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REVIEW

Perioperative fluid management in renal transplantation: a narrative review of the literature

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Summary

Adequate volume maintenance is essential to prevent acute renal failure during major surgery or to ensure graft function after renal transplantation. The various recommendations on the optimum fluid therapy are based, at best, on sparse evidence only from observational studies. This article reviews the literature on perioperative fluid management in renal transplantation. Crystalloid solutions not exerting any specific side-effects are the first choice for volume replacement in kidney transplantation. The use of colloids should be restricted to patients with severe intravascular volume deficits necessitating high volume restoration. The routine application of albumin, dopamine, and high dose diuretics is no longer warranted. Mannitol given immediately before removal of the vessel clamps reduces the requirement of post-transplant dialysis, but has no effects on graft function in the long term. There is insufficient evidence on the best use of dialysis, but it seems peritoneal dialysis pretransplant is associated with less delayed graft function, whereas the preference of dialysis post-transplant is not yet well-founded. This review article should provide better guidance for fluid management in kidney transplantation until best-evidence guidelines can be established based upon more research.

Introduction

Delayed graft function (DGF), a term interchangeably used for acute renal failure (ARF) after transplantation, exerts an enduring and powerful effect on the subsequent clinical course after kidney transplantation [1]. DGF is grossly defined by the need for dialysis in the first week post-transplant. It may be considered as the result of an accumulation of various deleterious factors for the kidney graft. Donor related characteristics such as age, tissue quality, and brain death play a key role in transplant success. Factors related to procurement, cold storage, and reperfusion injury are crucial for the early performance of the graft and affect its long-term functioning [2–5]. Variables related to the recipients, including prerenal causes, immunosuppressive drugs, human leukocyte antigen-matching and sensitization have an impact on the risk of DGF. It is well recognized that DGF enhances the susceptibility for rejection [6–8]. The complex interrelationship of DGF and allograft immunogenicity has been summarized elsewhere [9].

Implementing an intervention before the damage has occurred is the best way to attenuate DGF. Fluid therapy has been shown to be effective for preventing ARF in certain clinical scenarios. However, in acute tubular necrosis (ATN), only supportive care has been shown to be efficacious. In kidney transplantation, partially self-contained modalities for perioperative fluid management have been developed in recent decades. These therapies must be evaluated on the basis of evidence from more recent clinical data, in regards to their efficacy, potential side-effects and patient outcomes. In this article, we review the available literature on fluid management in renal transplantation. PubMed was searched using the key-terms 'renal transplantation', 'fluid therapy', 'fluid management', 'crystalloids', 'colloids', 'albumin', 'mannitol', 'dopamine', 'dialysis', 'acute renal failure', and 'delayed graft function'.

Avoidance of hypovolemia

On points where there is insufficient evidence specifically on kidney transplantation, comparable studies on fluid management in the critically ill and in patients undergoing major surgery are reviewed. Perioperative fluid management must ensure the restoration and maintenance of the intravascular volume, in order to obtain an appropriate graft function. In experimental animal models of ischemic ATN, renal perfusion is linearly dependent on the mean arterial pressure, even in the normal blood pressure range. Paradoxical renal vasoconstriction occurs at a low mean arterial pressure [10,11]. In transplantation, denervation adds to a deteriorated hemodynamic autoregulation of the kidney graft [12–15]. Thus, mild or severe decreases in blood pressure can further reduce renal perfusion and thereby result in repeat ischemia to the transplanted kidneys. Under physiologic conditions, the intravascular volume is tightly regulated by various mechanisms, including the transmembrane filtration pressure, interstitial hydrostatic pressure, colloid osmotic pressure, lymphatic transport, sympathoadrenergic system, and renin-angiotensin system [16,17]. Severe intravascular volume deficiency can overextend the compensatory capacity of the effector mechanisms. Consequently, maldistribution of the nutritional blood flow and tissue hypoxemia may occur [18–22]. Rectification of intravascular volume deficiencies is therefore essential to obtain an adequate systemic circulation and microcirculation [23,24]. Ensuring adequate volume status must be part of any treatment strategy.

