlusive crises (VOCs), as dehydration possibly promotes and sustains erythrocyte sickling. Patients with sickle cell disease (SCD) are at risk of developing diastolic dysfunction and fluid overload due to IV-FT. However, data on the adverse effects of IV-FT for VOC is sparse. We aimed to evaluate the incidence and risk factors of fluid overload due to IV-FT in patients with SCD. Consecutive hospitalisations for VOC treated with IV-FT between September 2016 and September 2018 were retrospectively analysed. The median (interquartile range) age was 25·0 (18·3–33·8) years and 65% had a severe genotype (HbSS/HbSβ^0-thal). Fluid overload occurred in 21% of 100 patients. Hospital stay was longer in patients with fluid overload (6·0 vs. 4·0 days, $P = 0{\cdot}037$). A positive history of fluid overload ($P = 0{\cdot}017$), lactate dehydrogenase level ($P = 0{\cdot}011$), and top-up transfusion during admission ($P = 0{\cdot}005$) were independently associated with fluid overload occurrence. IV-FT was not reduced in 86% of patients despite a previous history of fluid overload. Fluid overload is frequently encountered during IV-FT for VOC. IV-FT is often not adjusted despite a positive history of fluid overload or when top-up transfusion is indicated, emphasising the need for more awareness of this complication and a personalised approach.

Keywords: sickle cell disease, vaso-occlusive crisis, fluid therapy, fluid overload, pulmonary oedema.

Introduction

Acute painful vaso-occlusive crisis (VOC) is one of the clinical hallmarks of sickle cell disease (SCD).[1] VOCs account for the vast majority of SCD-related hospital admissions and are associated with significant morbidity and mortality, and negatively impact quality of life.[2–5] Despite the improvements made in our understanding of the pathophysiology of VOC, its treatment still primarily consists of supportive care.[6] Besides treatment of a potential underlying cause, extra [intravenous (IV)] fluids, (opioid) analgesics, and occasionally oxygen support are part of the treatment of VOC.

Intake of ample fluids or administration of IV fluids is by many perceived as an important part of VOC treatment, as a decrease in body fluid levels is thought to promote and sustain the sickling process. Patients with SCD are particularly prone to dehydration due to multiple factors. Renal concentrating defects as a result of continuous haemolytic and vaso-occlusive damage of the renal medulla render patients with SCD susceptible to hypovolaemia and dehydration.[7,8] Additionally, patients with SCD tend to reduce their intake during a period of illness and especially during severe pain. The resulting increased plasma osmolality may lead to red blood cell (RBC) dehydration, thereby contributing to increased sickle haemoglobin (HbS) polymerisation and ultimately vaso-occlusion.[9,10]

In vitro studies have shown that administration of hypotonic fluids improved hydration of sickle RBCs, reduced HbS polymerisation and RBC sickling, decreased RBC adhesion to endothelial cells, and ameliorated microvascular blood flow.[11–13] Administration of sufficient fluids also decreased the proportion of sickle-shaped RBCs *in vivo*.[13] However, there is little evidence from clinical trials regarding the effectiveness or potential adverse events of IV fluid therapy (IV-FT) for VOC. As a result, there is no clear consensus on the amount, rate and type of the administered fluids.[14] Consequently, IV-FT for VOC is more experience- than evidence-based, resulting in inconsistency in treatment protocols.

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Fluid overload during IV-FT for VOC is frequently encountered. However, exact data on incidence and risk factors are lacking. Haynes *et al.*[15] previously described four cases of pulmonary oedema in a cohort of 51 episodes of VOC (5%). An autopsy study in 21 patients who were hospitalised for VOC and died unexpectedly found that 15 patients had some form of lung pathology and seven (47%) of these 15 patients had pulmonary oedema, probably due to fluid overload.[16] A more recent study by Gaut *et al.*[17] revealed that the amount of administered fluids was significantly associated with any form of adverse events, such as transfer to the intensive care unit (ICU). However, fluid overload as a specific outcome was not evaluated.

Sickle cell disease is complicated by diastolic dysfunction and pulmonary hypertension, which in combination with the large amounts of IV and oral fluids may increase the risk of fluid overload with pulmonary oedema in patients with SCD.[18,19] Pulmonary oedema, in turn, can lead to an increased risk of acute chest syndrome (ACS), a potentially fatal complication of SCD.[20,21] On the other hand, hypoxia and shortness of breath due to fluid overload can also be mistaken for ACS, resulting in improper treatment with antibiotics and/or blood transfusion.

