

# The influence of fluid therapy on short- and long-term outcomes in patients undergoing liver resection for malignant indications

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Although fluid therapy in hepatic surgery affects the postoperative course and morbidity, there is a paucity of unequivocal guidelines in the literature as to which of three fluid strategies to use: liberal, restrictive or goal-directed. We performed a review of literature regarding fluid management strategies in major abdominal procedures, focusing on hepatic surgery. The quantity and quality of fluids infused perioperatively is often dependent on the preference of the physician, institutional experience and practices. A liberal fluid regimen carries the risk of impaired wound healing and prolonged ileus, furthermore in liver surgery it may increase blood loss. Restrictive fluid therapy is the mainstay of the anesthetic management in hepatic resections, keeping the central venous pressure low controls outflow from the liver and results in a decrease in intraoperative blood loss. In recent years, goal-directed fluid therapy (GDFT), as a component of enhanced recovery pathways after surgery (ERAS) programs, has gained in popularity. It is based on the concept of hemodynamic optimization in order to ensure optimal tissue perfusion and oxygen delivery. Furthermore, a fluid infusion strategy should be individualized in terms of the unique pathophysiology of the patient (e.g. cirrhosis) and the specific requirements of the surgical technique (laparoscopic procedures). Controversy regarding often contradictory data, leaves the clinician at a loss as to which fluid strategy will best serve the patient. Therefore, it is imperative to design and conduct clinical trials in a homogenous group of patients to define the optimal type and amount of fluid for patients undergoing hepatic surgery.

**Key words:** liver resection, fluid management, goal-directed therapy, restrictive therapy, enhanced recovery pathways after surgery

## Fluid regimes in major abdominal surgery

Relevant articles were searched for using the Pubmed database with the following terms: “liver resection”, “liver surgery”, “goal-directed therapy”, “fluid management” and “enhanced recovery after surgery”. The results were independently assessed by the authors for scope and relevance.

Many factors influence the normal postoperative course of patients undergoing extensive liver surgery. One of those

is a fluid infusion strategy; preoperatively – in urgent cases – intraoperatively and in the postoperative period. Transfusion of the optimal fluid volume during surgical procedures and in the postoperative period affects the course of the operation, as well as postoperative morbidity. Both excessive and insufficient fluid intake can be harmful [1, 2]. The main goal is to restore and maintain fluid volume to ensure homeostasis in terms of euvoemia, electrolyte balance and tissue perfusion.

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[3]. Intra- and postoperative fluid transfusion strategies have been the subject of numerous studies. Both surgeons and anesthesiologists have different approaches to fluid management. The confirmation of the thesis that fluid therapy depends mainly on individual preferences of the physician is a study by Lilot et al., which included a group of 5,912 patients undergoing various abdominal procedures. The authors concluded that a patient weighing 75 kg can receive from 500 to 5400 ml of crystalloids depending on the physician's preference [4]. There are generally three main strategies of perioperative fluid therapy: "liberal", "restrictive" and "goal-directed". Each of these strategies has its supporters and opponents, and each has been the subject of randomized trials. After years of a "liberal" approach, a paper by Brandstrup et al. was published comparing "liberal" and "restrictive" strategies. The results of the study clearly indicated a statistically significant increase in the number of complications in the patients from the "liberal" group [5]. Over the following years, the "restrictive strategy" has gained popularity, as one of the components of the "enhanced recovery after surgery" (ERAS) protocols. In 2018, a multicenter study was published comparing the two strategies. The study included a group of 3,000 patients. One of the key results of the study was the finding of a statistically higher incidence of acute kidney injury in patients who received fluids according to restriction protocol [6].

The adopted perioperative fluid therapy strategies have been extensively studied especially in patients undergoing gastrointestinal procedures. Some researchers believe that excessive fluid loading impairs the healing of intestinal anastomoses, delays the return of gastrointestinal motility, increases the overall incidence of complications, increases the length of hospital stay and the cost of treatment [7–9]. While this is true in patients undergoing procedures on the large intestine [10], it has been shown that the use of restrictive fluid therapy does not bring such benefits in cases of pancreatoduodenectomy [11, 12]. With regards to abdominal surgery, it should be noted that the specificity of individual procedures (the number of intestinal anastomoses, the need to open the retroperitoneal space, the presence of vascular anastomoses) affects the movement of fluids between compartments. In order to recommend a "surgery specific" fluid strategy, studies should be carried out in homogeneous groups.

