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Are there any benefits to the use of renal replacement therapy during liver transplantation: a narrative review

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Abstract

Background: **Renal dysfunction is a common co-morbidity in patients needing liver transplantation. This may contribute to the intraoperative challenges due to an increased risk of severe electrolyte disturbances, of metabolic acidosis, of fluid overload and perhaps of cerebral edema. It has been suggested that intraoperative continuous renal replacement therapy reduces the incidence of the problems and some centers, therefore, use it intraoperatively.**
Methods: **Narrative literature review. We searched the Medline and Embase database for literature between 2008 and 2021 using the following search terms: (liver transplantation OR liver transplant) AND (renal replacement therapy OR renal support OR hemodialysis). Results: In total, we obtained 10 publications, of which 9 were retrospective and 1 was a randomized controlled trial.**
Conclusions: **Studies showed that intraoperative renal replacement therapy is feasible and safe. It may help to maintain electrolyte and acid-base balance and volume homeostasis. It has not been demonstrated that this leads to less perioperative complications or better short- and long-term outcomes regarding patient and graft survival. Unfortunately, most studies are retrospective, without matched control groups. Prospective randomized trials would be useful to identify patients whose outcome can be improved by the possible benefits of intraoperative RRT during liver transplantation.**

MeSH terms: **Continuous Renal Replacement Therapy, Liver Transplantation.**

Introduction

Liver transplantation (LT) is a lengthy and complex procedure, with a great risk of major complications such as significant hemodynamic instability, coagulopathy and metabolic disturbances[1].

Renal dysfunction (acute kidney injury, chronic kidney disease or acute on chronic kidney disease) is common in patients with liver disease, with an estimated prevalence in liver transplant candidates of 20 - 30%[2]. Although it is possible that the renal and liver failure result from a common pathologic mechanism, most frequently the renal failure develops gradually as a consequence of the hepatic pathology. This is most frequently seen in advances cirrhotic disease but can also be seen as a result of acute liver failure. The pathophysiology is complex but involves a few mechanisms. First there is a reduced renal blood flow. This comes from either a reduction in circulating blood volume or a possible selective increase in renal vascular resistance. Second, an increase in renal tubular sodium reabsorption, which can be a physiologic response to the reduced renal blood flow or an independent response triggered by neural or humoral signals from hepatic origin.

Last, in the advanced stages of liver failure, ischemia, nephrotoxic agents and inflammatory mediators can cause direct impairment of the renal tubular function. Depending on the dominant feature and the severity of the renal dysfunction, the clinical presentation can range from subclinical renal hypoperfusion to several forms of acute renal failure, including hepatorenal syndrome[3].

A preoperatively impaired kidney function may contribute to the intraoperative challenges due to an increased risk of severe electrolyte disturbances, of metabolic acidosis, of fluid overload and perhaps of cerebral edema. It has been suggested that intraoperative renal replacement therapy (RRT)

reduces the incidence of these problems. This can be under the form of continuous renal replacement therapy or hemodialysis.

In addition, liver transplant recipients have a rather high risk of developing postoperative renal dysfunction. Kidney failure after liver transplantation increases postoperative morbidity and mortality[4,5].

Therefore, in some centers, renal replacement therapy (RRT) is used intraoperatively to prevent or attenuate the possible problems associated with preexisting renal dysfunction[6]. However, there are no uniform guidelines regarding this practice.

In this narrative review of the literature, we attempt to clarify to the following questions:

- What are the indications for CRRT during liver transplantation?
- What are the benefits of intraoperative CRRT during liver transplantation?
- What are the disadvantages and complications of intraoperative CRRT during liver transplantation?

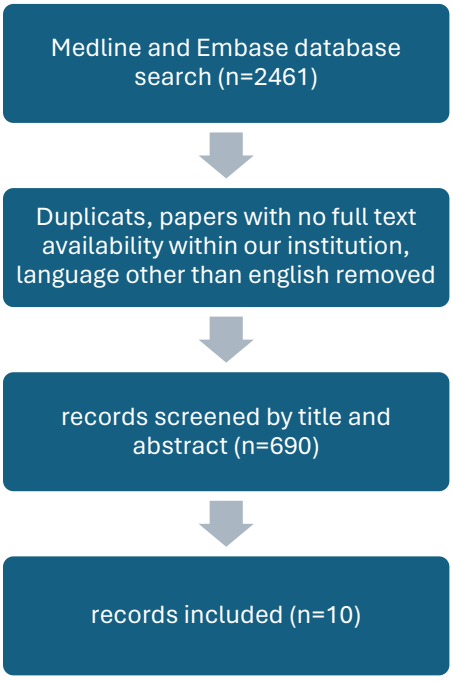
Methods

We performed a literature search on the use of intraoperative RRT during liver transplantation. We searched the Medline and Embase database for literature between 2008 and 2021 using the following search terms: (liver transplantation OR liver transplant) AND (renal replacement therapy OR renal support OR hemodialysis).

