The challenges of hypervolemic therapy in patients after subarachnoid haemorrhage

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A B S T R A C T

Purpose: The triple-H therapy is widely used for cerebral vasospasm (CV) prevention and treatment in patients after subarachnoid haemorrhage (SAH). However, this practice is based on low level evidence. Aim of this study was to evaluate errors in fluid administration, fluid balance monitoring and bedside charts completeness during a trial of triple-H therapy.

Materials and methods: An audit of the SAH patient charts was performed. A total of 508 fluid measurements were performed in 41 patients (6 with delayed cerebral ischaemia; DCI) during 14 days of observation.

Results: Underestimating for intravenous drugs was the most frequent error (80.6%; 112), resulting in a false positive fluid balance in 2.4% of estimations. In 38.6% of the negative fluid balance cases, the physicians did not order additional fluids for the next 24 h. In spite of that, the fluid intake was significantly increased after DCI diagnosis. The mean and median intake values were 3.5 and 3.8 l/24 h respectively, although 40% of the fluid balances were negative. The positive to negative fluid balance ratio was decreasing in the course of the 14 day observation.

Conclusions: This study revealed inconsistencies in the fluid orders as well as mistakes in the fluid monitoring, which illustrates the difficulties of fluid therapy and reinforces the need for strong evidence-based guidelines for hypervolemic therapy in SAH.

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1. Introduction

1.1. Purpose

The purpose of this study was to measure the physicians’ adherence to fluid intake recommendations and the accuracy of fluid status monitoring by the nurses at the NICU (Neurosurgical Intensive Care Unit) and the NHDU (Neurosurgical High-Dependency Unit). More specifically, we aimed to find whether more errors occurred at a specific ward (NICU vs. NHDU) or during a stage of treatment (before vs. after occurrence of DCI; Delayed Cerebral Ischaemia) and whether they were attributed to the neurointensivists or the nurses. The following baseline hypotheses were presumed: better fluid monitoring in the NICU than NHDU and higher adherence to the recommendations by nurses than physicians.

1.2. Background

The most common cause of subarachnoid haemorrhage (SAH) is a ruptured cerebral aneurysm, which is associated with high mortality and morbidity rates [1]. If a patient survives the SAH, early neurological or endovascular aneurysm-securing procedures are preferred as rebleeding occurs in up to 17% of cases within the first 72 h [2]. Thereafter, an intensive care nursing team deals with both the general and the SAH-specific critical care principles including the prevention, diagnosis and treatment of cerebral vasospasm (CV). The clinical signs of neurological deterioration are associated with delayed cerebral ischaemia (DCI), which may be the consequence of CV [3]. Hypovolemia is one of the factors responsible for lowering brain perfusion, correlated with DCI and CV development after SAH [4]. Healthy humans need two litres of water per day [5], but after SAH the daily fluid intake should increase to 3.0–3.5 l [4].

Hypertensive hypervolemic hemodilution (triple-H therapy) is a simple treatment concept, which is widely used for the prevention and treatment of CV after SAH and thus to reduce DCI rate [6–8]. Its aim is to increase the cerebral blood perfusion pressure, which was shown in some preliminary studies [9–11]. Authors supported the use of triple-H therapy in CV treatment and emphasised the beneficial role of prophylactic hypervolemia and hypertension in the clinical outcome [12,13]. There is a consensus among the specialists regarding the triple-H therapy in patients with symptomatic vasospasm [8]. However, as of yet there are no meta-analyses, or large, prospective and randomised trials proving the effectiveness and safety of the triple-H therapy or its separate components [9]. Only three small and inconclusive RCTs were conducted so far [14–16]. Furthermore, there are no published guidelines for the diagnosis and treatment of CV [17]. Moreover, hypervolemia and hypertension are related to the complications, including cardiopulmonary failure, renal dysfunction, pulmonary oedema, exacerbation of cerebral oedema or rupture of the partially-secured aneurysm [4,14,18–20]. If administered to inappropriately selected patients, the hypervolemic therapy may lead to a prolonged stay at an intensive care and poor neurological outcomes [20]. For this reason, the unproved benefits of the triple-H therapy should outweigh the potential complications. Furthermore, the current recommendations for hypervolemic therapy in SAH are based on low-level evidence, are regarded as difficult to follow in case of conscious patients with oral fluid intake and need further study [4].

