Special Article

Pitfalls in Fluid Management for Critically Ill Patients in Thailand

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Fluid management is one of the most important treatments for critically ill patients. It has an influence in patients outcomes and is considered one of the most common pitfalls encountered in the management of the critically ill patient. In Thailand, fluid overload (>10% of fluid accumulation), mismanagement of fluid restrictions and the "bolusing" of colloid solutions are the main pitfalls that may lead to serious complications. These complications can compromise the patient in areas such as decreasing the oxygen index, putting the patient in cardiac failure and possible acute kidney injury (AKI). They can also increase resource utilization and the mortality of critically ill patients. More than 80% of critically ill patients, who are admitted to the intensive care units, are reimbursed from the "universal coverage". Universal coverage does not support the use of albumin solution, which has been reported to improve the function of the endothelial glycocalyx layer, vascular permeability and improved outcomes in the hypoalbuminemic patient (serum albumin ≤2.5 mg/dL) with severe sepsis, in septic shock or undergoing major abdominal surgery. Therefore, primary colloids used for resuscitation the patients are 6% hydroxyethyl starch (HES), 4% gelatin and fresh frozen plasma. AKI and renal replacement therapy (RRT) continue to be a major problem when using these synthetic colloids especially in the high-risk patients who receive large amounts of fluids. Evaluation of the fluid responsiveness for goal directed therapy is another problem in Thailand. This has been predominant in critically ill surgical patients both intra-operatively and postoperatively. To obtain optimal benefits of fluid therapy and for the prevention of complications associated with this treatment, physician need to acquire more knowledge, choose the right strategy, choose the proper type and amount of colloid and assure the correct mode of evaluation.

Keywords: *Fluid management, fluid overload, fluid restriction, acute kidney injury, type of fluid, hydroxyl ethyl starch, gelatin, albumin, fluid responsiveness, ICU*

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Fluid therapy is one of the most important treatments for critically ill patients and can influence patient outcomes. Substantial information has been reported about the problems and pitfalls associated with fluid therapy, especially in the critically ill patient. The amount of fluid, types, prescribed and the evaluation of fluid therapy are the main problems in fluid management here, in Thailand. To help improve the quality and safety of fluid therapy, this critical review focuses on the common pitfalls of fluid management for the critically ill patients.

"Fluid overload (FO)" is one of the crucial pitfalls resulting from improper fluid management for the critically ill patients here, in Thailand. Although the primary rationale for fluid therapy is to correct hypovolemia, increase cardiac output and subsequently cardiac output but aggressive fluid resuscitation with a resulting positive fluid balance and fluid accumulation is associated with increased morbidity and mortality[1-3]. Regarding bodily responses, fluid administration beyond normovolemia can trigger an endogenous cascade that eliminates excessive intravascular volume and prevents hypervolemic cardiac decompensation[4]. This cascade includes the suppression of the rennin-angiotensin-aldosterone system and stimulates the release of atrial natriuretic peptide. These result in increase dieresis and vasodilatation. Additionally, this natriuretic hormone can trigger the degradation, disruption and shading of endothelial glycocalyx layer (a web membrane bound glycoproteins and proteoglycans on the luminal side of endothelial cell). This is seen particularly in hypervolemia caused by resuscitation with crystalloids[4-6].

The definition of FO is a fluid accumulation relation to a patient's ideal body weight (IBW) (total input- total output)/IBW), of more than 10%[7]. FO is a

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significant predictor of a decreased oxygenation index, increased adverse outcomes, increase ventilator days, extended ICU lengths of stay[8] and mortality. This is of note for patients who develop acute kidney injury (AKI)[9] and those who are at the initiation of renal replacement therapy (RRT)[2]. In pediatric patients, every 1% increase in FO is associated with a 3% increase in mortality[10]. Thus, a FO >20% has showed an odds ratio (OR) for a mortality rate of 8.5 as compare to the odds ratio for lower percentage FO. In the biological environment of the human body, persistent FO leads to the following: (1) interstitial edema and decreased tissue perfusion, (2) increased pulmonary pressures and cardiac failure[11], (3) increased closed space pressure especially when this turning to be intra-abdominal hypertension (IAH) and (4) organ dysfunction syndrome which occurs by cell separation, abnormal oxygen consumption, decrease lymphatic drainage and the distortion of normal tissue architecture. IAH can compromise mesenteric and renal perfusion. These adverse events compromise encapsulated organ function. For example, IAH results in renal venous congestion, decrease glomerular filtration rates and AKI[12].