We hypothesised that fluid overload is frequently encountered during IV-FT and is under reported in current literature. Additionally, we contemplate that fluid overload might contribute to more complicated or prolonged hospital admission. Therefore, in the present retrospective study, we assessed the incidence and potential risk factors of fluid overload during IV-FT for VOC, as per the Dutch guideline. We evaluated whether fluid overload is related to the volume of IV-FT, SCD-related organ damage, use of blood transfusion or hydroxyurea and various laboratory parameters.

Methods

Patient selection and definitions

Data were collected in two hospitals in the Netherlands (Amsterdam UMC, Amsterdam, tertiary SCD hospital, and Flevo Hospital, Almere). Electronic records of patients with SCD [sickle cell anaemia (HbSS), sickle-haemoglobin C disease (HbSC), HbS-β^0 thalassaemia (HbSβ^0-thal) and HbS-β^+ thalassaemia (HbSβ^+-thal)] admitted for VOC between September 2016 and September 2018 were screened. The current Dutch guideline recommends 3 l/24 h of NaCl 0·65% in adult patients with SCD during VOC, regardless of their concomitant oral intake. Before 2018, adult patients were primarily treated with NaCl 0·9%. In paediatric patients a total fluid intake (oral + IV NaCl 0·45%/glucose 2·5%) of 3 l/m^2/24 h is recommended. We will refer to these guidelines as IV-FT (for VOC) throughout this manuscript. Patients are generally also encouraged to drink actively. A fluid bolus is not given, as is supported by previous data.[22] IV-FT is tapered or stopped after 72 h. To reliably study IV-FT per protocol, admissions in which IV-FT was not started and hospitalisations of <72 h were excluded. Repetitive admissions of the same patient were allowed for inclusion. For each eligible admission, patient and disease characteristics were collected.

Electronic patient records were reviewed manually by two study physicians to capture all study variables and characteristics. Additionally, several automatic search terms were used to detect cases of fluid overload. If fluid overload was described by the treating physician at the time of hospitalisation, these cases were retrospectively reviewed by the two study physicians to adjudicate a case of fluid overload using a combination of clinical parameters and symptoms. At least one of the following criteria was mandatory: lung oedema on chest X-ray, weight gain, or increased peripheral oedema. In all cases, these criteria were accompanied by one or more of the following items: signs of lung crackles, dyspnoea and/or oxygen requirement, reduction or stop if IV-FT and/or treatment with diuretics. In case of doubt by the two reviewing physicians, the episode of presumed fluid overload was not defined as such in this study.

Vaso-occlusive crisis was defined as musculoskeletal or visceral pain not otherwise explained and for which the patient required hospital admission. Steady-state transthoracic echocardiograms (ECGs) are routinely performed every 5 years in adult patients with SCD. Each patient's most recent ECG was assessed. Diastolic dysfunction was defined by the criteria of Sachdev *et al.*[23] A maximal tricuspid regurgitant jet velocity (TR V_{max}) cut-off of 2·5 m/s was used.[24–26] Steady-state N-terminal prohormone of brain natriuretic peptide (NT-proBNP) levels were retrospectively collected and a cut-off of 160 ng/l was used as previously described.[26,27]

Statistical methods

Continuous data were depicted as means with standard deviations (SDs) or medians with interquartile ranges (IQRs) as appropriate. Categorical data were presented as a percentage of the total number of applicable patients. Comparisons between groups for numerical data were performed with the Student's *t*-test or Mann–Whitney *U*-test. Binary variables were compared between groups using Pearson's chi-square test or Fisher's exact test as appropriate. A two-tailed $P \leq 0{\cdot}05$ was considered statistically significant and 95% confidence intervals (CIs) were used. Variables with significant missing data were excluded from analyses.