2. Materials and methods

2.1. Inclusion criteria

We performed a prospective clinical observation of triple-H therapy in patients operated due to a ruptured cerebral aneurysm derived from anterior circulation in September 2009–March 2011 at one of the regional neuroscience centres in Europe (catchment area of approximately 2 million inhabitants, with supraregional referrals of patients with SAH). All grades of radiological appearance of haemorrhage (Fisher scale 1–4) diagnosed by computer tomography (CT) imaging were accepted. The study was restricted to neurological clipping followed by ventriculostomy, therefore patients after endovascular treatment were excluded. The time from initial SAH symptoms to neurological clipping of ruptured aneurysm was ≤48 h. Neurological status was evaluated on admission using the Hunt-Hess scale, Glasgow Coma Scale (GCS) and World Neurosurgical Federation Scale (WFNS). Poor clinical condition on admission (Hunt-Hess grade 4 or 5 and WFNS grade IV or V), endovascular aneurysm securing, surgery >48 h from admission, large intracerebral haematoma evacuation or postoperative deep sedation comprised the exclusion criteria (Fig. 1). NICU postoperative care always preceded further NHDU stay. Ambulating patients were routinely transferred from NICU to NHDU after two days post-surgery. The observation period of fluid balance started from the day of admission to NICU and lasted for the following 14 days after SAH. Patients remained under the care of neurointensivists (neurosurgeons or neurosurgical anaesthesiologists).

2.2. Study protocol

After a literature review on the triple-H therapy, the neurointensivists developed the departmental recommendations for standard fluid management after SAH (Tables 1a and 1b). All the medical personnel were reminded of the above departmental recommendations just before the start of the study. Neurointensivists ordered the fluids. Total intravenous and oral fluid intake, fluid output and balance were manually noted, monitored and collected at the bedside by nurses. At least two nurses working in 12-hour shifts completed the daily fluid measurements. Electrolyte abnormalities and haemoglobin were monitored routinely every twelve hours. Significant anaemia requiring erythrocyte mass transfusion was defined as haemoglobin level <9 g/dL.

The neurological condition of patients was verified every 6 h (±2 h) by a neurosurgeon using the GCS and National Institutes of Health Stroke Scale (NIHSS). The diagnosis of neurological deterioration was established by a decrease of the GCS score by 1 or the NIHSS score by 2 points. The complete diagnosis of DCI (as a clinical sign of CV) was established after the exclusion of other causes of deterioration. Septicaemia, anaemia, electrolyte abnormalities, hydrocephalus, cerebral oedema or seizures were verified by physical, laboratory,
imaging and bacterial culture examinations. The confirmation of CV in CT angiography or digital subtraction angiography was obligatory. The management for DCI patients included all components of triple-H therapy. When a patient completed the observation period, investigators thoroughly recalculated all fluids (intake, output and balance) and compared them with the total values from bedside charts. The protocol of this study was accepted by the University’s Ethics Committee.

Descriptive statistical methods were used to characterise the patient group. Selection of adequate statistical testing was based on the normal distribution of continuous variables, which were confirmed by the Kolmogorov–Smirnov test. The Student’s t-test or the non-parametric Mann–Whitney U-test were applied for comparisons of continuous variables. The analysis of recalculated sums of fluid intake, output and balance were performed using the Student’s t-test or Pearson’s correlation. Statistica v.10.0 (StatSoft, Inc.) software with significance (p-value) set at <0.05 was used for all calculations.