### **Evolution of aim-directed fluid protocols. Optimization of oxygen delivery to tissues**

In addition to the restrictive and liberal strategies discussed so far, or rather, as a result of the inconclusive results of conducted studies, a third strategy named goal-directed therapy (GDT) was introduced.

This strategy was created not only in response to the contradictory results of studies on the previously mentioned liberal and restrictive strategies, but also stemmed from in-depth analysis of the pathophysiology of the phenomena leading to

increased number of complications, prolonged hospitalization and postoperative deaths in patients undergoing non-cardiac surgery. It was proven that intraoperative tissue perfusion (tissue blood flow), arterial oxygen saturation, hemoglobin concentration and cardiac output – components of the parameter referred to as oxygen tissue delivery ( $DO_2$ ) – affect mortality and morbidity. The conducted studies have shown that perioperative fluid therapy, optimized on the basis of hemodynamic parameters significantly reduces the number of postoperative complications and the risk of death. At the same time, it has been shown that traditional parameters monitored intra- and postoperatively, i.e., blood pressure and heart rate, are not sensitive enough to detect moderate hypovolemia, which may cause inadequate tissue perfusion, especially in the visceral bed [13–15]. Goal-directed therapy is based on the premise that perioperative fluid administration is essential to maximizing  $DO_2$ . Therefore, it should be based on dynamic flow-dependent parameters, i.e., stroke volume (SV) and its variability in response to fluid bolus (stroke volume variation – SVV) [16, 17]. The results of randomized trials, where the primary endpoint was the occurrence of postoperative complications (as in other studies evaluating the liberal and restrictive strategy) are contradictory. The FEDORA study showed a statistically significant lower complication rate in patients from the GDT group who underwent abdominal procedures [15]. However, the work of Pestania et al. (POEMAS study) showed no such relationship [18].

### **Concept of perioperative euvoemia**

Most studies refer to intraoperative fluid administration. Some papers treat this topic more broadly and include the preoperative and postoperative period as well. The protocols regarding the intake of fluids before abdominal surgery clearly indicate the benefits of the lack of restrictions in oral administration up to 2 hours before the induction of anesthesia [19]. Postoperative fluid therapy should continue as long as the patient is unable to tolerate oral intake. Its primary goal is to maintain intravascular volume while avoiding a positive fluid balance which, among others, leads to delayed healing of the wounds and anastomoses, consequently leading to a longer hospital stay, prolonged ileus and other complications [20]. In recent years the term "goal-directed therapy" has been introduced in literature in relation to intraoperative infusions, and "zero balance" – in relation to postoperative management.

### **Fluid therapy in liver surgery**

The incidence of liver tumors is on the rise [21]. Indications to liver resections are mainly oncological, with the majority of cases being hepatocellular carcinoma and metastatic tumors. The basic differences in the approach to intraoperative and postoperative fluid therapy in patients undergoing liver surgery will be presented below. Clinical situations related to patients who are hemodynamically unstable prior

to emergency surgery will be intentionally omitted. Septic patients, as well as those receiving total parenteral nutrition will not be discussed either. Thus, we will concentrate on fluid therapy in ASA  $\leq 3$  patients undergoing elective liver procedures.

Liver surgery can be divided into hepatic parenchymal surgery, biliary tract surgery and cholecystectomy. The aim is to discuss the strategy of intra- and postoperative fluid therapy in large (including excision of more than 3 segments) liver resections.

### Limitation of blood loss in liver surgery

One of the key aspects of liver surgery is the bloodless surgical field. The inflow to the liver may be controlled, e.g. by the Pringle maneuver (a temporary tightening of the hepatoduodenal ligament). Back bleeding from valveless hepatic veins is prevented by low central venous pressure. CVP of 5 mmHg is recommended to provide unobstructed outflow and limit blood loss. It has been shown that maintaining low central venous pressure effectively reduces bleeding, limiting the need for blood product transfusions, morbidity and postoperative mortality. At the same time, it has been shown that it does not significantly affect the incidence of postoperative acute kidney injury [22–27].

### Looking for a silver bullet in fluid management

Recently, the role of central venous pressure (CVP) as a reliable parameter for assessing volemia has been increasingly questioned. Hemodynamic parameters as guides to volume management have gained popularity, although analysis of the literature reveals that these methods also have limitations. Problematic situations include mechanical ventilation and cardiac arrhythmias to name a few [28].