In general, any volume replacement is better than none in the hypovolemic state, and an appropriate volume amount is probably more important than the kind of fluid [25,26]. Furthermore, there is only sparse evidence to suggest that the fluid type in patients with risk for ARF should be different from that for other critically ill patients [27]. Crystalloid solutions are usually the first choice to correct for fluid and electrolyte imbalances in these patients [28]. However, in instances of severe hypovolemia colloid solutions may be preferable for obtaining sufficient tissue perfusion, particularly in situations of enhanced capillary permeability [29]. In addition to restoration of the intravascular volume, colloid solutions may ameliorate impaired microcirculation [29–31]. Treatment of intravascular hypovolemia has changed significantly during recent decades. There has been a widespread shift in clinical practice from natural colloids, such as blood, albumin, and fresh-frozen-plasma, over to crystalloids and synthetic colloids, such as hydroxethyl starch (HES), bovine derived gelatin products, and dextrans. These crystalloids and synthetic colloids are now the preferred substitutes for the treatment of hypovolemia. Despite a large number of studies and recommendations from consensus meetings, the optimal type of resuscitation fluid in patients with impending ARF is still not yet well established.

The choice of a particular fluid in a given clinical situation can be guided by an understanding of the solutions' properties, but nonetheless there is still an ongoing debate on the relative merits of crystalloid and colloid solutions. Crystalloid therapy increases the formation of edemas, but colloids have known adverse side effects. There are experimental studies both that support [32,33] and that refute [34] the assertion that tissue oxygen extraction is disabled by the accumulation of interstitial fluid. Evidence from a randomized phase III clinical trial suggests that fluid resuscitation with colloids expedites recovery in the postoperative period after major surgery [35]. Patients assigned to receive Hextend, a physiologically balanced plasma expander for large volume use, had less nausea, vomiting, and severe pain. This was attributed to the lower degree of interstitial fluid accumulation in these patients. Nonetheless, until specific side effects of the colloids cannot be excluded at all, crystalloids probably remain preferable for most situations.

There is no clear evidence to date that the fluid type administered has an influence on mortality. Several randomized controlled trials (RCT) have been conducted comparing colloid and crystalloid fluid therapy in a variety of clinical settings. Of these, only a limited number of large-scale studies have evaluated the effects of the different fluid classes on patient outcomes. The vast majority of the studies were neither designed nor sufficiently powered to investigate mortality as an endpoint. Meta-anlyses found no survival benefit in favor of either treatment. This holds true for both the comparison of crystalloids with any colloid [36,37], as well as for comparisons within the group of the various colloid preparations, including albumin, dextrans, gelatins, and HES [26]. The most recent meta-analysis published by the Cochrane Collaboration [37] involved a total of 7576 patients from randomized and quasi-randomized trials of colloids compared with crystalloids. The pooled estimate of the relative risk was 1.02 (95%CI: 0.93–1.11). Thus, clinicians' main focus should be foremost on maintaining an adequate volume level, and only secondarily on which fluid they use to do it.

Use of crystalloid solutions

Isotonic crystalloid solutions, such as 0.9% saline solution and Ringer's lactate solution, are the first choice for volume restoration and for correcting of imbalances in homeostasis. Unlike plasma expanders, crystalloid solutions have no nephrotoxic or other specific side-effects. Isotonic crystalloid solutions are distributed rapidly into

the interstitial compartment and have a half-life of 20–30 min in the intravascular space. Consequently, the effect on plasma volume expansion is limited and does not exceed 20% of the volume applied [17,23]. To compensate for blood loss, crystalloid solution require a quantity four to five times greater than colloid solutions to exert the same volume effect [28], but crystalloids alone are incapable of restoring microcirculation in cases of severe bleeding [38,39]. Kidney transplantation can usually be performed without the need for plasma expanders, because major blood losses are uncommon during this operation.