To prevent bias of repetitive inclusions, most analyses were performed in each patient's first hospitalisation during the study period. As steady-state transthoracic ECGs are routinely performed in adults, but not in children, analyses regarding steady-state ECG results were performed in adult patients only. To investigate the relationship between fluid overload and various characteristics, uni- and multivariable logistic regression analyses were performed with adjustments

for confounders specific for each parameter. Confounders were determined based on clinical relevance and associations previously described in the literature. For these regression analyses, only each patient's first admission (patients with no fluid overload) or first admission with fluid overload (patients with at least one episode of fluid overload) were used to prevent bias towards characteristics of patients with frequent hospitalisations and to ensure adequate capture of fluid overload events respectively.

Results

A total of 230 consecutive hospitalisations for VOC in 100 patients were eligible for inclusion, of which there were 46 in 20 paediatric patients. The median (IQR) age was 25·0 (18·3–33·8) years, 41% of patients were female, 65% had a severe genotype (HbSS/HbSβ^0-thal) and 53% used hydroxyurea. The median (IQR) time to fluid overload occurrence was 3 (2–3) days after admission.

During the 2-year study period, 21 patients developed fluid overload due to IV-FT for VOC. Four patients had two episodes of fluid overload during the study period, bringing the total number of fluid overload episodes during this study to 25 (11% of the 230 hospitalisations). Of these 25 cases of fluid overload, 16 (64%) had signs of pulmonary oedema on chest X-ray, one (4%) had peripheral oedema, two (8%) had weight gain and six (24%) had a combination of two or more of these criteria. A total of 33 patients had at least one episode of fluid overload in their past medical history. The proportion of patients with a positive history of fluid overload was significantly larger in patients developing fluid overload during the study period (12/21; 57%) than that in patients not developing fluid overload during the study period (21/79; 27%, $P = 0{\cdot}012$). When combining all episodes of fluid overload during the 2-year study period and in the medical history, 42% of the patients had developed at least one documented episode of fluid overload.

There was no significant difference in the rate of fluid overload between adult and paediatric patients, nor between female and male patients. Steady-state haemolysis parameters such as lactate dehydrogenase (LDH), haemoglobin concentration and reticulocyte counts did not differ between patients with and without fluid overload. Also, the proportions of patients with micro-albuminuria and renal insufficiency were not different between the groups (Table I).

Characteristics during hospital admission are presented in Table II. At the Emergency Department (ED), oxygen support was more frequent and respiratory rates higher in patients that would later develop fluid overload [38% vs. 0%, $P = 0{\cdot}000$ and with a median (IQR) of 20 (16–24) vs. 17 (15–21)/min, respectively, $P = 0{\cdot}048$]. The median (IQR) LDH levels at ED presentation were higher in patients developing fluid overload than in those not developing this complication, at 453 (354·5–484·0) *versus* 368 (265·0–511·8) u/l ($P = 0{\cdot}004$). Top-up RBC transfusions (1 or 2 units of 300 ml RBCs) were given more often in the hospitalisations of patients developing fluid overload than in those without (43% vs. 14%, $P = 0{\cdot}004$). In the 11 hospitalisations with fluid overload who received top-up transfusion, most patients developed fluid overload after the RBC transfusion. One patient developed fluid overload almost immediately after the transfusion, in six other cases fluid overload occurred within 2–3 days after the transfusion. In four cases fluid overload preceded the transfusion. In only one case, the volume of IV-FT was actively reduced due to transfusion during IV-FT. In the other patients, IV-FT was only temporarily stopped during transfusion to prevent using another cannula. The indication for the top-up transfusion was anaemia in all 11 cases.

Hospitalisations resulting in fluid overload had a significantly longer duration of hospital stay compared to those not developing fluid overload, at a median (IQR) of 6·0 (4–10) *versus* 4·0 (3–6) days ($P = 0{\cdot}037$). There were no differences in antibiotics use, ACS occurrence, readmission rates or ICU transfers.

Figure 1 shows selected criteria for subgroup analysis of admissions in adult patients with a positive history of fluid overload. IV-FT was not adjusted in 86% of hospital admissions of adult patients with a documented positive history of fluid overload. Moreover, in 11 (20%) of these hospitalisations, IV-FT was extended beyond 72 h or >3 l of IV fluid/24 h was given, mainly due to severe or persistent pain.

