



## Fluid therapy: Too much or too little

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Review Article

# Fluid therapy: Too much or too little

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## KEYWORDS

Endothelium;  
Glycocalyx;  
Third-space;  
Blood transfusion;  
Anemia

**Abstract** There is much debate regarding the amount of perioperative fluid administration in relation to patient outcome.

Fluid shifting towards the interstitial space is of two types (physiologic and pathologic) across the vascular endothelial membrane. This membrane, of 1  $\mu\text{m}$  thickness, is formed of an endothelial layer coated by glycocalyx, a small concentration of albumin, and a non-circulating part of plasma. It acts as a gateway to the interstitial space with a primary molecular filler function, generating an effective molecular filter function, generating an effective molecular gradient across its thickness. Since the early sixties, perioperative fluid requirements were calculated by considering pre-existing deficits, maintenance volumes, and third-spaces loss, depending on the type of surgery. Based on this, a goal-directed “liberal” fluid approach was modulated. On the other hand, a “restrictive” fluid approach was later suggested to achieve better patient outcome. Extremes of either approach were shown to induce hyper- or hypovolemia, respectively. However, there are no clear definitions to describe the volume status of patients.

The literature is currently characterized by inconsistency and contradiction regarding patient outcome parallel to perioperative “too much” or “too little” fluid administration. There is no single fluid regimen which provides optimal fluid volumes to all surgical patients all the times.

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So, available literature is discussed in this article with an early evidence of a preferred “adequate” rather than a “liberal” or a “restrictive” fluid approach.

Further systematic reviews of randomized controlled trials are recommended to predict the volumes and types of administered fluids, and its timing as important determinants of postoperative patient outcome. Special evidence is also needed for “liberal” versus “restrictive” hemoglobin therapy to determine the same goals.

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## 1. Background

There is much debate regarding the amount of perioperative fluid administration in relation to patient outcome.

Regarding healthy individuals, perioperative fluid requirements are well-established for different age groups, as avoiding excessive fluid loss or administration provides successful homeostasis [1].

Regarding critically-ill patients, perioperative fluid therapy is complex, as there may be much fluid deficits with impaired capacity to maintain homeostasis. Some complicating factors include comorbidities, systemic inflammation, increased anti-diuretic hormone liberation, together with disturbances in the rennin-angiotensin system, and the atrial natriuretic peptide. So, the perioperative outcome of critically-ill patients may be linked with the volumes of perioperative fluid administration [2,3].

The intravascular fluid compartment in the normal adult comprises two-thirds of total body water. The remaining one-third designates the extracellular compartment, consisting of plasma and interstitial fluid, where water and small solutes can easily exchange for cell nutrition. This physiological distribution of fluids is maintained by biological membrane barriers and oxygen – consuming ion pumps.

According to Ernest Starling [4], the hydrostatic pressure in blood vessels is high, as is the colloid osmotic pressure. The interstitial fluid contains low amounts of protein with low hydrostatic pressure. A small net amount of fluid and protein shifts out of the blood vessels all the time, and returns to the intravascular space by the lymph vessels.

The relation between the interstitial space and the so-called third-space needs to be clarified. The third-space is divided into two components; anatomical and non-anatomical. The anatomical component represents the functional interstitial space, allowing physiologic fluid shifting across the intact vascular

barriers. As long as it is quantitatively managed by the lymph system, a physiologic shift does not cause interstitial edema [5]. The non-anatomical component is a non-functional one, separated from the interstitial space. Examples are the peritoneal cavity and the traumatized tissues. A non-functional third-space component does not normally exist [6]. If it pathologically exists, it is not in equilibrium with the functional component, being anatomically separated [7].

Fluid shifting towards the interstitial space is of two types. Type 1 is a physiologic shifting occurring across a healthy biological barrier. Type 2 is a pathologic shifting due to lymph vessels destruction by surgery, or endothelial damage by inflammation, increasing vascular permeability [8].

So, it is mostly the condition of the biological membrane that counts in the fluid shifting process.

The healthy biological vascular barrier is coated by the endothelial glycocalyx, consisting of proteoglycans and glycoproteins. It is considered the natural gateway to the interstitial space [7]. It is bound with a small concentration of albumin [9], and 700–1000 ml of plasma fixed within the endothelial surface layer [10], to form a functional thickness of about 1  $\mu\text{m}$  [11]. This non-circulating part of plasma volume is in dynamic equilibrium with the circulating part. The presence of such a healthy vascular membrane maintains a barrier to prevent excessive fluid shifting [9]. It acts as a primary molecular filter, and generates an effective oncotic gradient across its thickness [4].