Regardless of the monitoring methods used, the aim of the anesthetic technique is to maintain the free outflow of the blood through the hepatic veins. This is achieved by simultaneously employing several methods: fluid restriction, head-elevated patient positioning and ventilation techniques with pressure limitation in airways. Vasodilators (nitroglycerin) sublingually or intravenously are also used. It should be emphasized that these strategies are limited to the stage of parenchymal transection. Fluid infusion is being restricted to 1 ml/kg/h of buffered crystalloid plus additional volume to make up for the ongoing blood loss at a ratio 1:1. Intraoperative fluid therapy strategies are the subject of randomized trials. Correa-Galle et al. compared a conventional strategy with “goal-directed fluid therapy”. Randomization was performed after the resection stage. The “conventional” group received an infusion of crystalloid at a dose of 6 ml/kg/h. The “goal-directed” group received infusion at a rate of 1 ml/kg/h with the simultaneous supplementation of albumin solution with an aim to restore stroke volume variation (SVV) to the level measured at the induction of anesthesia. In both groups, additional fluid volume was administered to main-

tain systolic blood pressure  $\geq 90$  mmHg or diuresis  $> 25$  ml/h. Red blood cell concentrate was also given to ensure hemoglobin concentration  $\geq 7$  g/dl. In the postoperative period, conventional fluid therapy of 1.2 ml/kg/h was used with additional infusion in order to maintain the above-mentioned targets. There was no statistically significant difference in terms of the incidence of postoperative complications, the length of hospital stay or other variables specified in the study. A statistically significant difference was observed in the total volume of fluids infused during the post-hepatectomy phase. In the “goal-directed” group it was lower by an average of 900 ml [29]. Another study by Weinberg et al. compared the addition of a fluid restrictive intraoperative cardiac output-guided algorithm to standard fluid protocol. The “conventional care” group consisted of patients in whom the amount of fluid and catecholamines administration were at the discretion of the anesthesiologist. In both groups a higher incidence of postoperative complications was found, compared to the previously cited study, and these were mainly grade I and II complications according to the Clavien-Dindo classification. This trial showed a statistically significant lower fluid balance in the study group compared to the control group. There were no differences in the incidence of acute kidney injury between the groups [30].

Studies conducted by Kim Y. et al. [31] and Lilot M. et al. [32] showed that despite the recommendations regarding intraoperative fluid therapy in patients undergoing abdominal procedures, including liver resections, there is a very large discrepancy regarding the amount of fluids administered between individual centers and even physicians. Hepatic resections are procedures that can significantly affect hemodynamics, e.g. by compressing the inferior vena cava during surgical maneuvers, which causes a decrease in venous return and consequently cardiac output. In addition, the liver because of its metabolic function, i.e., contributing to lactate clearance, affects the acid-base balance.

Taking into account these facts and the protocols of enhanced recovery after surgery (ERAS) [33], which recommend intraoperative fluid restriction but not at the cost of organ hypoperfusion, the following can be suggested: the most appropriate approach to perioperative fluid therapy in liver resections should be goal-directed therapy with fluid restriction until transection completion (low central venous pressure) with subsequent volemia restoration under SVV guidance. Indicators of organ perfusion, e.g. serum lactate concentration should be monitored and included in decision-making regarding fluid therapy in the postoperative period with the aim to stabilize hemodynamic parameters, maintain diuresis and improve metabolic hemostasis [34, 35].

In the postoperative period, methods based on techniques that assess the diameter of the inferior vena cava, its collapsibility, extensibility and the Doppler spectrum of the portal vein and hepatic veins can be used to guide fluid therapy [36, 37]. To date, there are no reports on the effectiveness of these methods in liver surgery.

There are no data concerning the impact of the applied fluid strategy on early and long-term prognosis in resections performed for oncological reasons. Restrictive and goal-oriented therapy facilitates visualization in the operating field, which may improve the radicality of the procedure. No studies have investigated the relation between the type of perioperative fluid regimen used as regards tumor recurrence risk. Further research in this direction is warranted.

### Laparoscopic techniques

Laparoscopic liver resections have been gaining popularity. There are no randomized prospective studies comparing different strategies (liberal, restrictive and goal-directed) in resections performed laparoscopically. Nevertheless, in the published trials, the technique of maintaining low central venous pressure in the transection phase was adopted as a standard, with the aim of reducing bleeding. However, low central venous pressure together with increased intra-abdominal pressure increases the risk of gas embolism (carbon dioxide) [38, 39]. It seems prudent to use SVV rather than CVP monitoring as an indicator of vascular bed filling and use it as a guide to fluid therapy during the transection phase. In laparoscopic procedures, central venous pressure is notoriously unreliable due to the influence of the pneumoperitoneum on the inferior vena cava pressure [40, 41].