3. Results

3.1. Baseline patient characteristics

The study consisted of 41 patients: 27 (65.8%) females and 14 males (34.2%), aged 18–75 years old (mean age = 50.7 years (SD ± 12.9)), with 4 patients (9.8%) >65 years old. 51.2% (n = 21) of the patients were treated for arterial hypertension, whereas 46.5% (n = 19) had a Body Mass Index (BMI) >25. For the majority of patients the only pre-admission clinical signs of aneurysm rupture were severe headache, vomiting and nuchal rigidity, whereas 12 (29.3%) experienced a transient loss of consciousness and 2 patients (4.9%) developed seizures. Other SAH-specific symptoms were noted in 13 cases (31.7%). Aneurysm size, location, patient’s clinical condition (Hunt-Hess, GCS, WFNS scales) as well as haemorrhage appearance in CT imaging (Fisher scale) was evaluated for all cases on admission (Table 2). Four patients died before end of the study.

3.2. Vasospasm occurrence

Transient or persistent neurological deterioration during hospitalisation was noted in 10 patients (24.4%). In 2 cases DCI was excluded as isolated cerebral oedema without ischaemia, based on CT imaging in absence of angiographic CV. One significant early neurological complication occurred: vast ischaemia derived from the anterior cerebral artery and rebleeding from an unsecured aneurysm. A total of 3 patients died: 2 of brain oedema and 1 of the aforementioned early neurological complication. In one case, significant anaemia resulted in a transient 2 point decrease in the GCS score, with recovery after erythrocyte mass transfusion. There was no observed neurological deterioration due to hydrocephalus, septicaemia, electrolyte abnormalities or seizures.

Out of 10 patients with neurological deterioration, 6 were affected by DCI. In 3 cases, cerebral subtraction angiography confirmed DCI resulting from CV. Median time from the initial SAH to DCI occurrence was 4 days (2–11; mean = 5.3; SD ± 3.5). Transient neurological deterioration due to DCI was noted in 4 patients. One patient with DCI died (9 days post-op). DCI resulted in permanent neurological deficit on discharge in 2 other cases. No adverse events related to hypervolemia therapy were noted.

3.3. Fluid measurement considerations

The patients’ fluid volume on the day of the surgery varied from 3534 to 10,020 mL due to different intraoperative volume intake. Hence, the analysis of volume status began on the first postoperative day and lasted for the following thirteen days (Fig. 2). Out of the 508 fluid level charts, 322 were complete (63.4%) in the whole group, 49 were complete in the DCI group (49 of 74; 66.2%) and 273 from patients without or before DCI (273 of 434; 62.9%). There were no significant differences in the chart completeness of patients with and without DCI (p = 0.60). However, the fluid charts in the NICU were significantly (p < 0.01) more often complete (80.2%; 89 of 111) than in the NHDU (58.7%; 233 of 397). The proportion of complete to incomplete fluid balance records was decreasing parallel to the presence of central venous line (CVL) over time. In the whole observation period, the percentage of patients with complete fluid balance measurement (61.6%) was higher than the percentage of cases with (CVL) (63.4%; p < 0.01) (Fig. 3).

The audit of fluid intake and balance charts revealed numerous errors. Fluid intake miscalculations (139 of 508; 27.4%) resulted in incorrect net fluid balance. The most
Table 1a – Intraoperative and departmental recommendations for fluid therapy after SAH.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Induction</th>
<th>Pre-clipping</th>
<th>Post-clipping period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaesthetics</td>
<td>Etomidate iv</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial blood pressure</td>
<td>Norepinephrine (if needed, especially during induction with Etomidate)</td>
<td>SBP 120–140 mmHg is maintained until clipping.</td>
<td></td>
</tr>
<tr>
<td>Crystalloid solution</td>
<td>Crystalloids to maintain normovolemia (SAH induces a hypovolemic state; a patient requires ~3 l)</td>
<td>Hypervolemia (CVP ±10 mmHg) maintained with crystalloids +0.5 l of HES</td>
<td></td>
</tr>
<tr>
<td>Colloid solution</td>
<td>None</td>
<td></td>
<td>0.5 l dextran 40,000</td>
</tr>
<tr>
<td>Overall fluid balance</td>
<td>Neuroanaesthesiologists ordered volumes of crystalloids and were responsible for fluid balance maintenance. Total fluid intake depended on time of surgery, clinical status at admission and blood loss. The study protocol did not influence fluid balance during the surgery.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Postoperative management

