Restricted Versus Liberal Fluid Management Pros and Cons

18

David Liska

Abstract

Perioperative maintenance of adequate intravascular volume status is important to achieve optimal outcomes after surgery, but there are controversies regarding the appropriate volume of fluid therapy. Multiple small and some larger randomized controlled trials have demonstrated that liberal fluid management is associated with higher risk for poor postoperative outcomes, including postoperative ileus, increased length of stay, and overall morbidity. However, restrictive fluid regimens have not uniformly shown to be beneficial, with some studies showing increased risk for postoperative complications, especially acute kidney injury. To reconcile these conflicting findings, it is important to critically analyze the available data, while acknowledging differences in definitions, patient populations, and treatments. While some patients may benefit from goal directed fluid therapy, many patients can be optimally managed with a balanced fluid protocol aiming at maintenance of normovolemia.

Key Points

1. The volume of intravenous fluids administered during and after surgery has significant implications on patient recovery and outcomes.
2. Multiple randomized controlled trials have demonstrated that liberal fluid management with resultant volume overload and weight gain is associated with adverse outcomes, including higher rate of postoperative ileus, overall complications, increased hospital length of stay and costs.

D. Liska (✉)
Department of Colorectal Surgery, Digestive Disease & Surgery Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: liskad@ccf.org

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3. An overly restrictive fluid management protocol can also increase the risk for complications, in particular the risk for kidney injury, and especially if hypovolemia is not detected and corrected.
4. Optimal outcomes can be achieved with a fluid therapy protocol that focuses on maintenance of normovolemia by only replacing sustained fluid losses, while allowing for a fluid balance slightly above zero when needed.
5. Standardization of definitions and protocols is essential to optimize patient management and to facilitate further research.

Introduction

The goal of perioperative intravenous fluid (IVF) therapy is to reestablish and maintain normal physiology and organ function by using the appropriate volume of the correct fluid to achieve a state of homeostasis. Determining the correct volume of perioperative IVF has become an active area of research over the last few decades. The multitude of trials and reviews published on this topic, some with conflicting results and conclusions, highlight the controversies that have emerged over time. While there still remains a lack of standardized terminology in the literature, IVF regimens for abdominal surgery have been classified as restrictive (<1.75 liters per day), balanced (1.75–2.75 liters per day), and liberal (>2.75 liters per day) [1]. Liberal fluid management in most surgical patients was still the norm in the 1990s. However, with data showing that volume overload following surgery is common and detrimental to patients' safe recovery from surgery, restrictive fluid management was recommended and became an important component in many enhanced recovery after surgery (ERAS) pathways. On the other hand, more recently, studies have shown that overly restrictive fluid management strategies can also lead to morbidity, in particular with regards to postoperative kidney injury [2]. Goal-directed fluid therapy (GDFT), using various invasive or non-invasive measurements of volume status and/or end-organ perfusion, promises a bespoke approach to fluid therapy. However, indiscriminate use of GDFT devices may prove not to be practical or cost-effective and has not consistently demonstrated to be of benefit when compared to non-goal-directed judicious fluid management [3]. This chapter will review the current state of evidence regarding optimal perioperative fluid volume management strategies.

State of the Evidence

Traditional teachings in perioperative fluid management focused on the correction of hypovolemia caused by a confluence of assumed factors including: Preoperative fasting, mechanical bowel preparation, intraoperative acute blood loss, anesthesia-induced vasodilation, and surgery induced "third-spacing" of fluids [4]. This approach to fluid management was shown to result in the administration of approximately 6 L on the day of surgery and around 3 L daily on the first 3 postoperative

days, which was associated with a 3–4 kg postoperative weight gain [5, 6]. In the early 2000s this traditional approach to perioperative fluid management was challenged by several randomized controlled trials (RCTs). There exists significant heterogeneity between these trials, as some differ in their definition of what is considered liberal versus restrictive fluid management. Most trials reviewed here focus on major abdominal surgery, with a predominance of these focusing on colorectal resections, however some trials also included other abdominal surgeries. The majority of trials were relatively small, with many RCTs including less than 100 patients, with the distinct exception being the trial by Myles et al. [2], which included 3000 high risk patient undergoing abdominal surgery. It is also important to note that the period for fluid therapy and outcome endpoints were inconsistently defined with the primary outcome being different across these trials, albeit with significant overlap among secondary outcomes (Table 18.1).