The biological membrane prevents leukocyte and platelet adhesion, against both inflammation and edema formation [8]. Its destruction allows transcapillary fluid shifting to equalize hydrostatic and oncotic pressures between blood and tissues leading to a catastrophe [7]. This implies, perioperatively, that the endothelial biological barrier should be preserved to inhibit a pathological type 2 fluid shifting into the interstitial space. Diminution of destruction of the membrane can improve its integrity.

Treating vasodilatation caused by anesthesia with colloids, ignores the fact that the intravascular volume expansion is expected to terminate at the end of surgery, with restoration of the vascular tone. Relative hypervolemia follows [12], and the kidney is not of much help in this situation due to its reduced excretory capacity [13]. Such hypervolemia may induce glycocalyx damage [14].

With this background, anesthetists and intensivists must apply art as well as science to adapt fluid regimens in order to optimize fluid therapy, because adherence to a fixed regimen may be a recipe for disaster [15].

## 2. Fluid administration

According to current knowledge, perioperative fluid administration must replace two kinds of fluid loss:

- Positive loss in the form of insensible perspiration and urine, and a negative deficit due to preoperative fasting. The preoperative fasted patient is considered hypovolemic due to these losses [16]. So, preoperative volume loading is considered mandatory by many [17–20].
- Loss of blood due to trauma and surgery, which should be replaced by blood and plasma transfusion.

Since the early sixties, fluid management is calculated by considering pre-existing deficits, maintenance requirements, and replacement of loss depending on mild, moderate, or major surgery. A practice of large amounts of fluid administration was established to replace third-space loss.

Recently, it is suggested that for management of type 1 physiologic fluid shifting, crystalloids should be used to replace insensible perspiration and urine loss, while colloids are used to substitute blood loss [7]. There is no rationale to replace blood loss with a three- or fourfold volumes of crystalloids. Nor is there evidence to increase crystalloid infusion rate when patients are clinically hypovolemic during surgery [7]. For management of type 2 pathologic shifting, the biological barrier should be protected. To achieve such a goal, atraumatic surgical techniques with minimal lymph vessels destruction, neuro-axial anesthetic blockade to reduce the stress response, and trying to avoid hypervolemia are to be considered.

## 3. Fluid therapy: too much or too little

Some authors advocate “liberal” or high volume fluid administration [18,21–24], while others advocate “restrictive” or low volume fluid administration [17,25,26]. At present, perioperative “too much” versus “too little” fluid administration is an issue for scientific evidence.

## 4. The “liberal” approach

Perioperative “liberal” fluid approach includes fluid preloading before establishment of anesthesia to counteract drug-induced vasodilatation, high intraoperative fluid volumes, with not uncommon positive fluid balance in the postoperative period [27].

The “liberal” approach aims to optimize total blood volume. To assess the volume status of patients, a wide range of clinical (e.g. capillary refill), physiological (e.g. heart rate, urine

output), and biochemical (acid–base deficits, lactate levels) parameters are useful. Commonly used continuous parameters as circulating and filling pressures do not correlate with the volume status [28].

However, blood volume responsiveness, occasionally referred to as goal-directed approach [7], can be achieved by stroke volume variations [29], or esophageal Doppler-guided intravenous fluid boluses [7]. But, it is impossible to apply the latter to an awake patient [7]. The goal-directed approach, aiming for supranormal oxygenation, proposes that increased oxygen delivery ( $> 600 \text{ ml/min/m}^2$ ) targeted by high cardiac output ( $> 4.5 \text{ L/min/m}^2$ ) is the most significant factor in determining lower morbidity and reduced length of hospital stay [30]. But, excessive fluid overload was shown to encourage edema formation, anastomotic leaks, coagulation factors dilution, and prolonged hospital stay [17], against previous beliefs that accumulation of fluids in the tissues was harmless [31], and that hypervolemia induced minor problems [32]. According to such beliefs, unpredictable fluid shifts towards the third-space required generous fluid substitution [33].

The global goal-directed haemodynamic fluid approach has been challenged by a regional splanchnic-directed fluid approach aiming to normalize the intramucosal pH [34]. We suggested a combined global and regional fluid approach, as both sides of the coin, for resuscitation in severe sepsis and septic shock, with satisfactory patient outcomes [35,36].

A study in 1990 concluded that postoperative fluid overload is not a benign problem. This is because infusion of large amounts of crystalloids, and if necessary blood products, has proved to be followed by postoperative weight gain that correlates with mortality. In patients who gained  $< 10\%$  of body weight, mortality was 10%. In patients who gained 10–20% of body weight, mortality was 32%. In those who gained  $> 20\%$  of body weight, mortality was 100% [37]. What is actually puzzling is that in 2004, an important randomized, double-blind study including 16 ICU populations in Australia and New Zealand, compared Saline versus Albumin Fluid Evaluation (SAFE) for resuscitation, but with similar mortality outcome at 28 days. The study concluded that both saline and albumin should be considered clinically equivalent treatment for intravascular volume resuscitation in a heterogeneous patient population in the ICU [38].