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Volume [daily]</th>
<th>Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colloid solution</td>
<td>0.25 l of dextran 40,000</td>
<td>Five days following surgery</td>
</tr>
<tr>
<td>Crystalloid solution</td>
<td>0.5 l of HES</td>
<td>Five days following surgery</td>
</tr>
<tr>
<td>Intravenous intake</td>
<td>&gt;1.5 l of crystalloids (5% dextrose and/or multi-electrolyte solution)</td>
<td>Duration of the observation period (13 days)</td>
</tr>
<tr>
<td>Intake volumes</td>
<td>&gt;3 l</td>
<td>Duration of the observation period (13 days)</td>
</tr>
<tr>
<td>Additional intakes</td>
<td>0.5 l of crystalloids for every 1°C</td>
<td>Till patient’s temperature &lt;37.0 °C</td>
</tr>
<tr>
<td>Overall fluid balance and arterial blood pressure</td>
<td>Neurointensivists ordered volumes of crystalloids and nurses were responsible for fluid balance maintenance. There were not developed any strict recommendations for RR maintenance; neurointensivists ordered norepinephrine if MAP &lt; 90 mmHg.</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ICP – intracranial pressure; CBF – cerebral blood flow; RR – blood pressure; SBP – systolic blood pressure; CVP – central venous pressure; MAP – mean arterial pressure; HES – hydroxyethyl starch.

Table 1b – Departmental recommendations for management for DCI patients.

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Medication</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure</td>
<td>Norepinephrine</td>
<td>SBP &gt; 140 mmHg</td>
</tr>
<tr>
<td>Volume of intake</td>
<td>0.25 l dextran 40,000 and 0.5 l HES</td>
<td>&gt;5 days</td>
</tr>
<tr>
<td>Total volume of fluid intake</td>
<td>Exceeding 3.5 l</td>
<td></td>
</tr>
</tbody>
</table>

Neurointensivists ordered volumes of crystalloids and nurses were responsible for fluid balance maintenance.

Abbreviations: SBP – systolic blood pressure; HES – hydroxyethyl starch.

common error in fluid intake calculations was an underestimation of intake (80.6%; 112 of 139), most often due to omitting the volume of the intravenous drugs (66.9%; 93 of 139). The retrospective recalculations of fluid intake resulted in a change of fluid balance from net negative to net positive in 12 cases (12 of 508; 2.4%). Many abnormalities in positive balance maintenance were noticed. As per the departmental recommendations, additional fluids should be ordered for the following day (excluding 25 measurements upon discharge or patients’ death), yet 101 occurrences of negative fluid balance there were noted (101 of 483; 20.9%). Furthermore, in 1/3 of these cases (39 of 131; 38.6%) the same or even smaller amounts of fluids were administered. As many as 41.2% (7 of 17) of patients diagnosed with DCI and 38.1% (32 of 84) of patients without DCI had negative fluid balance occurrences in which additional amounts of fluid were not dispensed. There were no significant differences between patients with and without DCI in terms of additional fluid supplementation after the occurrence of a negative balance (p = 0.06).

3.4. Fluid balance analysis

Mean and median fluid intake values in the DCI and non-DCI groups exceeded 3.5l per 24h. A quarter of the patients received <3l of fluids before DCI was diagnosed. The comparison of intake records revealed that DCI occurrence prompted physicians to dispense additional fluids. The difference in mean fluid intake values before and after DCI diagnosis was only 283 ml (p = 0.02), resulting in an insignificant 75 ml increase in the mean fluid balance. There were no differences in the mean fluid output, mean fluid balance values, nor in the positive fluid balance ratios between DCI and non-DCI patients. Therefore, the desired hypervolemic effect of the triple-H therapy was not achieved (Fig. 4).