Fluid Management and Postoperative Gastrointestinal Recovery

Postoperative Gastrointestinal (GI) dysfunction or postoperative ileus (POI) remains a major problem after abdominal surgery, increasing perioperative complications, postoperative hospital length of stay (LOS), and costs. Preclinical studies [7] demonstrated that GI edema increases gastric emptying time, suggesting that perioperative volume overload may be an important contributor to POI. Liberal fluid resuscitation can also lead to splanchnic edema which may result in increased abdominal pressure with decreased mesenteric blood flow, which in turn elicits tissue hypoxia and ultimately leads to ileus and anastomotic complications [8, 9]. To assess the effect of fluid management strategy on postoperative recovery of GI function, Lobo et al. [5], in an early small RCT (n = 20), demonstrated that liberal fluid management was associated with significantly longer gastric emptying times, delayed return of bowel function (flatus 4 vs 3 days; stool 6.5 vs 4 days) and significantly longer length of stay (LOS) (9 vs. 6 days, p = 0.001). There was also increased incidence of postoperative complications when compared to the restricted group. A RCT by Nisanevich [10], examining the effects of fluid management on postoperative morbidity and mortality, with return of bowel function as a secondary outcome, found that patients with liberal fluid management passed flatus and stool significantly later (flatus: 4 vs. 3 days; $P < 0.001$; stool: 6 vs. 4 days; $P < 0.001$). A just recently published large retrospective study of 4205 patients undergoing colorectal surgery within the context of a well-established ERAS pathway also confirmed the importance of fluid management on GI recovery [11]. In this patient population, POI occurred in 9% and on multivariate analysis was significantly associated with day of surgery fluids of >3 L (OR = 1.65 (95% CI, 1.13–2.41); P = 0.009) and postoperative day 2 weight gain of >2.5 kg (OR = 1.49 (95% CI, 1.01–2.21); P = 0.048). Not all studies demonstrated a difference in GI recovery based on fluid management. MacKay et al. [12] randomizing 80 patients undergoing colorectal surgery to restricted or liberal fluid regimens, did not find a difference in time to first flatus (2.9 vs. 2.9 days; P = 0.466) or bowel motion (4.7 vs. 4.9 days; P = 0.802). Similarly, a

Table 18.1 Summary of selection of randomized controlled trials assessing the impact of restrictive versus liberal fluid therapy on outcomes

First author year	N Res/Lib	Surgery	Primary Outcome	Favors Res or Lib	Bowel Function[a] Res/Lib (days)	Complications Res/Lib	LOS Res/Lib (days)
Lobo [5]	10/10	Colectomy	Gastric emptying	Res	4/6.5[b]	1/7[b]	6/9[b]
Brandstrup [6]	69/72	Colorectal resections	Complications	Res	NR	21/40[b]	NR
Nisanevich [10]	77/75	Abdominal surgery	Complications	Res	4/6[b]	13/23[b]	8/9[b]
Kabon [17]	124/129	Colectomy	SSI	ND	NR	NR	7.3/7.0
MacKay [12]	39/41	Colorectal resections	LOS	ND	4.7/4.9	ND	7.2/7.2
Holte [13]	16/16	Colectomy	Pulmonary function	Res	2/2	6/1	3/2.5
McArdle [22]	10/11	AAA repair	Major complications	Res	NR	1/14[b]	8/16[b]
Gonzalez-Fajardo [26]	20/20	Abdominal vascular	LOS	Res	4.6/5.3	NR	8/12[b]
Vermeulen [27]	30/32	Abdominal surgery	LOS	Lib	3.7/3.5	12/5[b]	12.3/8.3[b]
Abraham-Nordling [19]	79/82	Colorectal resections	LOS	ND	3/2 (first flatus)	31/47[b]	6.0/6.0
Gao [28]	93/86 (age > 65)	Abdominal surgery	Complications	Res	NR	31/39	NR
Peng [29]	84/90	Abdominal surgery	Complications	ND	NR	46/86	NR
Myles [2]	1490/1493	Abdominal surgery	Disability free survival	ND	NR	AKI: 8.6/5.0[b]	6.4/5.6