This search identified 2461 articles. Based on the abstracts, duplicates were eliminated, as well as papers with no full-text availability within our institution and a language other than English. In total we came up with 690 results. These were filtered manually to select papers on the benefits, indications, feasibility, and adverse effects of the intraoperative use of RRT.

In total we obtained 10 studies (Table I).

Table I.



Results

We retained 10 publications, of which 9 were retrospective and 1 was a randomized controlled trial (Table II).

In a small randomized, open-label, controlled pilot trial, Karvellas et al. included 32 patients undergoing liver transplantation with MELD ≥ 25 and preoperative acute kidney failure (RIFLE category RISK or higher) and/or glomerular filtration rate < 60 mL.min-1.1.73 m-2[7]. They compared the use of intra-operative CRRT with standard of care to evaluate the feasibility and safety of intraoperative CRRT. There were no significant differences in perioperative complications or 1-year survival rates. There were a few access-related issues, but no filter clotting or no other complications related to intraoperative RRT[7].

Townsend et al. performed a retrospective descriptive study assessing the logistical feasibility and clinical safety of intraoperative CRRT during liver transplantation[8]. They reviewed 636 liver recipients over a 10 year period, of which 41 (6,4%) were treated with intraoperative RRT. All patients had acute kidney injury, with 63,3% on preoperative RRT. Most patients were critically ill with a high rate of high MELD, ICU admission, and vasopressor dependency. The decision to use intraoperative CRRT was made by the transplant team and based on preoperative kidney function, severity of illness, concern for poor tolerance of intraoperative management and/or an anticipated need for postoperative RRT. A vast majority (92.7%) of patients with intraoperative RRT had a zero or negative intraoperative fluid balance. At 1 year postoperatively, 100 % of survivors (75.6 % 1-year survivors) were independent of RRT, although most had chronic kidney disease. Filter clotting occurred in 40 % of patients (the vast majority received no anticoagulation) and these patients received significantly more platelets. There were no other complications related to CRRT. The authors concluded that CRRT during OLT is logistically feasible and safe[8].

In a retrospective matched cohort study Parmar et al. compared 36 patients receiving intraoperative RRT with 36 controls matched for age, gender and MELD[9]. The decision to use intraoperative CRRT was made preoperatively by the multidisciplinary

Table II.

Reference	*Design*	*n*	*Strengths*	*Limitations*
Karvellas et al.	Randomized controlled trial	32		- Inability to balance illness severity between cases and controls - Single center trial - Trial stopped prior to enrolment of the intended target - Possible institutional bias towards preferential use of intraoperative RRT
Townsend et al.	Retrospective cohort study	41		- Single center, small and retrospective - no control group
Parmar et al.	Retrospective matched cohort study	72		- single center, small and retrospective - limited statistical power - prone to type I error - Inability to balance illness severity between cases and controls
Nadim et al.	Retrospective study	238	- Largest to ever demonstrate the feasibility and safety of RRT in critically ill patients	- Single center retrospective - Not possible to determine a control group with similar severity of illness
Agopian et al.	Retrospective study	99	- Development of a practical risk score to identify recipients who will benefit from intraoperative RRT	- Retrospective - Large experience in center
LaMattina et al.	Retrospective study	21		- Retrospective, single center - Small cohort
Zimmerman et al.	Retrospective study	30		- Small, single center, retrospective
Baek et al.	Retrospective study	240		- Retrospective, single center - Non-optimal method of calculating the estimate GFR in cirrhotic patients - Not able to find a cut-off value for GFR to maximize the efficacy of intraoperative RRT
Safwan et al.	Retrospective study	142		- Retrospective, small, single center

transplant team, based on preoperative kidney function, severity of illness, concern for poor tolerance of intraoperative management without the use of RRT and/or an anticipated need for postoperative RRT. In spite of the attempt to match controls for MELD score, patients receiving intraoperative CRRT were generally sicker, with a significantly higher MELD score, a significantly higher incidence of acute kidney injury and RRT, a significantly greater need for vasoactive drugs and a significantly longer preoperative hospitalization time than the control group. Intraoperatively, patients with intraoperative CRRT had significantly smaller changes in serum sodium levels than controls, while all other acid/base and metabolic parameters were similar for both groups. Postoperatively, patients in the intraoperative CRRT group required a longer time of mechanical ventilation and of ICU and hospital stay. There were no significant differences between groups in complication rates, ICU re-admission rates or hospital mortality[9].