The ECG characteristics and steady-state NT-proBNP values of all unique adult patients ($n = 80$) are listed in Table III.[23] The median (IQR) time between hospitalisation for VOC and the ECG was 19·8 (8·1–37·3) months. Diastolic dysfunction was reported in 15% of adult patients and did not differ significantly between groups, neither did steady-state NT-proBNP levels. In adult patients who developed fluid overload during the study period, a larger proportion of patients had a TR V_{max} of ≥2·5 m/s compared to patients without fluid overload (43% vs. 18%, $P = 0{\cdot}026$).

No differences in the incidence of fluid overload [unadjusted odds ratio (OR) 0·856, 95% CI 0·229–3·194; $P = 0{\cdot}817$] or vital parameters such as blood pressure and heart rate during hospital stay were found between adult patients treated with NaCl 0·9% ($n = 128$) and those treated with NaCl 0·65% ($n = 34$) (data not shown).

Table IV.[23] shows selected characteristics for which regression analyses were performed. This was also performed for adult and paediatric patients separately (Table SI). A previous episode of fluid overload (adjusted OR 3·395, 95% CI 1·241–9·200; $P = 0{\cdot}017$), higher LDH levels upon hospital admission (unadjusted OR per 1 unit increase 1·003, 95% CI 1·001–1·006; $P = 0{\cdot}011$), and the requirement of top-up blood transfusion during admission (adjusted OR 6·490, 95% CI 1·769–23·803; $P = 0{\cdot}005$) were independently associated with fluid overload occurrence. Although TR V_{max} of ≥2·5 m/s was more frequent among patients developing fluid overload, no significant association between TR V_{max} ≥2·5 m/s and fluid overload was found in the regression

Table I. Baseline characteristics of individual patients (n = 100).

Characteristic	Total (N = 100)	Fluid overload (n = 21)	No fluid overload (n = 79)	P
Age, years, median (IQR)	25 (18·3–33·8)	27 (16–40)	24 (20–330	0·660*
Age categories, n (%)†				
Paediatric patients	20 (20)	7 (33)	13 (16)	0·086‡
Adult patients	80 (80)	14 (66)	66 (84)	
Gender, n (%)				
Female	41 (41)	8 (38)	33 (42)	0·760‡
Male	59 (59)	13 (62)	46 (58)	
Genotype, n (%)§				
HbSS/HbS-β^0 thalassaemia	65 (65)	15 (71)	50 (63)	0·490‡
HbSC/HbS-β^+ thalassaemia	35 (35)	6 (29)	29 (37)	
Medical history of: n (%)				
Fluid overload	33 (33)	12 (57)	21 (27)	0·012‡
Frequent VOCs¶	59 (59)	15 (71)	44 (56)	0·190‡
Acute chest syndrome	40 (40)	10 (48)	30 (38)	0·580‖
Microalbuminuria	30 (30)	8 (38)	22 (28)	0·560‖
Treatment, n (%)				
Hydroxyurea	53 (53)	15 (71)	38 (48)	0·057‡
Chronic blood transfusion**	42 (42)	12 (57)	30 (38)	0·240‖
Steady state laboratory parameters‖, median (IQR)				
Haemoglobin, g/l	97 (85–111)	97 (80–106)	97 (85–112)	0·550*
Reticulocyte count, $\times 10^9$/l	360·0 (148·5–312·9)	223·3 (140·4–359·2)	205·0 (153·4–311·7)	0·908*
LDH, u/l	360·0 (273·5–443·0)	406·0 (333·0–430·0)	347·0 (267·0–450·0)	0·563*
Total bilirubin, µmol/l	38·0 (24·3–62·0)	39·5 (18·8–57·5)	37·5 (25·0–63·5)	0·807*
Ferritin, µg/l	264·0 (137·0–588·0)	329·5 (162·8–830·3)	260·0 (129·5–573·0)	0·407*
WBC count, $\times 10^9$/l	9·1 (6·9–11·5)	10·2 (6·7–13·8)	8·8 (6·9–10·9)	0·139*
Creatinine, µmol/l	63·0 (50·5–80·0)	63·5 (49·3–77·8)	63·0 (52·3–81·0)	0·649*