Res Restricted group, *Lib* Liberal group, *ND* No difference

[a]First passage of stool, *LOS* length of stay, *NR* not reported, *SSI* surgical site infection, *AKI* acute kidney injury

[b]$P \leq 0.05$

RCT by Holte et al. [13], including 32 colorectal surgery patients, found no difference in the return of bowel function or GI transit time, determined by radio-opaque marker transit study. On meta-analysis of 8 trials assessing POI [14], patients in the restricted group had a shorter time to first flatus in comparison with the liberal group (pooled difference in the mean = −0.67, 95% CI −1.28 to −0.06, P = 0.031). Given the significant impact of POI on postoperative recovery and LOS, avoiding fluid overload has become an integral component of most ERAS pathways.

Fluid Management and Surgical Site Infections

Surgical site infections (SSIs) remain a significant cause of patient morbidity and mortality, and are the third-most common source of hospital-acquired infection [15]. SSIs are relatively common, occurring in up to 20% of abdominal procedures, prolong the length of hospital stay and escalate hospital costs. Since many SSIs are considered preventable, they have become a key indicator of quality of care. SSI prevention is complex and requires the integration of a range of measures before, during, and after surgery [16]. Perioperative fluid therapy can play an important role in reducing risk of SSIs. With volume status being one of the important factors determining end-organ perfusion and tissue oxygenation, it is only logical that perioperative fluid management could have implications on wound healing and SSIs. Since SSIs are an important quality metric, studies have examined the effect of liberal versus restrictive fluid therapy on SSIs as primary or secondary outcome. In a relatively large RCT by Kabon et al. [17], where 253 patients undergoing open colorectal resections were randomized to restrictive versus liberal fluid administration, they authors hypothesized that a liberal fluid regimen would result in increased tissue oxygenation and thereby decrease surgical wound infections following colorectal surgery. However, no difference in surgical site infections or wound healing rate was found, suggesting that liberal fluid administration does not decrease the risk for SSIs. Most other RCTs comparing liberal to restricted fluid management were not specifically designed for SSI as outcome. The RCT by Brandstrup et al. [6], examining overall post-operative complications, found double the number of minor wound related complications (infection, hematoma, or dehiscence) in the liberal group (18/72 vs. 9/69) when compared to the restricted group. In the RCT by Nisanevich [10], wound complications were also more common in the liberal group (11/75 vs. 7/77). In a systematic review and meta-analysis published in 2016 [18], wound infections were found to be more common in the liberal group. On the other hand, the RCT by Nordling et al. [19], comparing an "extremely" restricted fluid protocol to a standard regimen, found no difference in wound infections between the two groups (10/79 vs. 11/82). Holte et al. [13] found an increase in SSIs and wound complications with restricted fluid management (5/16 vs. 0/16), including 3 anastomotic leaks in the restricted group. Similarly, the large 2018 trial by Myles [2], found that SSIs were more common in the restrictive group (245/1481 vs. 202/1487; p = 0.02), although this was not statistically significant when adjusting for multiple comparisons. In the absence of more trials powered to specifically

assess the impact of restricted versus liberal fluid management on wound infection, it remains controversial if current perioperative fluid management strategies directly impact the risk for developing SSIs.