Nadim et al. retrospectively looked at the feasibility, safety and clinical outcomes of patients with a high MELD score receiving intraoperative hemodialysis (IOHD) during isolated OLT or combined liver-kidney transplantation. 10 Over a 10-year period 737 liver transplantations were performed in adults and 238 patients received continuous IOHD (155 single liver and 83 liver-kidney recipients). The decision to use intraoperative RRT was made multidisciplinary, based on the degree of renal dysfunction (creatinine > 2.0 mg/dL or on RRT), a low urine output, severity of illness and an expected difficult intraoperative management. A majority (80 %) of patients was treated with RRT at the time of transplantation, with 54 % receiving CRRT preoperatively. The mean MELD score was 37. Intraoperatively, there were no IOHD related adverse events, electrolytes were stable and at the end of surgery the vast majority of patients had a negative or zero fluid balance. At 90 days postoperatively, almost all survivors were free of dialysis (99 % of single liver recipients and 100% of liver-kidney recipients)[10].

Agopian et al. retrospectively examined prospectively collected data from 500 consecutive patients receiving single-pass hemodialysis or CRRT before liver transplantation[11]. Three subsets of patients were identified: no intraoperative RRT (IORRT) (n= 401), planned IORRT (n=70), and unanticipated emergent IORRT (n=29). The decision for planned IORRT was based on institutional consensus guidelines including the following preoperative parameters: serum potassium, acid/base status, and the need for either CRRT or vasopressors to maintain systemic arterial pressure. Reasons to start emergent IORRT were significant hyperkalemia with corresponding electrocardiographic changes or severe acidosis refractory to medical treatment and consequently hemodynamic instability with

resistance to vasopressors. Compared with both the planned IORRT and the no-IORRT group, the emergent IORRT group had significantly greater frequencies of post-reperfusion syndrome, intraoperative arrhythmias, coagulopathy requiring abdominal packing and overall complications. There were no significant differences between the planned IORRT and the no-IORRT regarding adverse intraoperative and postoperative outcomes besides more coagulopathy and longer posttransplant ICU and hospital stay in the planned IORRT group. There were no complications associated with the IORRT, except for 1 case of clotting of the dialysis circuit (without adverse consequences).

The authors developed a risk score to accurately identify patients who might benefit from IORRT[11]. Independent pretransplant predictors of the need for IORTT in patients with end-stage liver disease (excluding acute liver failure) and preoperatively on RRT were a liver from a DCD donor, retransplantation, pretransplant potassium, pretransplant vasopressors, pretransplant continuous RRT, cold ischemia time, pretransplant bilirubin, and receptor BMI[11].

La Mattina et al. retrospectively reviewed 21 liver transplant recipients with new-onset renal failure requiring preoperative RRT[12]. Fourteen patients received intraoperative CRRT. The decision to use intraoperative CRRT was made multidisciplinary, based on preoperative factors such as oliguria, hyperkalemia, or perceived bleeding risk, in addition to the new-onset renal failure. Preoperative potassium and sodium were significantly higher in the intraoperative CRRT group, but still within normal range. Preoperative lactate was significantly higher in the CRRT group. There were no statistically significant differences in blood product transfusion in the first 24 hours postoperatively, nor in the length of ICU stay or total length of hospitalization. Short-term survival rates were not significantly different between groups. One year survival rates were respectively 86% for patients receiving intraoperative CRRT and 71% for patients not receiving intraoperative CRRT, but this difference was not statistically significant.

There were no complications related to the use of CRRT in the perioperative period[12].