Generally, FO occurs in situations when a patient requires large amounts of fluid resuscitation (particularly with crystalloids), increase vascular permeability, low intravascular oncotic pressures (low serum albumin)[1,13,14] and aggressive replacement for third spaced losses[15]. In head and neck surgery, FO has been reported as one of the significant risk factors of anastomosis thrombosis of free TRAM flap that has been used for breast reconstruction[16]. In colorectal surgery, maintaining the patients' body weight has been shown to reduce postoperative cardiovascular, respiratory and tissue healing complications[17]. In pancreaticoduodenectomy, a high intra-operative intravenous rate (>15 ml/Kg/hr) has been found to be associated with worse peri-operative outcomes when serum albumin levels drop to $\leq$3 mg/dL[14]. Transfusion-associated circulatory overload (TACO) also is considered a serious complication of fresh frozen plasma transfusion. This type of fluid overload is associated with lengthy hospital stays and increased hospital costs per admission[18]. FO was found to be a predictor of early AKI in critically ill, septic non-cardiac surgical patients[19] and administration of a crystalloid >30 ml/Kg/day was a factor in the prediction of AKI for the critically ill, non-septic, non-cardiac surgical patient[20].

Maintaining fluid balance is one important strategy in the prevention of FO. Early renal replacement therapy to remove fluid and resolve the overload has been reported to improve the outcomes both resource utilization and survival rate from AKI in the critically ill patients[1,11]. In clinical practice, charting quantitative fluid input and output has been reported to be more accurate in measuring body weight[21].

Restrictive intra-opertaive fluid regimen and decreasing the replacement of third space that was believed to be minimal[22] compose one strategy in the prevention of a positive fluid balanced, FO and postoperative complications[15]. Nevertheless, this is also one of the common pitfalls in fluid management for the critically ill surgical patients and during perioperative. As complication such as hypovelemia and tissue hypoperfusion has been reported[15], one should understand the strategies and complication of this therapy thoroughly before implementing. First, the patient should be maintained at an adequate intravascular volume and avoid becoming hypovolemia; second, the physician should avoid and limit unnecessary fluids[8,23,24]; third, close monitoring of the adequacy of the patients' tissue perfusion (urine output, blood lactate levels) and prompt resuscitation should the patient suffer acute blood or fluid loss is critical. To be cautious, this regimen should not be used in situations of on-going loss from either, macro or microcirculation as noted in severe sepsis or septic shock[25].

There is a need to be attentive to the rate of fluid replacement during resuscitation. In case of sepsis, slow infusion rates have shown to expand the plasma volume of colloid solution more efficiency than faster infusion rate[26]; the bolus technique has been proven dangerous to the patient. As fluid bolus of both colloids and crystalloids during resuscitation have shown to increase the 48-hour mortality rate in severely septic children with malaria, mortality increases predominantly from cardiovascular collapse[27].

The type of fluid is also an important issue. In crystalloid induced FO, the dilution of the plasma protein concentration can hinder the attachment of these proteins to the EGL and subsequently lose the tight network system with a resulting in an increase in vascular permeability[28,29]. The amount of crystalloids infused intra-operatively has a significant impact on the functional (bursting pressure) and structural (hydroxyproline) stability of the intestinal anastomosis[30]. Intra-operative crystalloid overload can lead to a substantial inflammatory infiltration of the intestinal anastomoses resulting in a deleterious effect on anastomotic healing and the increase of postoperative complications in digestive tract surgeries[31]. In pulmonary resection surgeries and esophagogastrectomies, excessive fluid (notably crystalloids) administration has been shown to be a significant risk factor for lung injuries when the lung's lymphatics and pulmonary endothelial are damaged[28].

Chloride overload is another problem in crystalloid therapy. Both pre-clinical and clinical studies have shown that when 0, 9% NSS was given as a primary resuscitation fluid, the side effects including dilutional hyperchloremia acidosis could occur when large amounts of fluids are infused in a short period of time[32,33]. In animal studies, high serum chloride levels may have adverse effects on kidney function such as renal afferent arteriolar vasoconstriction, increased renal vascular resistance, decrease glomerular filtration rates and lower rennin activity[34-36]. However, the clinical relevance of this hyperchloremia is still in question due to the fact that this situation usually resolves without intervention in 2 days[37]. Patients with vulnerable kidney function such as kidney transplant recipients might be compromised. This may result as a more pronounced acidosis and higher serum potassium concentration in a patient who has been resuscitated with 0.9% NSS as compared to those resuscitated with Ringer's lactate solution[38]. These have the same positive clinical outcomes (postoperative morbidity and gastric mucosal perfusion) on patients undergoing open abdominal surgery and who have received balanced crystalloid solution[39].