Acute Kidney Injury

With avoidance of hypervolemia becoming a recommended component of ERAS pathways, there was an increase in reports of the potential harm in restrictive fluid regimens. In particular, there was concern for acute kidney injury (AKI), due to renal hypoperfusion in an overly restrictive protocol or due to renal interstitial edema in settings of hypervolemia [20, 21]. Brandstrup et al. [6] reported a significantly lower serum creatinine in the liberal group upon arrival in the recovery room, however there was no difference found in the subsequent days. McArdle et al. [22] measured the urinary albumin/creatinine ratio in 22 patients undergoing abdominal aortic aneurysm repair randomized to restricted or liberal fluid administration. They reported a significantly higher value in the liberal group, suggesting impaired renal endothelial function due to volume overload. However, there were no cases (0/11) of renal failure reported in the liberal group compared with one case (1/11) in the restricted group. The most significant study to highlight the potential detrimental consequence of restricted fluid protocols on renal function was the international multicentered RELIEF trial by Myles et al. [2] that randomized 3000 high risk (age $\geq$ 70, or heart disease, diabetes, renal impairments, or morbid obesity) patients to liberal or restrictive IVF regimen. The primary outcome was disability-free survival at 1 year. The investigators found that a restrictive fluid regimen was not associated with a higher rate of disability-free survival than a liberal fluid regimen but was associated with a higher rate of acute kidney injury (8.6% vs 5.0%; $P < 0.001$) and there was a trend towards higher requirement of renal-replacement therapy (RRT) in the restricted group (0.9% vs. 0.3%; $P = 0.048$). Despite the large sample size in this trial, there are some limitations that temper the conclusions one can draw from this trial. The study's pragmatic design lead to perioperative care that was not standardized and there was a wide variation in the anesthetic and analgesic techniques, including use of epidural analgesia, variable intraoperative hemodynamic management, and variable postoperative care. The total fluid volume administered during and up to 24 hours after surgery was 3.7 versus 6.1 L in the restrictive and liberal groups, respectively. These amounts are similar to typical restrictive and liberal fluid strategy totals. However, the reported increase in body weight was relatively minor—1.6 kg in the liberal fluid group and only 0.3 kg in the restrictive fluid group, which represent increases that are far lower than those in other fluid management trials. This modest increase in body weight, together with the absence of a protocol driven monitoring and standardized response to postoperative hypovolemia, oliguria, and hypotension may have contributed to the increase in AKI events in the restrictive group. The authors are therefore correct in interpreting their results cautiously and they conclude that a modestly liberal fluid regimen is safer than a truly restrictive regimen.

Overall Complications and LOS

In one of the seminal trials examining perioperative fluid management, Brandstrup et al. [6], examining post-operative complications as primary outcome, randomized 172 patients undergoing colorectal surgery to either liberal or restricted fluid management. The restricted fluid management protocol was associated with a significant reduction in overall complications (33% vs. 51%, P = 0.003). This was true for both major (such as anastomotic leak, sepsis, bleeding, and pulmonary edema requiring assisted ventilation) and minor (superficial wound infections, pneumonia, and urinary tract infection) complications. Independent of fluid management protocol being followed, there was a dose-response relationship between complications and increasing volumes of fluid and increasing body weight, confirming the importance of volume overload on postoperative outcomes. Since then there have been several systematic reviews and meta-analyses published to integrate the data generated from many different RCTs, especially with regards to overall perioperative outcomes and hospital LOS. Considering the conflicting results from individual RCTs, it is not surprising that meta-analyses are unable to provide conclusive evidence when combining data from these heterogenous patient populations. However, of note, on a meta-analysis by Jia et al. [14] (published in 2017), despite there not being a statistically significant benefit to restrictive fluid therapy with regards to overall complications (OR = 0.59, 95% CI 0.34–1.04, P = 0.068), hospital LOS was significantly shorter with a restrictive regimen (pooled difference in the mean = −1.51, 95% CI −2.90 to −0.12, P = 0.033).