## 5. The “restrictive approach”

Some authors applied a “restrictive” low volume fluid approach during the management of their patients [17,24,25]. Fluid restriction was sometimes estimated as 10% less volumes than the standard [39].

The “restrictive” fluid approach was shown to induce postoperative hypovolemia and reduced tissue perfusion with or without shock [17,24,25]. This might be due to depriving patients from their actual needs of fluids. However, Matol et al. appraised the “restrictive” approach to reduce postoperative morbidity and hospital stay [40].

On the other hand, a careful comparison of different study protocols showed that many “restrictive” approaches actually represented “adequate” fluid “substitution”, exhibited by hemodynamic stability [17]. This might be true because the extracellular deficit after the usual preoperative fasting proved to be negligible [41], and the basal fluid loss via insensible peri-

spiration or urine production proved not to exceed 1 ml/kg/h during major abdominal surgery [42].

It remains to be clear that we are in actual need for evidence-based guidelines for perioperative fluid administration [43].

### 6. A preliminary evidence of “adequate” approach

Holte et al. [44] compared “liberal” versus “restrictive” Ringer Lactate administration during laparoscopic cholecystectomy, a minimally invasive surgery. They found that an intraoperative “liberal” approach of approximately 3 L of Ringer Lactate (40 ml/kg over 1.5 h starting from induction of anesthesia), significantly improved perioperative organ functions and recovery with shortened hospital stay. They also suggested that an intraoperative “restrictive” regimen of approximately 1 L of Ringer Lactate (15 ml/kg over 1.5 h starting from induction of anesthesia), resulted in postoperative functional hypovolemia. In the same direction, a gynecological laparoscopy study reported decreased postoperative nausea and vomiting, when using intraoperative “liberal” versus “restrictive” Ringer Lactate regimen [45].

Holte et al. [46] carried out a further study to investigate whether their previously demonstrated improved patient outcome after “liberal” fluids during laparoscopic cholecystectomy, could be due to avoidance of postoperative hypovolemia. A volume kinetic analysis of identical pre- and postoperative volume loads of Ringer Lactate (12.5 ml/kg), was the method used to prove the presence or absence of postoperative hypovolemia. The technique of volume kinetic analysis offers a method to prove that the body strives to maintain volume homeostasis of fluid spaces [47]. The model proved effective for evaluating perioperative fluid shifting, and for distinguishing normovolemic versus hypovolemic conditions [48]. Using this model, Holte et al. [46] proved the absence of hypovolemia after intraoperative “restrictive” fluid administration. They concluded that the differences in functional outcome between the two fluid regimens could be attributed to the minimally invasive surgery – per se rather than being influenced by the amount of intraoperative fluid administration. However, as a conclusion of a systematic review of 80 randomized controlled trials (RCTs), Holte and Kehlet [49], have recommended “avoiding fluid overloading during major surgical procedures”. So, a role of anesthesia and surgery – per se – was suggested to affect patient outcome [46]. Previous studies found significantly decreased clearance of infused crystalloids during and immediately after several types of anesthesia (epidural, spinal, isoflurane, and propofol) [50–53] and surgery (thyroid, gall-bladder, and colon) [53–55] due to activation of stress hormones prompting fluid retention. In all such conditions, fluid elimination would be much slower during and immediately after the actual anesthetic or surgical procedures. In a RCT, although there was non-significant differences in 60 days morbidity, a neutral fluid balance was associated with improved lung function and shortened duration of mechanical ventilation [56]. Earlier studies and earlier clinical guidelines suggested benefits associated with a net even approach to fluid therapy [57].

It is clear through some studies that the “adequate” fluid therapy by “substitution” is of value, rather than the “liberal” or the “restrictive” approach [46,56,57]. It may be also clear through the SAFE study that patient outcome is similar after administration of either albumin 4% or saline [38]. It may be

clear again that surgery – per se, or anesthesia – per se may have a finger-print on patient outcome, rather than the volumes or types of administered fluids.

### 7. Hemoglobin therapy: too much or too little

Blood transfusion is a commonly performed medical procedure in hospitalized patients. However, this life-saving strategy is not without risks including transfusion-transmitted infections and immunomodulating effects that may increase the risk of nosocomial infections and possibly the development of autoimmune diseases later in life [58].