Higher incidences of AKI, renal replacement therapy (RRT) and mortality have been reported with the use of synthetic colloids in particularly hydroxyl ethyl starch (HES) in critically ill septic and non-septic patients[40-42]. Thus, questions arise about the reasons for these complications and the rationale for the use of this synthetic colloid in the critically ill patients. There are four possible factors for these adverse outcomes. First: Raw materials that are mixed in the solution such as waxy maize starch-base, potato starch-base and gelatin. Potato starch-base is associated with greater incidence of AKI in the intensive care unit when compared with the waxy maize starch-base[43] and higher molecular weight starch such as pentastarch is associated with more AKI[44]. Second: Carrier solution or solvent components such as a balanced solution with less sodium and chloride create less renal impairment than 0.9% NSS[45]. Third: High doses of synthetic starch are thought to be associated with the development of AKI and more information is required regarding the safety dosage[46]. Forth: High-risk patients such as the patient with renal impairment (serum creatinine 1.3 mg/dL[47]) or recipients of kidney transplantation, in the situations that reduce renal blood flow (kidney surgery, exposure to renal toxic substances such as radiographic contrast or aminoglycosides).

Albumin solution has been reported to help improve the function of the endothelial glycocalyx layer[48], vascular permeability[49] and outcomes in hypoalbuminemia patients in severe sepsis or septic shock who had serum albumin level $\leq$2.5 mg/dL[50,51] and critically ill surgical patients undergoing major abdominal surgery[30,31,52]. Most critically ill patients admitted to an intensive care unit in Thailand are reimbursed from the universal coverage plan; however, this plan does not support the high cost of albumin. Therefore, synthetic colloids (6% HES and 4% gelatin) and fresh frozen plasma are the primary colloid solution currently used for resuscitation despite the fact that they maintain a low serum albumin level. Complications associated with these synthetic colloids in some special patients who have developed AKI and the patients who require RRT, are the big problem here, in Thailand. In most current information, a few physicians continue to prescribe these synthetic colloids for high-risk patients in high amounts and bolus administration. These can compromise the patients' outcomes. In an attempt to decrease the severity of these complications, patient selection is as important as trying to avoid using synthetic colloid in high-risk patients. It is important to choose proper synthetic colloid and limit its use to a safe dose.

Some other considerations for the use of synthetic colloids are accumulation, side effect (renal, coagulation defect), and hemodilution effects. Thus, this fluid should be used with extreme caution. However, there is no current evidence regarding a safety dose of gelatin other than its dilutional effects[53]. HES should not be used in patient with severe sepsis and/or in septic shock. The recommended dosages (ml/kg/day) have ranges between 20-50 ml/kg based on the company's information leaflet but the true safety dose per day is still being investigated[54]. Anyhow, information obtained from a large single center study[19,20] found that 6% (130/0.4) HES in dosages higher than 14 ml/kg/day and 20 ml/kg/day for non-cardiac surgical patients with and without sepsis were subsequently associated with early AKI.

Evaluation of fluid responsiveness for goal-directed therapy is also one of the common pitfalls in fluid management. This has influenced the outcomes of the population of patients who require large amounts of fluid replacement. Static and dynamic variables are use to predict cardiac preload and fluid responsiveness in the critically ill patient here in Thailand[55]. The static hemodynamic monitoring commonly used in Thailand is central venous pressure (CVP) due to the ease and safety of this procedure and can be used in the situation of spontaneous breathing and cardiac arrhythmias. This value can, additionally, give basic information about the cardiac preload volume. If the CVP number is low this reflects that the cardiac preload volume is low and volume replacement is necessary. The CVP can be used as a guide for fluid responsiveness in fluid challenge tests. However, CVP is the pressure that reflects the cardiac filling pressure and changes with changes in intrathoracic pressure, intracardiac pressure, ventricular function and cardiac compliance[56]. Thus, static cardiac filling pressure may not be sensitive and specific in predicting cardiac preload and predicting fluid responsiveness[57]. Additionally, this static parameter is not a single point monitor and if this is used, multiple point measurements should be used with the adjustment of all confounders and with the addition of more information when necessary. Right/left end-diastolic volume/area measured from echocardiography[58], a volumetric, static parameter is used occasionally in Thailand[55]. Problems exist due to the facts that a referral to a tertiary center is necessary as these methods require specially trained personal, and patients are not continuously monitored. These parameters possibly do not possess the sensitivity for evaluating fluid responsiveness. Global and diastolic volume (GEDV) obtained from a PICCO device can be monitored continuously and has been reported as a good value for evaluating fluid responsiveness[59] by detecting acute change in the patient's preload. However, this method requires special techniques for a femoral line placement, expensive equipment and requires optimal calibration.

A dynamic parameter is the change of cardiac preload induced by positive pressure ventilation that intermittently decreases; right ventricular end-diastolic volume, venous return and left ventricular preload. Additional dynamic parameters such as passive leg raising, positive responses to fluid challenges, pulse pressures or systolic pressures or stroke volume variations are also used for the evaluation of fluid responsiveness here, in Thailand[54]. The limitations of these are pitfalls in techniques and interpretations that still occur as these parameters require positive pressure ventilation of the patients, a closed chest and the patient should be in sinus rhythm on the electrocardiograms. Understanding the factors that affect the outcomes of dynamic measurements is important in decreasing the errors made in these variable measurements. Some of these are; spontaneous breathing, tidal volumes, effects of intra-abdominal hypertension, increases intrathoracic pressure, PEEP and the influences of vasopressors for example norepinephrine[60].