CRP, C-reactive protein; IQR, interquartile range; LDH, lactate dehydrogenase; VOC, vaso-occlusive crisis; WBC, white blood cell.
P values represent the comparison of patients who did experience fluid overload *versus* patients who did not experience fluid overload.
*P values were calculated using the Mann–Whitney U-test.
†Results are expressed as n (%), or median (IQR), significant P values are given in bold. Percentages are rounded off to the nearest integer.
‡P values were calculated using the chi-square test.
§HbSS and HbSβ^0 thalassaemia represent severe genotypes. HbSC and HbSβ^+ thalassaemia represent mild genotypes.
¶Frequent VOCs were defined as ≥2 hospital admissions due to VOC/year.
‖P values were calculated using the Fisher's exact test.
**Chronic blood transfusion represent all patients who receive top-up blood transfusion or exchange transfusion according to a set, repetitive schedule as treatment for SCD.
††Steady-state laboratory values represent laboratory values collected during regular outpatient clinic evaluation (without symptoms of VOC).

analyses. We did not find an association between (recurrent) fluid overload and other potential risk factors such as age, genotype, diastolic dysfunction or renal insufficiency (data not shown).

Discussion

Intravenous FT is part of VOC treatment in many clinical guidelines. To our knowledge, this is the first study to systematically analyse the occurrence of iatrogenic fluid overload due to IV-FT during admission for VOC in a large cohort of consecutive patients. The present study shows that fluid overload is a frequent complication of IV-FT in patients with SCD, occurring in 21% of patients during the 2-year study period.

Fluid overload in patients with SCD has been previously described, but in small cohorts and post-mortem studies, without correlations to IV-FT use.[15,16] A recent study by Gaut *et al.*[17] examined the relation between FT volumes during VOC treatment and adverse events, such as ACS, oxygen requirement and ICU transfer. The authors observed an association between higher fluid volumes and any adverse event during hospitalisation, clearly indicating the potential downside of aggressive FT. Although fluid overload was not addressed specifically in that study, the aforementioned adverse events could, at least in part, have been mediated by fluid overload. In our present study, most adult patients received 3 l IV fluids/24 h for 72 h. As IV-FT was reduced or stopped prematurely almost exclusively in patients who developed fluid overload, it was not feasible to perform

Table II. Characteristics of individual patients during hospital admission (n = 100).

Characteristic	Total (N = 100)	Fluid overload (n = 21)	No fluid overload (n = 79)	P
Intensive care transfers, n (%)*	4 (4)	2 (10)	2 (3)	0·197†
Readmission, n (%)‡	20 (20)	6 (29)	14 (18)	0·282§
Duration of hospital stay, days	4 [3–7]	6 [4–10]	4 [3–6]	**0·037**¶
Treatment, n (%)				
Top-up blood transfusion during admission‖	20 (20)	9 (43)	11 (14)	**0·004**†
Antibiotics treatment	43 (43)	11 (52)	32 (41)	0·329§
Total amount of IV-FT during admission, median (IQR)	9 (8·3–11)	9 (4·9–12·0)	9 (9–10·5)	0·776¶
ED Laboratory parameters, median (IQR)				
Haemoglobin, g/l	92 (79–108)	92 (76–105)	95 (79–113)	0·075¶
Reticulocyte count, $\times 10^9$/l	275·4 (153·9–374·8)	391·2 (200·5–422·3)	269·4 (146·9–328·5)	0·037¶
LDH, u/l	421·0 (290·0–528·0)	453·0 (354·5–484·0)	367·5 (265·0–511·8)	**0·004**¶
Total bilirubin, µmol/l	42·0 (22·0–70·5)	54·0 (23·0–84·0)	39·5 (21·0–64·5)	0·256¶
WBC count, $\times 10^9$/l	13·4 (9·6–16·5)	13·5 (8·3–18·1)	12·1 (9·5–16·2)	0·213¶
CRP, mg/l	5·3 (3·0–15·1)	7·8 (3·8–15·4)	5·8 (3·4–21·1)	0·774¶
Creatinine, µmol/l	61·5 (51·3–86·3)	78·0 (56·5–97·5)	63·0 (51·0–88·5)	0·606¶
ED vital signs				
Heart rate, beats/min	78 (70–91)	73 (66–92)	78 (71–91)	0·512¶
Temperature, Fahrenheit	99·0 (98·1–99·9)	98·6 (97·5–99·3)	99·1 (98·2–100·0)	0·134¶
Respiratory rate, breaths/min	18 (16–21)	20 (16–24)	17 (15–210	**0·048**¶
Oxygen requirement, %	8 (8)	8 (38)	0 (0)	**0·000**§

CRP, C-reactive protein; ED, Emergency Department; LDH, lactate dehydrogenase; WBC, white blood cell.