The conventional “transfusion trigger” of a hemoglobin (Hb) level of 10 g/dl and hematocrit (Hct) of 30% has been recently challenged. The minimum tolerable level of Hb is not well-established, and considerable variations exist in transfusion practice.

Patients with acute anemia in the preoperative period or if critically-ill, have been shown to need blood transfusion with Hb < 6 g/dl and not to need blood transfusion with Hb > 10 g/dl [59].

Packed red blood cells (PRBCs) are used to increase the Hb concentration and improve the oxygen carrying capacity of the blood. A unit of PRBCs of 250–300 ml and Hct of 60–80% increases the Hb level by 1 g/dl and the Hct by 3–4% in an average sized adult. Clinical factors needed to perform blood transfusion include the cause of anemia, its severity and acuity, and the patient ability to compensate. Transfusion is not routinely needed in patients with chronic anemia or cancer unless it is expected to improve their exercise fitness.

Limited data are available on patient outcome with transfusion therapy regarding a “liberal” or a “restrictive” approach.

A systematic review including 10 RCTs compared outcomes with a “liberal” (transfusion trigger of 9–10 g/dl Hb) versus a “restrictive” (transfusion trigger of 7–9 g/dl Hb) preoperative transfusion strategy [60]. Another meta-analysis of 35 RCTs, observational and experimental studies identified “liberal” and “restrictive” approaches of 10–12 g/dl and 7–9 g/dl, respectively [61]. In both situations, the “liberal” approach was associated with increased adverse clinical outcome, while the “restrictive” approach was associated with decreased adverse clinical outcome including lower morbidity and mortality (M/M) and shorter length of hospital stay. They support the use of the “restrictive” strategy in patients free of serious cardiac diseases, although an increased incidence of complications was reported at very low Hb levels, in agreement with other studies [62,63].

The Transfusion Requirements In Critical Care (TRICC) investigators found that a “restrictive” approach was associated with lower morbidity in critically-ill patients, with the conclusion that the “restrictive” approach is as effective or even superior to the “liberal” one [64]. Other authorities showed that Hb “transfusion trigger” of 7 g/dl had no negative impact on M/M, either in the general ICU patients or in patients with coexisting cardiac diseases [64,65]. In patients with coexisting cardiac disease, however, higher postoperative Hb trigger of 8 g/dl was justified, given the likelihood of postoperative tachycardia and compromised oxygenation [59].

Perioperative blood transfusion therapy in hospitalized patients could be withheld as long as a patients Hb level remained at 7 g/dl or higher, and the patient was not actively bleeding [60]. On the other hand, patients with cardiac diseases might need to

increase their Hb threshold to 10 g/dl or higher to raise their oxygen carrying capacity and to improve their quality of life [60].

## 8. Conclusions

It may be concluded that an “adequate” rather than a “liberal” or a “restrictive” perioperative fluid approach may represent the gateway to improved patient outcome. An “adequate” approach implies a careful “substitution” of fluid deficits, losses, and needs, because the body normally strives to maintain its volume homeostasis.

Blood should be transfused for all patients with Hb < 6 g/dl and not to be transfused for any patient with Hb > 10 g/dl. Transfusion of blood may be withheld as long as a patient's Hb remains at 7 g/dl or higher, and he is not actively bleeding. A blood “transfusion trigger” may be 9–10 g/dl for a patient with cardiac disease to raise his oxygen carrying capacity. Further systematic reviews of RCTs are needed for evidence-based perioperative fluid regimens, including Hb therapy.

## 9. Key-points

- After the ongoing controversy on colloids versus crystalloids, the main focus is now on the amount of applied fluids in general.
- Perioperative blood volume is normal (after replacement of blood loss), because losses following fasting, urine formation, and insensible perspiration are negligible, and a third-space is non-existent.
- A distinction should be made between type 1 (physiologic) and type 2 (pathologic) fluid shifting, that should be treated accordingly. Crystalloids physiologically load the interstitial space. Colloid loading may induce hypervolemia with destruction of glycocalyx, a vital part of the biological membrane.
- A successful plan should address the right kind of fluids, in appropriate amounts, at the right time to reduce the endothelial barrier damage.
- An “adequate” or “substitution” rather than a “liberal” or a “restrictive” fluid approach might be the proper gateway to improve patient outcome.
- Blood transfusion should be withheld in patients with non-cardiac diseases and who are not actively bleeding, so long as their Hb is 7 g/dl or higher. Patients with cardiac diseases need a “transfusion trigger” of 9–10 g/dl to raise their oxygen carrying capacity.
- Further systematic reviews of RCTs are needed to formulate evidence-based guidelines for perioperative fluid management.

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