Balanced crystalloid solutions are often preferable to saline-based fluids in major surgery. Large-volume administration of 0.9% saline may result in hyperchloremic metabolic acidosis, because of the high chloride load. By contrast, balanced crystalloid solutions are not associated with the same disturbance of the acid-base status and electrolyte status [40–43]. Patients randomly assigned to balanced solutions, when compared with those receiving saline-based fluids, showed less impairment of hemostasis [35] and enhanced gastric perfusion [42]. Renal function may also be better preserved [42]. Balanced crystalloid solutions containing potassium should be avoided though during renal transplantation, because they can aggravate hyperkalemia in instances of impaired graft function. Hyperkalemia may be life threatening and require acute hemodialysis. Thus, clinicians who consider switching to balanced crystalloid solutions in patients with impending graft function must be aware of this complication. Close monitoring of serum electrolytes remains a cornerstone of care for guiding fluid therapy in kidney transplantation.

Use of colloid solution

Natural colloids such as albumin are being widely replaced by synthetic colloids such as dextrans, gelatins, and solutions of hetastarch. Colloids are retained in the intravascular compartment because of their content of macromolecules. The degree of plasma volume expansion exerted by colloids is determined by their concentration, molecular weight, and structure, as well as by the colloid osmotic pressure, metabolism, and elimination rate [17,28]. The rate of loss through the capillary endothelial barrier into the interstitial compartment and through the glomerular basement membrane into the proximal tubule obeys the molecular size and surface charge characteristics. The predominant effect on whole blood viscosity is mediated through simple hemodilution, thereby enhancing blood flow characteristics [44]. However, the semi-synthetic colloids also affect red cell aggregation, which adds to their overall effect on the blood flow characteristics. Furthermore, all of the semi-synthetic colloids may prolong coagulation. HES solutions exert varying effects on clotting characteristics, which depend on the size of the HES molecules and the degree of hydroxethyl substitution [45,46]. Impaired platelet function, a von Willebrand-like syndrome (with reduction in vWF and factor VIIIc), and impaired coagulation as measured by thromb-elastography have been reported to arise during the administration of HES [47–49]. This raises some concern for end stage renal disease (ESRD) patients undergoing kidney transplantation, because they are prone to bleeding complications because of uremic platelet dysfunction [50–52]. Although it is rare, severe and life-threatening anaphylactic reactions have been observed in association with any of the commonly used semi-synthetic colloids and with albumin. The incidence of severe anaphylactic reactions is probably more frequent for gelatins (0.35%) and for dextrans (0.27%) than for albumin (0.10%) or for starches (0.06%) [53]. This needs to be taken into account when balancing the merits for the use of plasma expanders with crystalloid solutions.

Human albumin has been widely used as the 'natural colloid' for the treatment of hypovolemia in critically ill patients in past decades. Albumin administration is costly though and does not provide any outcomes benefits for patients with hypovolemia or hypoalbuminemia [54,55]. In the clinical situation of capillary leakage, the administration of albumin may even expedite edema formation, because of an increased shift of plasma proteins to the interstitial compartment [23,24]. There is currently little evidence that warrants the use of albumin in the ICU setting. A systematic review of human albumin in the critically ill suggested that administration might even be associated with a higher mortality [56]. That review was widely criticized though for the heterogeneity of the studies included. More recent data from the SAFE Study involving 6997 patients in a large multicenter RCT suggested that there was no difference in mortality between patients managed with either 4% albumin or normal saline for fluid resuscitation [57]. Nonetheless the low-cost benefit ratio and associated risks argue against the further use of albumin in general surgery.

Although there is little evidence supporting the use of albumin for hypovolemia or hypoalbuminemia in critically ill patients, several observational studies have been published which suggest that volume expansion with human albumin improves the short-term and long-term outcomes of kidney transplant recipients. In particular, human albumin improves the onset and the extent of the urine volume output post-transplant, the renal function, and the 1-year graft survival rate [58–60]. The largest series, involving 438 recipients of renal transplants from deceased donors, revealed a statistically significant benefit

from the usage of albumin, though mannitol, furosemide, and electrolyte solutions were given concomitantly [60]. Protective properties have also been attributed to the intraoperative administration of mannitol during the vascular phase [61–63]. Apart from the induction of osmotic diuresis, the salutary effect is thought to be mediated through the antioxidant properties of sugar alcohols and chemically related substances [9,64]. Controlled clinical data investigating only the effect of albumin infusions in kidney transplantation are not available, so their use in this setting should proceed with caution until more research is available.