P values represent the comparison of patients who did experience fluid overload *versus* patients who did not experience fluid overload.

*Results are expressed as n (%), or median (interquartile range), significant P values are given in bold. Percentages are rounded off to the nearest integer.

†P values were calculated using the Fisher's exact test.

‡Re-admissions were defined as admission for VOC within 30 days after discharge.

§P values were calculated using the chi-square test.

¶P values were calculated using the Mann–Whitney U-test.

‖Top-up blood transfusions during admission represent all simple transfusions given during hospitalisation excluding exchange transfusions.

statistical analyses regarding the association of fluid overload with the volume of IV-FT.

We propose two possible explanations for the high incidence of fluid overload (21%) observed in our present study. First, SCD is associated with diastolic dysfunction and higher TR V_{max} values, which increases the risk of fluid overload.[18,19] We found that patients developing fluid overload often had a prior episode of fluid overload in their medical history (57%), possibly indicating a proneness to fluid overload development. We found no differences in diastolic dysfunction between the patients with and without fluid overload during the study period. However, as was described by Machado *et al.*,[28] TR V_{max} increases significantly upon admission for VOC. The resulting increase in diastolic dysfunction might render some patients more susceptible to cardiac failure (fluid overload). We are not informed about the changes in TR V_{max} during VOC in the present study. The second possible explanation for fluid overload in the present population could be related to the IV-FT itself. Evidence regarding the best volume and route of administration of FT is lacking.[14] In the Netherlands, for paediatric patients, a total fluid intake (oral + IV NaCl 0·45%/glucose 2·5%) of 3 l/m^2/24 h is recommended. Adult patients are treated with 3 l IV fluids/24 h. The IV fluid is tapered or stopped after 72 h. A comparison of treatment protocols in 25 institutions in the USA found more modest fluid regimens, varying from no IV fluids to administration of 1·5× maintenance volume or greater IV, which is calculated based on body weight.[29] Some experts even suggest the use of maintenance fluids after reaching euvolaemia.[10,30–33] The relatively high incidence of fluid overload in our present study indicates that the volume of IV-FT for VOC recommended in the current Dutch guideline, which is comparable with several other European countries, might be too high. The observation of seemingly higher incidence of fluid overload among paediatric patients as compared to adults (35% vs. 18%) supports this hypothesis, as paediatric patients with SCD probably receive higher volumes of fluid per m^2 body surface area than adult patients.

We identified a history of fluid overload as an independent risk factor for its recurrence. Interestingly, however, fluid administration was not adjusted in 86% of patients with a history of fluid overload, indicating a need for more awareness of the increased risk of fluid overload during IV-FT and personalised hydration protocols.

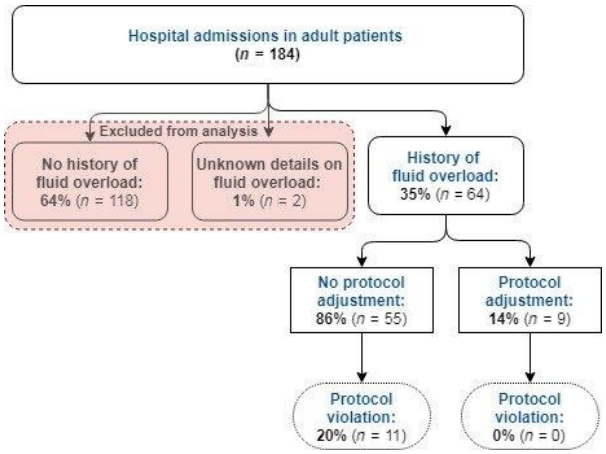

Fig 1. The use of intravenous (IV) fluid therapy (FT) during vaso-occlusive crisis (VOC) in adult patients with a previous history of fluid overload. IV fluid regimen was extracted for all patients and compared to the standard Dutch protocol for adult patients with sickle cell disease: 3 l/24 h of sodium chloride (NaCl) 0·65%, regardless of their concomitant oral intake. [a]In patients with a positive history of fluid overload, IV-FT was often not adjusted and in some cases standard IV-FT protocol was exceeded. [a]Only adults were included due to the use of a different protocol in paediatric patients. Protocol violation depicts admissions wherein a higher daily fluid volume than 3 l/24 h for 72 h was given, or admissions wherein IV-FT was continued for >72 h. [Colour figure can be viewed at wileyonlinelibrary.com]

Table III. Cardiopulmonary parameters in adult patients with sickle cell disease (n = 80).