Zimmerman et al. retrospectively examined the safety and the impact on 1-year survival of intraoperative CRRT (veno-venous hemodiafiltration or hemodialysis) during liver or liver-kidney transplantation[13]. They identified 3 groups in a cohort of 96 patients: patients with pretransplant renal dysfunction and IORRT (Group I, n= 30), patients with pretransplant renal dysfunction but without IORRT (Group II, n= 9) and patients without evidence of preoperative impaired renal function (Group III, n= 57). Renal dysfunction was defined as patients receiving preoperative RRT and/or with chronic kidney disease qualifying them for combined liver-kidney transplantation. The decision to use IORRT was based on institutional multidisciplinary developed guidelines. IORRT was used in patients with renal dysfunction and at least one of the following: urgent pretransplant RRT (due to severe acid/base derangement, electrolyte abnormalities, or significant fluid disturbances), creatinine > 2.0 mg/dL, oliguria or anuria, high acuity of illness (based on MELD, pretransplant ICU management, and 2 or more vasopressors), and the anticipated need for the intraoperative transfusion of large volumes of blood products (> 8 units due to an INR > 3, platelet count < 30000/μL, fibrinogen < 100 mg/dL). Although MELD score was significantly higher in both groups with renal dysfunction than in Group III, there was no significant difference in 1-year survival between Group I and Group III (78 % vs 88 % respectively). There was also no significant difference in patient survival between the 3 groups at a median follow-up of 17.7 months[13].

Baek et al. retrospectively reviewed 240 liver transplantation patients with preoperative renal dysfunction (GFR < 60 mL.min-1.1.73 m-2), comparing those receiving intraoperative CRRT (n= 142) and those not treated with CRRT intraoperatively (n= 98)[14].Patients on chronic hemodialysis were excluded. The decision to use intraoperative CRRT was made by a nephrologist with input from the transplant team. Indications were medically refractory hyperkalemia, acidosis, and oliguria. All patients preoperatively treated with RRT (n= 66) received intraoperative CRRT, with the exception of 1 patient. Patients in the intraoperative CRRT group were generally sicker (higher MELD and more severe co-morbidity).

Intraoperatively, the maximum serum potassium concentrations and the frequency of hyperkalemia (potassium > 5.5 mmol/L) were not significantly different between groups. The CRRT group had significantly less large changes in sodium concentration during surgery. There were no significant differences between groups for perioperative body weight change (increase or decrease), although perioperative increased body weight was significantly less prevalent in the intraoperative CRRT group. The duration of postoperative RRT (38.0 vs 9.3 days), the duration of mechanical ventilation (9.7 vs 4.6 days), the duration of ICU stay (54.9 vs 30.7 days) and the total length of hospital stay (86.0 vs 61.0 days) were significantly longer in the group who received intraoperative CRRT. Outcomes for patient survival, graft survival,

recovery of renal function, neurological function and postoperative complications were significantly worse for the intraoperative CRRT group[14].

Safwan et al. retrospectively compared data from 3 groups of patients with pretransplant renal failure or renal dysfunction (glomerular filtration rate <30ml/min): patients who were on RRT before the transplantation and received intraoperative CRRT (elective RRT) (n= 70), patients identified with acute renal failure immediately before transplantation and managed with intraoperative CRRT (urgent RRT) (n= 15), and patients identified with acute renal failure immediately before transplantation but managed without intraoperative RRT (no RRT) (n= 57)[15]. For the latter two groups (patients with renal dysfunction identified immediately before transplantation) the decision to use intraoperative RRT was made multidisciplinary. Intraoperative mean values for electrolytes and acidosis were similar for the 3 groups. Nevertheless, in the group not managed with intraoperative RRT, 10 out of 57 patients had significant intraoperative metabolic disturbances (potassium > 6 mmol/L and/or pH < 7.2) and 1 of these patients died intraoperatively post-reperfusion with very high potassium values and severe acidosis. Early graft dysfunction was significantly higher, and length of hospital stay was significantly longer in the group receiving urgent RRT than in both other groups. In the elective CRRT group the rate of postoperative RRT was significantly higher than in the other groups, but there were no differences in renal function at 3 months, 6 months and 1 year post transplantation. Graft and patient survival at 1 year were lower in the elective RRT group, but the differences were not statistically significant[15].

Koscielska et al. performed a retrospective study of 102 liver transplantation patients treated with intraoperative hemodialysis (ioHD)[16].The decision to use ioHD was made cooperatively by the surgeon, anesthesiologist and nephrologist, based on the degree of renal failure and severity of illness.

There were no unified biochemical markers to make the decision and ioHD was not always initiated at the start of the surgery.