Two of the synthetic colloids that have widely replaced albumin in clinical practise – dextrans and gelatins – do not seem on the whole to be preferable to albumin. A randomized study comparing intraoperative albumin and dextran-40 in renal transplant recipients from a living related donor did not find any difference between the two treatments in regards to urine volume output and serial serum creatinine concentrations, post-transplant [65]. The value of this study may be limited, because with only 17 patients the researches may not have had enough statistical power to detect outcome differences. Dextran solutions have been associated with serious side-effects, such as coagulation disturbances [18,66,67], highly severe hypersensitivity reactions [53,68–70], and the onset of oliguric or anuric renal failure [71–75]. This has led to major concern on their usage for volume expansion in the critically ill and in kidney transplantation. Likewise, gelatin preparations do not fulfill the first-choice requirements in the ICU setting [28]. Gelatins exert a more limited effect on intravascular volume resuscitation, because they contain a high proportion of low-molecular weight components. A colloid fluid regimen confined to gelatin may be less effective for patients with severe volume deficiency [23,76]. To some extent, the absence of dose limitations outweighs the disadvantage of low efficacy for volume expansion [28]. The high potassium and calcium contents of 3.5% urea-cross-linked gelatin renders them inapplicable for ARF and for perioperative care during kidney transplantation [77]. Thus, there is no reason to use dextran or gelatin instead of albumin.

By contrast, the recent trend to using solutions of hetastarch instead of albumin seems generally founded in the evidence. Solutions of hetastarch (HES, hydroxyethyl-starch) are synthesized from natural polymers of amylopectin. The pharmacokinetics of HES depend on the degree of substitution at carbons 2, 3, and 6 in the glucose ring in combination with the molecular weight, because the C2/C6 hydroxyethylation ratio influences their degradation mainly by nonspecific plasma amylases [46,78]. The optimum HES solution combines the lowest *in vivo* molecular weight above the threshold for renal elimination with a low degree of hydroxyethyl substitution [78]. Easily degradable HES solutions, dominated by medium molecular weight, meet these specifications. They are clinically applied for various indications including isovolemic hemodilution, perioperative volume substitution, cardiac surgery, trauma, and sepsis [55,79–85]. They do not have considerable side-effects regarding bleeding complications, the reticuloendothelial system, or renal function, if given below their upper dosage limits. With regard to safety considerations [84], HES solutions with a low to medium *in vivo* molecular weight may offer the best risk to benefit ratio among the available synthetic colloids [28].

There has been some debate about whether HES specifically impairs renal function. An 80% rate of osmotic, nephrosis-like lesions was reported in transplanted kidneys after routine administration of HES 200/0.62 to brain-dead donors [86]. This prompted a prospective randomized trial comparing HES 200/0.62 and gelatin for plasma-volume expansion in brain-dead organ donors. The study found that HES was associated with impaired immediate renal function in kidney transplant recipients, because of a more frequent necessity of hemodialysis and because of significantly higher serum-creatinine concentrations 10 days after transplantation. Furthermore, renal biopsies showed osmotic, nephrosis-like lesions only in the HES treated group, although starch was not found in the vacuoles of the proximal tubular cells [87]. The clinical relevance of these lesions has however been questioned [88], because tubular vacuolizations are not a specific morphological finding and have also been observed in association with dextran, 20% mannitol, and with intravenous immunoglobulin, with and without accompanying ARF [74,89–95]. Considering the pathogenesis of hyperoncotic renal failure [96], it may be hypothesized that all colloids can induce this kind of renal function impairment. In the absence of a direct chemical toxicity, the most likely mechanism for HES-induced renal dysfunction may be swelling and vacuolization of tubular cells and tubular obstruction due to the production of hyperviscous urine. The risk of high plasma colloid osmotic pressure and subsequent renal dysfunction presumably increases with repeated doses of highly concentrated, slowly degradable HES of high molecular weight and high degree of substitution [74,97]. A more recent retrospective study concluded that HES compounds given at a maximum dose of 15 ml/kg/day to organ donors have no detrimental influences on graft function in kidneys preserved in University of Wisconsin (UW) solution or histidin-tryptophan-ketoglutarate (HTK) solution [98].