Wide ranges of fluid balance values and low percentage of positive fluid balance were noted in both DCI and non-DCI groups. The proportion of positive to negative fluid balance occurrences in the whole group were significantly decreasing over time (r = −0.22; p < 0.01). It started from 84.6% on the day
following surgery and further decreased to 2.6% two weeks later. Negative correlations between fluid balance values and time was also observed in non-DCI group \( r = -0.25; p < 0.01 \). The diagnosis of DCI caused a trend change; fluid balance scores were similar on consecutive days \( r = -0.08; p = 0.58 \) (Figs. 4 and 5).

4. Discussion

We focused on an issue omitted in literature: the adherence of medical personnel to the departmental recommendations which are based on low level evidence.

![Graph showing fluid balance charts](image)

Fig. 3 – The percentage of patients with complete fluid balance on the consecutive days (darker line). The percentage of patients with CVL (lighter line). CVL – central venous line.

![Graph showing DCI diagnosis](image)

Fig. 2 – Division of all complete fluid records into two groups: ‘DCI fluid measurements’ and ‘non-DCI fluid measurements’. DCI – delayed cerebral ischaemia. Fluid volume analyses were based on 322 complete records. The number of 273 ‘non-DCI fluid measurements’ contained records of all patients who did not experience DCI as well as from all patients before DCI incident. ‘DCI fluid measurements’ consisted of 49 records after DCI diagnosis when additional fluid intake was dispensed.

4.1. Fluid balance charts

It is a commonly-held opinion that fluid balance maintenance of the unconscious patients in the NICU is verified more scrupulously, in contrast to the conscious patients with oral fluid intake. Therefore, the conscious patients with oral fluid input are potentially at risk of iatrogenic fluid imbalance. However, as of yet the literature has not addressed whether the same holds true for NICU patients after SAH. One of the aims of our study was to examine this issue. The significant differences in fluid chart completeness at our NICU and NHDU suggest that more scrupulous bedside charting occurs in the NICU than in NHDU. The same nurses rotate between the two wards on a monthly basis and the typical ratio is 2 nurses per...
NICU patient. Therefore, there are no differences between the NICU and NHDU nursing staff in terms of years of education or the length of experience with neurosurgical patient care. Since the calculations of fluid balance calculation takes place several times a day on our ward, the miscalculations are not likely due to a specific time during the shift [21].

Whiteley et al. first mentioned the difficulty of maintaining reliable fluid charts of patients with SAH: only 1/3 of fluid charts were complete in her series. In our study, 1/4 of fluid charts were miscalculated. We made a step forward by investigating the reasons for charts incompleteness. The positive correlation between the presence of a CVL and the fluid balance completeness is difficult to interpret and could be incidental.

In our study, 1/4 of fluid charts were miscalculated. Most of the errors were attributable to omitted intravenous drugs volume in the fluid intake calculations. Data inaccuracy makes proper sequential and incremental care virtually impossible, challenges the outcome data as well as the validity of documentation of fluid management and underlines the need for on-going and independent surveillance. Electronic bedside charts can potentially reduce these errors [22]. It has been

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**Fig. 4** – Fluid status, grouped according to DCI. DCI – delayed cerebral ischaemia.

**Fig. 5** – Changes of positive fluid balance ratio on consecutive days.
suggested that fluid chart completeness strategies should include clear departmental guidelines, signatures on the nursing documentation and hypervolemic therapy revisions in other NICU/NHDU departments [4]. Problems with documenting the fluid balance are relevant not only to NICU but also to other ICUs [23] and our study emphasised a significant difference in fluid chart completion between the NICU and the NHDU. However the positive correlation between the presence of a CVL and the fluid balance completeness is difficult to interpret and could be incidental.

The observation that mean and median fluid intake exceeded 3.5 and 3.8 l before and after DCI occurrence respectively, may obscure another observation that less than 3.3 l of fluids were dispensed to as many as 1/4 of the patients. Moreover, a positive fluid balance was found only in approximately 40% of measurements. The presence of DCI did not significantly increase the positive to negative fluid balance ratio. We hypothesise that the entire clinical team was aware of the low level of evidence supporting the new departmental fluid recommendations. Therefore, our results show the neurointensivists’ reluctance to prescribe large volumes of fluids and the nurses’ difficulties in precisely measuring and calculating the resulting fluid balances. Specific reasons for inaccurate recording of fluid balance may be the ambulating patients’ lack of cooperation with nurses, imprecise (“eyeball”) measurements, and insufficient coordination of the measuring/calculating process.