Because of the heterogeneity of the study population, patients were allocated to one of three groups: group 1 consisted of patients with a preoperative serum creatinine of < 2 mg/dl (n=22), group 2 included patients with a preoperative serum creatinine of ≥ 2 mg/dl (n= 73), and group 3 contained patients receiving a simultaneous liver-kidney transplant (n= 7). Patients in group 1 were less acutely ill and generally needed ioHD because of unexpected severe intraoperative metabolic problems. Consequently, intraoperative dialysis was started later and was of shorter duration in group 1 than in group 2. In all groups, post-reperfusion potassium levels were < 4 mmol/L and central venous pressure was decreased. Significant differences between group 1 and 2 regarding postoperative renal function and several graft function parameters were observed. There were no differences for ICU length of stay. Overall, in-hospital mortality was 34.3 %, with no differences between groups. Dialysis circuit clotting occurred in 7 patients[16].

Discussion

Liver transplantation is a complex procedure, often performed in critically ill patients with multiple co-morbidities. Intraoperatively there is a risk of severe acid/base derangements, electrolyte disturbances (hyperkalemia, major sodium fluctuations), large fluid shifts and transfusion requirements, and hemodynamic instability. Liver recipients with renal dysfunction or renal failure have a risk for severe hyperkalemia, metabolic acidosis, and hypervolemia. In addition, acute kidney injury, particularly in patients on RRT, is associated with a significantly worse outcome and higher mortality after liver transplantation[2]. It has been suggested that continuous intraoperative renal replacement therapy reduces the risk of severe electrolyte fluctuations, acid/base disturbances, fluid overload, cerebral edema, and ischemic reperfusion injury, and therefore might improve outcome in severely ill patients.

The use of intraoperative CRRT has become more frequent since the early 1990s. Some centers use intraoperative CRRT on a large-scale during liver transplantation, for example in every patient with preoperative renal dysfunction or preoperatively treated with RRT, while other centers are more selective.

Regarding the indications for the use of RRT during liver transplantation, preoperative factors contributing to the decision to use intraoperative CRRT are generally associated with acuity of illness: MELD score, refractory hyperkalemia and metabolic acidosis, preoperative ICU management, vasopressor need, and a concern for poor tolerance of the procedure[8-10,12-14]. Other reasons to use intraoperative RRT are a perceived risk of major bleeding with transfusion of large volumes of blood products, and the anticipated need for postoperative RRT[8,9]. Generally, the preoperative decision to use intraoperative CRRT is made multidisciplinary. While most patients have renal dysfunction or renal failure and/or are severely ill, the use of intraoperative CRRT is often based on parameters which vary between centers and are

not always clearly or uniformly defined. There is only one publication proposing a practical score to help identify patients on preoperative RRT who are likely to benefit from intraoperative RRT[11]. For patients with end-stage liver disease Agopian et al. identified a DCD donor liver, retransplantation, pretransplantation potassium, pretransplantation vasopressors, pretransplantation CRRT, cold ischemia time, pretransplantation serum bilirubin and receptor body mass index as independent predictors of the need for intraoperative RRT[11]. This practical score has not been validated in a prospective trial.

Several purported benefits associated with the use of intraoperative RRT may theoretically have a beneficial effect on the perioperative course of liver transplantation[9].

Acid-base imbalances and electrolyte disturbances, such as hyperkalemia, frequently occur during liver transplantation and may contribute to life-threatening arrhythmias and hemodynamic instability, during the reperfusion phase. Judicious management of intraoperative CRRT can help to maintain potassium levels and acid-base status within the normal and safe range. In the studies we evaluated, patients receiving intraoperative CRRT generally had potassium levels within normal limits and no significant metabolic acidosis [6,10,11]. On the other hand, in a few studies there was no significant difference in potassium levels and acid-base status between patients treated with intraoperative RRT and patients without intraoperative RRT[9,14]. Agopian et al. concluded that, in patients treated with RRT before liver transplantation, emergent unplanned intraoperative RRT for reasons such as severe hyperkalemia with electrocardiographic changes or refractory acidosis with hemodynamic instability, was associated with more intraoperative complications and a worse postoperative outcome compared to planned or no intraoperative RRT[11]. While CRRT can help control electrolyte and acid-base disturbances during liver transplantation in patients with renal dysfunction, it has not been demonstrated that it is necessary to avoid severe acidosis or hyperkalemia, and there are other management strategies to successfully avoid these problems (5). Nevertheless, intraoperative RRT can be indicated in an emergency situation such as life-threatening arrhythmias and severe hemodynamic instability caused by intractable hyperkalemia and/or metabolic acidosis.