A difficult clinical situation in the evaluation of fluid responsiveness is with the patient with increased intra abdominal pressure. This is due to the fact that both static and dynamic variables become less sensitive and non-specific in estimating the actual preload. Administering too much fluid or an insufficient amount might make the outcomes worse. Gradually giving fluid and observing the responses on the improvements in the macro and microcirculation may be the appropriate technique to keep the patient safe and decrease complications[60].

Conclusion

Fluid management is considered an important treatment for the critically ill patient and can influence patient outcomes. Some pitfalls in the administration and evaluation of these fluids persist here, in Thailand. To improve the outcomes and gain the maximum benefits of fluid resuscitation, additional knowledge about the amounts of fluids to be infused, the type of fluids prescribed, and the evaluation of the fluid response need to be provided to caregivers. Albumin needs to be more readily available for the patient in hypoalbuminemia. This might help prevent the complications of fluid therapy and improve outcomes in the patient undergoing major abdominal surgery and the patient with severe sepsis or in septic shock.

Potential conflicts of interest

None.

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อันตรายแอบแฝงของการบริหารสารน้ำแก่ผู้ป่วยที่เจ็บป่วยระยะวิกฤตในประเทศไทย

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การให้สารน้ำแก่ผู้ป่วยภาวะวิกฤตถือว่าเป็นการรักษาที่มีความสำคัญยิ่ง มีผลต่อผลลัพธ์ของผู้ป่วยทั้งการเกิดภาวะแทรกซ้อนและการเสียชีวิต อีกทั้งเป็นการรักษาที่ยังคงมีความผิดพลาดในขบวนการรักษามากที่สุดเช่นกัน การให้สารน้ำเกิน (มากกว่าร้อยละ 10 ของสารน้ำที่สะสมในร่างกาย) และการจำกัดสารน้ำในการให้รวมถึงการ bolus สารน้ำกลุ่ม colloid เป็นขบวนการรักษาที่ยังคงมีความผิดพลาดมากในประเทศไทย ซึ่งอาจนำไปสู่ภาวะแทรกซ้อนที่สำคัญ เช่น มี oxygen index ลดลง การทำงานของหัวใจล้มเหลว ไตวาย ใช้ทรัพยากรเพิ่มขึ้นและเพิ่มอัตราตายในผู้ป่วยกลุ่มนี้ นอกจากนี้เนื่องจากมากกว่า ร้อยละ 80 ของผู้ป่วยภาวะวิกฤตที่เข้ารับการรักษาในหอผู้ป่วยวิกฤตในประเทศไทยใช้สิทธิ์การรักษาหลักประกันสุขภาพถ้วนหน้าซึ่งไม่สามารถเบิกค่าสารน้ำ albumin ซึ่งจะเป็นประโยชน์ต่อ endothelial glycocalyx, vascular permeability และผลลัพธ์ของผู้ป่วยที่มีระดับซีรัม albumin ในเลือดต่ำ (≤2.5 มิลลิกรัมต่อเดซิลิตร), ในผู้ป่วยที่มีภาวะ severe sepsis/septic shock และผู้ป่วยหนักทางศัลยกรรมที่มารับการผ่าตัดใหญ่ในช่องท้องดังนั้น สารน้ำกลุ่ม 6% hydroxyethyl starch (HES), 4% gelatin และ fresh frozen plasma จึงเป็นสารน้ำหลักที่นำมาใช้ในการ resuscitate ผู้ป่วยที่ต้องการ colloid, ปัจจุบันจึงยังพบภาวะแทรกซ้อนไตวายและต้องล้างไตในผู้ป่วยกลุ่มนี้ โดยเฉพาะเมื่อให้ในผู้ป่วยที่มีความเสี่ยงและให้ในปริมาณมาก นอกจากนี้การประเมินการตอบสนองต่อการให้สารน้ำเพื่อให้ถึงเป้าในการรักษายังคงมีความผิดพลาดในประเทศไทยโดยเฉพาะอย่างยิ่งระหว่างผ่าตัดและหลังผ่าตัด ทั้งนี้เพื่อให้เกิดประโยชน์สูงสุดจากการรักษาด้วยสารน้ำและป้องกันการเกิดภาวะแทรกซ้อน ผู้ให้การดูแลผู้ป่วยต้องมีความรู้เกี่ยวกับหลักการให้สารน้ำที่ถูกต้อง ทั้งชนิดและขนาดของสารน้ำที่ใช้รวมถึงมีการประเมินผู้ป่วยที่ถูกต้อง