### Challenges in cirrhosis

Data on fluid therapy in extensive resections in patients with cirrhosis is lacking. Published trials describe anesthesia complexity in this population, including strategies of fluid therapy [42, 43]. Taking into account the detailed data on the multi-organ consequences of cirrhosis and liver failure, it can be assumed that goal-directed therapy should be adopted.

Depending on the severity of cirrhosis and abnormal liver function (assessed according to the MELD or Child–Pugh scale), organ dysfunctions will vary, e.g. the presence of hepatorenal syndrome or the severity of hyperkinetic circulation with a relative or absolute intravascular volume deficit. Portal hypertension with collateral circulation, independently of other causes of coagulopathies, may increase the risk of bleeding at the stage of abdominal cavity incision. Multifactorial coagulopathy complicates anesthesia management. Vigilance over blood loss is essential with thresholds for red blood cells, platelets and plasma transfusions to maintain homeostasis. Fluid strategy, other than goal-directed, may exacerbate pathologies present in cirrhosis. The restrictive strategy may lead to hypoperfusion of vital organs, including the liver, intestines and kidneys, and as a result, lead to their failure. The liberal strategy, in addition to preexisting hypoalbuminemia, may lead to edema of the liver and the intestinal wall. Removal of the excess fluid may prove difficult, and, in some cases, impossible without implementing renal replacement therapy.

Performing major abdominal surgeries in patients with hepatic insufficiency, requires balancing the risk of exacerbation

of liver failure and its organ consequences with expected benefits. Mortality in cirrhotic patients decreased due to advances in surgical techniques, anesthesia and postoperative care. In group C according to the Child–Pugh scale, it is expected to be 12%, in comparison to previous years, when it was estimated at 82% [44, 45]. However, these estimates do not refer to hepatic surgeries. Scheduled liver resections in C group are contraindicated.

### Types of fluids

An increase in lactate concentration in patients undergoing liver resection is a common phenomenon. This is due to impaired lactate liver clearance but can also be caused by increased anaerobic metabolism associated with maintaining low central venous pressure and subsequent organ hypoperfusion. It is widely accepted to use balanced crystalloid solutions. A study by Weinberg et al. showed that acetate buffered crystalloids are recommended. Better biochemical and hematological indices are obtained in terms of electrolyte balance, acid-base balance and coagulation parameters compared to solutions buffered with lactates [46]. Data on the safety of hydroxyethyl starch solutions are conflicting and mainly drawn from studies of intensive care patients. However, most authors indicate a potentially higher risk of acute kidney injury and coagulation disorders in patients receiving these solutions [47–49]. No definitive conclusions can be drawn on gelatin solution use. Conclusive data from randomized trials is lacking. Acute kidney injury, coagulation disorders and remnant failure may complicate liver resection. Thus, in the author's opinion, the use of the above-mentioned solutions should not be encouraged during liver resection and in the postoperative period. Postoperative fluid therapy in patients undergoing laparoscopic liver resections does not differ significantly from what has been discussed previously. This technique results in fewer complications, faster recovery of gastrointestinal function, which encourages earlier oral fluid intake and a shorter hospital stay. The published results of studies on the safety of using albumin solutions cover mainly critically ill patients and patients undergoing abdominal surgery, not specifically liver resection [50, 51]. Although there are no studies on this group of patients, being aware of the possibility of liver failure after the procedure (sometimes before) and the physiological role of albumin i.e. in maintaining oncotic pressure, preventing the occurrence of edema, it can be assumed that their administration both intra- and postoperatively is beneficial – especially when large volumes of crystalloids would have to be used otherwise.

### Conclusions

Fluid transfusion in the perioperative period in major liver resections is a complex topic. The chosen fluid strategy has an impact on morbidity and the length of hospital stay. It is of the utmost importance to detect features of cirrhosis

and its complications which may largely determine the type of strategy adopted. In extensive liver resections without cirrhosis, restrictive fluid therapy is most often used. During liver resection in cirrhotic livers, goal-directed therapy is preferred. It should be emphasized that only close cooperation between the surgeon and the anesthesiologist during the procedure enables the rational implementation of the adopted strategy, depending on the progress of surgery and clinical situation. The type of fluid is equally as important as the volume. The use of balanced crystalloid solutions is recommended with the exception of lactate-buffered solutions. In cirrhotic liver resection, it is important to maintain an adequate concentration of albumin in the serum, which is justified by the pathophysiology of cirrhosis and its consequences.

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