An important meta-analysis performed by Varadhan and Lobo [1] helped reconcile some of the conflicting RCT results by standardizing the definition of fluid management strategy based on actual daily volume received (as detailed in our introduction above) and then reclassified study populations from RCTs into three groups: underhydration, normovolemia or balanced, and fluid overload. Without reclassification into these internally more consistent categories, meta-analysis showed no difference overall complications and LOS between liberal and restricted fluid therapy. However, following reclassification, meta-analysis showed that patients treated with a fluid balance (normovolemia) versus fluid imbalance had significantly fewer overall complications (RR 0.59; 95% CI 0.44–0.81) and shorter LOS (weighted mean difference—3.44 days (95% CI −6.33 – −0.54). A more recently performed meta-analysis on fluid restriction following abdominal surgery by Shen et al. [23] demonstrated similar findings. They included 16 RCTs with a total of 2341 patients that were treated with a restricted regimen and 2337 patients receiving liberal regimen (2983 of these patients are from the study by Myles et al. [2] discussed above). All sixteen studies compared the total complication rates between restricted and standard regimens in patients undergoing abdominal surgery. Similar to prior meta-analyses [1, 14], there was no benefit of a restricted regimen in reducing overall postoperative complication when combining the conflicting data from all included RCTs. However, on subgroup analysis, when assessing studies where the postoperative mean patient weight gain difference between liberal and restricted groups was ≥2 kg (8 RCTs with a total of 662 patients), there was a

significantly reduced risk for postoperative complications in patient on restricted protocols (RR 0.67, 95% CI 0.57–0.79). These results again confirm that the benefits of restricted fluid management are most apparent when compared to liberal fluid management that resulted in substantial hypervolemia associated with postoperative weight gain.

Normovolemia or Balanced Fluid Administration

Taken together, the above studies clearly show that excessive perioperative administration of intravenous fluid, which was common in traditional liberal approaches to fluid therapy, should be avoided. However, when following overly restrictive regimens, one risks complications related to hypovolemia, without any significant benefits compared to a moderately liberal protocol. The concept of an optimal "Goldilocks zone" of fluid management which lies between traditional liberal protocols and the strict fixed-volume, zero-balance approaches, has also been confirmed by recent large retrospective studies. Thacker et al. [24] studied large data from the Premier Research Database including patients undergoing colon (n = 84,722) or rectal surgery (n = 22,178) and hip or knee replacement (n = 548,526) to analyze the variability in perioperative (day of surgery) fluid utilization and its relationship with outcomes. A wide range of fluid utilization was observed, with 25% of patients receiving less than 1.7 L for colon, 1.5 L for rectal, and 1.3 L for hip/knee surgeries. On the other hand, 25% of patients received more than 5.0 L for colon, 5.4 L for rectal, and 4.1 L for hip/knee surgeries. When classifying patients into 3 groups based on fluid utilization they found that in colorectal and orthopedic surgery both low and high fluid volumes were associated with worse outcomes including increased LOS, POI, and hospital costs. This U-shaped association between the volume of fluid administered and postoperative complications was also demonstrated in a large retrospective registry study by Shin et al. [25] Here, 92,094 patients undergoing noncardiac surgery were evaluated with the primary exposure variable being intraoperative fluid administered and outcomes being 30-day survival, respiratory complications, AKI, LOS, and costs. Liberal fluid volumes in the highest quintile of fluid administration were significantly associated with respiratory complications whereas both liberal and overly restrictive (lowest quintile) volumes were significantly associated with acute kidney injury. Moderately restrictive volumes were consistently associated with optimal postoperative outcomes, including decreased mortality, LOS, and costs.

Summary and Considerations for Current Practice

While further well-designed prospective trials regarding some of the nuances of intraoperative fluid therapy are still needed, the current data demonstrates that both liberal and overly restrictive fluid regimen can significantly complicate a patient's recovery following surgery. This confirms the important role appropriate

perioperative fluid management, with the avoidance of excessive weight gain and hypovolemia, has in the surgical patient's safe and swift recovery from surgery. While some patients may benefit from cardiac-output driven GDFT, the majority of patients can safely be managed with a protocol that focuses on maintenance of normovolemia, which can usually be achieved by only replacing sustained fluid losses while allowing for a fluid balance slightly above zero when needed. Postoperatively, patients managed in the context of an ERAS protocol will usually not need any supplemental IVF. However, patients need to be monitored for signs of hypovolemia and end-organ hypoperfusion which then needs to be treated with supplemental IVF to avoid complications. The wide variability of fluid protocols currently employed, highlight the importance of developing institutional patient-specific protocols that should be rigorously implemented.

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