Another concern regarding electrolyte disturbances during liver transplantation are rapid shifts in sodium concentration[17]. Patients with end-stage liver disease often have severe hyponatremia and a too rapid increase in serum sodium concentration can cause central pontine myelinolysis, a rare but severe complication possibly causing permanent neurological damage. A few papers show that intraoperative changes of serum sodium concentration are smaller in patients treated with intraoperative RRT[9,14]. However, the incidence of central pontine myelinolysis is low and other factors can cause this complication in transplant liver recipients. Therefore, it is not possible to assess the clinical effect of intraoperative RRT on the risk of central pontine myelinolysis.

Intraoperative RRT, with the possibility of fluid extraction, allows good fluid management and prevention of excessive volume overload. A few authors describe a zero or negative intraoperative cumulative fluid balance in patients receiving intraoperative RRT[8,10]. Baek et al. demonstrated a lower incidence of volume overload in patients treated with intraoperative RRT in comparison with no RRT.

Although intraoperative RRT can be helpful to prevent severe hyperkalemia, metabolic acidosis, a too rapid correction of hyponatremia and excessive fluid overload, it has not been shown that this results in fewer complications or better short- or long-term outcomes after liver transplantation. Most publications show no difference in perioperative complications between patients treated or not treated with intraoperative RRT[12,13]. Also, outcome parameters such as ICU length of stay, ICU readmission, hospital length of stay, and short- and long-term graft and patient survival generally are similar for patients receiving or not receiving intraoperative RRT[7,12,13]. Nevertheless, there are a few reports of longer postoperative ICU and hospital length of stay, and even worse long-term outcomes in patients treated with intraoperative RRT[9,10,14,15]. Patients selected for intraoperative RRT generally have a higher acuity of illness, and it has been argued that intraoperative RRT makes it possible to achieve similar outcomes as in patients who are less severely ill and receive no intraoperative RRT. REFs At present, there are no good data to support this hypothesis since almost all studies are retrospective, most are descriptive without a control group, and often the number of patients included is small.

Despite the possible benefits of intraoperative RRT, there are also disadvantages and risks associated with RRT: complications related to the placement of a large-bore central line (bleeding, vascular injury, pneumothorax, thrombus, infection), filter clotting and circuit loss, air embolism, additional personnel to operate the RRT circuit, additional cost.

Some of the main concerns are the risks associated with exposure to an extracorporeal circuit, such as filter or circuit clotting, while the use of systemic

anticoagulation raises concerns for major bleeding complications during the surgery[18]. Most data show an acceptable filter lifespan without the use of systemic anticoagulation during intraoperative RRT[8,9]. The reported incidences of filter/circuit clotting vary widely between centers, from 0 to 40 %, but generally the incidence is low, and the filter can be replaced without adverse consequences[7,8,10-12,14].

Except for occasional filter or circuit clotting, other complications of RRT do not occur very often. There are a few reports of access related issues[7,14], but this appears to be rare. On the other hand, patients preoperatively treated with RRT had their dialysis catheters placed before surgery and complications related to catheter insertion are not known. Most papers report no other complications[10-12].

Karvellas et al. executed a small pilot randomized-controlled trial regarding the safety and feasibility of the use of intraoperative RRT. There were no episodes of filter clotting (without anticoagulation) or other adverse events related to the insertion of a dialysis catheter and intraoperative RRT. In this study, perioperative complications, graft related complications, short- and long-term renal function and 1 year survival rates were similar for patients treated with intraoperative RRT or standard of care[7].

Disadvantages of intraoperative RRT are the need for extra qualified personnel to manage the RRT and the additional costs of materials and personnel. In times of personnel shortages, not every center can provide qualified personnel at all times. At present there are no data demonstrating that the extra financial cost of materials and qualified personnel for intraoperative RRT is offset by a better graft and patient outcome.

Conclusions

At this moment there are no set indications for the use of intraoperative RRT. Most indications are related to the acuity of illness and are center-specific. Regarding the possible benefits, several studies show that intraoperative RRT may help to maintain electrolyte and acid-base balance and volume homeostasis. It has not been demonstrated that this leads to less perioperative complications or better short- and long-term outcomes regarding patient and graft survival.

To date, several studies show that intra-operative RRT during liver transplantation is feasible and safe and may help to maintain electrolyte and acid-base balance and volume homeostasis.

Unfortunately, most studies are retrospective without matched control groups. Prospective randomized trials would be useful to identify patients whose outcome can be improved by the possible benefits of intraoperative RRT during liver transplantation.

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