	Fluid overload (n = 14)	No fluid overload (n = 66)	P
Cardiopulmonary parameters, n (%)			
Diastolic dynfunction*,†	1 (7)	11 (17)	0·667‡
NT-ProBNP ≥160 ng/l§	2 (14)	6 (9)	0·620‡
TR V ≥2·5 m/s	6 (43)	12 (18)	0·026‡

NT-ProBNP, N-terminal prohormone of brain natriuretic peptide; TR V, tricuspid regurgitant jet velocity.

P values represent the comparison of patients who did experience fluid overload *versus* patients who did not experience fluid overload.

*Results are expressed as n (%), significant P values are given in bold. Percentages are rounded off to the nearest integer.

†Diastolic dysfunction was defined according to the criteria of Sachdev *et al.*[23] and was based on the most recent echocardiogram of adult patients only.

‡P values were calculated using the Fisher's exact test.

§NT-pro BNP levels represent the levels of NT-proBNP in steady state closest to the admission.

The median duration of hospitalisation in patients with fluid overload was significantly longer than that in patients without fluid overload. This might be due to prolonged oxygen supply, treatment with diuretics, or longer observation, although more severe SCD/VOC resulting in both fluid overload and longer hospital stay cannot be ruled out. Patients with fluid overload presented with higher respiratory rates and more often needed oxygen supply at the ED, suggesting a more severe presentation although other indicators thereof, such as antibiotic use, ICU transfer and readmission rates were not found in this group. Patients with fluid overload did receive significantly more top-up blood transfusions, which appeared to be an independent risk factor for fluid overload in regression analyses. In only one patient who received top-up transfusion during IV-FT, the volume of IV-FT was actively reduced. Therefore, transfusion might have added to the risk of fluid overload in the patients receiving transfusion during IV-FT. However the anaemic patients in need of RBC transfusion, might have been at risk of fluid overload due to severe anaemia and the resulting cardiac dysfunction. LDH levels upon ED presentation were related to the occurrence of fluid overload during that admission. This might be explained by haemolysis-induced oxidative damage with ensuing vasculopathy, potentially resulting in pulmonary hypertension and diastolic dysfunction.[34,35] Indeed, an elevated TR V_{max} was seen more frequently in patients developing fluid overload than those without this complication. Both elevated TR V_{max} and diastolic dysfunction, which are haemolysis-related complications, are associated with an increased risk of mortality.[25,36,37] However, as LDH levels in steady-state and other ED haemolysis parameters were not related to fluid overload, the increased LDH levels and fluid overload might both be an indication of acute tissue damage due to VOC.[38]

Previous research has shown that isotonic saline (NaCl 0·9%) induces increased stiffness of sickle erythrocytes, prolonged transit time and a decreased time to occlusion compared to more balanced fluids with lower osmolality.[11] Additionally, the relatively high concentrations of chloride in NaCl 0·9% may result in iatrogenic hyperchloraemia, resulting in lower pH levels, which can induce HbS polymerisation.[39,40] Also, (rapid) administration of hypotonic fluids during VOC resulted in improvement of pain and decrease of sickle cells in the circulation.[13,41] Based on the above-mentioned evidence, in 2018 the Dutch guideline changed its recommendation of IV-FT from NaCl 0·9% to NaCl 0·65%. In the present study, we did not detect any differences between patients receiving NaCl 0·9% (before 2018) and NaCl 0·65% (in 2018). However, only a minority of the patients in our present study received NaCl 0·65%, which limited the power of this comparison.

Based on the reduced concentrating capacity of the kidneys in SCD, leakage of fluids from damaged RBCs and the above-mentioned *in vitro* evidence, there is sufficient grounds for providing patients with SCD with some degree of FT during VOC. However, current protocols of (IV) FT are not based on strong clinical evidence. Our present study illustrates that IV-FT of 3 l/24 h is associated with significant complications potentially leading to a longer hospital stay. While a randomised clinical trial comparing various fluid volumes and

Table IV. Uni- and multivariable risk factor analysis for fluid overload (n = 100).