The inconsistent adherence to departmental recommendations by both physicians and nurses revealed how unconvincing the class IIa recommendations are. The administration of additional fluids after negative fluid balance occurrence was abandoned in approximately 40% of our cases, regardless of DCI, which confirms the above-mentioned issue. Decisions on which of the fluid therapy approaches is the most appropriate for a specific case are not always informed and makes is an task. This can then compound a ‘shared’ responsibility of physicians and nurses. Others also reported that adherence to evidence-based management is suboptimal [24]. Whereas another study shows that official multicentre programmes by a reputable clinical research association can improve guideline adherence [25].

4.2. **Triple-H therapy**

Our analysis only covered one component of triple-H therapy and prophylaxis: hypervolemia. This may be considered as a confounding factor of presented results. It is acknowledged that patients after SAH are often hypovolemic due to hypothalamic dysfunction and/or increased natriuretic peptides secretion [26]. Although the validity of hypervolemic therapy for CV prevention and treatment was discussed with staff before initiating our study and after the results were obtained, this did not influence the adherence to the departmental guidelines.

Avoiding hypovolemia is advisable, but according to class IIa, level B recommendations, there is no evidence that hypervolemia is of any clinical utility prior to CV occurrence [27]. Two randomised trials regarding hypervolemic CV prevention showed that triple-H therapy does not decrease the CV incidence and does not influence neither early nor late outcome [14,15]. Furthermore, the 2009 guidelines for fluid management after CV occurrence also provide class IIa, level B recommendation [6]. Surprisingly, those recommendations were based on the same 2 trials that questioned the usefulness of triple-H therapy in CV prevention [14,15]. Thus in our study, the hypervolemia for either CV prevention or treatment was a weak treatment recommendation for the neurointensivists and nurses [28,29].

The type of intravenous drugs and their volumes needed to achieve the goal of hypervolemic therapy still remain undefined [8]. Compared with the clinical outcome, the impact of hypervolemic hemodilution on physiological changes has received more direct attention. Increased fluid intake effectively increases cardiac filling, but does not change net fluid balance, blood volume or cerebral blood flow [15]. In contrast, hypervolemia above 41 increases blood pressure, blood volume, cardiac output and cerebral blood flow in patients with CV [30]. A recent study examined the impact of extremely increased fluid intake (above 8 l per day) on fluid balance, but no significant influence was detected [31]. If cerebral auto-regulation is affected, cerebral blood perfusion depends on cerebral blood flow, thus the seeming influence of induced hypervolemia on cerebral blood flow is the most plausible. However, a systematic review showed that the role of hypervolemic therapy in cerebral blood flow regulation after SAH is at least weak [9].

4.3. **Limitations**

Our analysis only covered one component of triple-H therapy: hypervolemia. Other potential sources of bias could be the exclusion of SAH in poor condition and the fact that each patient spent a different length of time at the NICU and NHDU.

4.4. **Study outcome**

The results of our audit were introduced to the NICU and NHDU nursing staff and lead to procedural changes such as the physicians’ verification of handwritten calculations and reporting of every negative fluid balance occurrence to a neurointensivist. However errors may continue to happen even after implementing a computerised calculation system, so it is wise to always anticipate an error rate [32]. Use of portable electronic devices for charting is considered by our Department. However, the lack of consensus on fluid management after SAH persists among our medical staff.

5. **Conclusions**

Our study revealed numerous prescribing, measuring and monitoring errors in the fluid therapy of post-SAH patients. Overall, the adherence to departmental recommendations was suboptimal and we hypothesise this was due to the low level of evidence supporting these recommendations. The role of nurses in the effectiveness of the hypervolemic component of the triple-H therapy should not be underestimated.
Conflict of interest

The authors do not report any conflicts of interest.

Acknowledgement and financial support

None declared.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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