Selected characteristics	OR (CI)	P
Age, years	1·019 (0·978–1·061)	0·373*
Gender	1·166 (0·434–3·130)	0·761*
Genotype severe vs. mild†	0·690 (0·241–1·974)	0·489*
History of iatrogenic fluid overload‡	3·395 (1·241–9·200)	0·017§
History of acute chest syndrome	1·204 (0·517–2·804)	0·667*
History of micro-albuminuria¶	0·865 (0·327–2·287)	0·770§
Top-up blood transfusion during admission‖	6·490 (1·769–23·803)	0·005§
Steady state LDH, per 1 unit increase, u/l	1·001 (0·998–1·005)	0·528*
Steady state reticulocyte count, per 1 unit increase, $\times 10^9$/l	1·001 (0·997–1·005)	0·511*
Steady state leucocyte count, per 1 unit increase, $\times 10^9$/l	1·111 (0·973–1·268)	0·119*
ED LDH, per 1 unit increase, u/l	1·003 (1·001–1·006)	0·011*
ED reticulocyte count, per 1 unit increase, $\times 10^9$/l	1·003 (0·997–1·009)	0·283*
ED leucocyte counts, per 1 unit increase, $\times 10^9$/l	1·047 (0·968–1·132)	0·249*
Diastolic dysfunction**,** Adults only, n = 80	0·874 (0·081–9·388)	0·912§
TR V ≥2·5 m/s§ Adults only, n = 80	2·604 (0·510–13·292)	0·250§
NT-proBNP >160 ng/l§,§ Adults only, n = 80	1·276 (0·071–22·999)	0·869§

CI, confidence interval; ED, Emergency Department; NT-ProBNP, N-terminal prohormone of brain natriuretic peptide; TR V, tricuspid regurgitant jet velocity.

*P values were calculated using univariable logistic regression.

†HbSS and HbSβ^0 thalassemia represent severe genotypes. HbSC and HbSβ^+ thalassemia represent mild genotypes.

‡Adjusted for Age, TR V and NT-proBNP.

§P values were calculated using multivariable logistic regression.

¶Adjusted for age and LDH (as continues variable).

‖Adjusted for age and Hb (as continues variable).

**Diastolic dysfunction was defined according to the criteria of Sachdev *et al.*[23] and was based on the most recent echocardiogram of adult patients only.

††Adjusted for LDH (as continues variable).

‡‡NT-pro BNP levels represent the levels of NT-proBNP in steady-state closest to the admission.

§§Adjusted for cardiac dysfunction.

routes of administration is warranted for future treatment of VOC and more insight in its complications, for the time being we recommend a stronger realisation of fluid overload as a complication of IV-FT and a personalised approach in patients with SCD during IV-FT as treatment of VOC.

A limitation of the present study is the retrospective character. Some data regarding (mild) episodes of fluid overload and changes in IV-FT (volume, type and exact duration) might have been missed. Nonetheless, as all medication and IV fluids are prescribed and registered electronically, we assume that our data are complete. However, we are not informed about the oral intake and fluid output in adult patients, as this is not routinely monitored. Therefore, we were not able to evaluate a potential association between fluid balance and fluid overload. Finally, consecutive admissions of the same patients were included, potentially introducing bias. To minimise this limitation, most analyses were performed in a subset of each patient's first hospitalisation during the study period (in patients without fluid overload) or the first hospitalisation with fluid overload (in patients with fluid overload).

In conclusion, the present study illustrates that fluid overload is a frequently encountered complication of IV-FT during VOC admissions, suggesting that the volume of hydration therapy as currently recommended by several guidelines might be too high. History of fluid overload, high LDH levels at presentation and top-up blood transfusion during admission were independently associated with fluid overload. Hydration therapy was not reduced in most patients with a prior history of fluid overload, nor in patients receiving top-up blood transfusions, indicating a need for more awareness of this complication and personalised fluid management. A prospective randomised study assessing the value of hydration therapy, the best volume and route of administration and its complications is warranted.

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Conflicts of interest

The authors have no conflicts of interest to declare

Ethics

This study was performed in accordance with the Declaration of Helsinki. Local ethics approval was obtained.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table SI. Risk factors for fluid overload in individual patients split by age.

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