Treatment with HES needs to be accompanied by sufficient amounts of crystalloid solution. Careful monitoring of kidney function and dose reductions are required in

patients with renal function impairment. Although HES 200/0.5 is considered an effective, safe, and economically attractive colloid solution in the critically ill, a restricted usage has been recommended for kidney transplantation because of the potential of side-effects [28].

Table 1 provides a summary of the key investigations on fluid type in kidney transplantation, as well as in the critically ill or in patients undergoing major surgery.

Mannitol, loop diuretics, and low-dose dopamine

Mannitol is widely used in kidney transplantation, immediately before opening the vascular anastomoses. Mannitol, an inert sugar, confers protection against renal cortical ischemia by expanding the intravascular volume, diminishing the potential of tubular obstruction and increasing tubular flow rate through prevention of water reabsorption in the proximal tubule. Furthermore, mannitol enhances the release of vasodilatory prostaglandins in the kidney [99] and may act as a free radical scavenger [100,101]. Clinical, single-center studies have found salutary effects of mannitol infusions in kidney transplantation [63,102–105]. Some of these studies have been retrospective analyses or have involved only a limited number of patients. Nonetheless, the sparse controlled data available have clearly shown that 250 ml of mannitol 20% given immediately before vessel clamp removal reduces the incidence of ARF, as indicated by a lower requirement of post-transplant dialysis [61,106,107] [Table 2]. However, 3 months after transplantation no difference was found in kidney function compared with patients who did not receive mannitol [61]. The usage of mannitol also has risks, because of the potential to induce rapid intravascular volume expansion, which leads to pulmonary edema. Concomitant hydration is indispensable for the optimal prevention of ARF. Overzealous administration (>200 g/day) may be harmful and can result in hyperoncotic kidney failure [90–92], as mentioned previously. Thus, mannitol should be used before opening the vascular anastomoses but moderately and with accompanying hydration.

Loop diuretics are thought to counteract the increased response of antidiuretic hormone to surgical stress [108]. They exert their pharmacological effect in the ascending loop of Henle. In kidney transplantation, furosemide is commonly given during the vascular anastomosis to stimulate diuresis, although it is unknown whether it actually improves early function or simply enhances the amount of urine production from a functioning kidney [109]. Despite their frequent use, there is no evidence that loop diuretics shorten the duration of ARF, reduce the subsequent requirement for dialysis, or improve outcomes in patients with ARF [110–114] [Table 2]. Loop

Table 1. Overview of studies and key references on types of fluid therapy in kidney transplantation and in critically ill/major surgery.

	Kidney transplantation				Critically ill/major surgery			
Treatment modality	Study design	Parameter of efficacy	Outcome	Reference	Study design	Parameter of efficacy	Outcome	Reference
Colloids versus crystalloids	No data	–	–	–	Meta-analysis of RCTs	Survival	No difference	Choi *et al.* [36]; Roberts *et al.* [37]
					Multi-center RCT	Postoperative recovery	Beneficial effect for colloids	Gan *et al.* [35]
Albumin versus crystalloids	Observational/ uncontrolled retrospective studies	Urine output, renal function, 1 year graft survival	Beneficial effect for albumin	Dawidson *et al.* [58]; Willms *et al.* [59]; Dawidson *et al.* [60]	Meta-analysis of RCTs Large multi-center RCT	Survival	No difference	Roberts *et al.* [37] Finfer *et al.* [57]
Comparison of colloid types	Single-center RCT	Urine volume s-creatinine	No difference	Dawidson *et al.* [65]	Meta-analysis of RCTs	Survival	No difference	Bunn *et al.* [26]

RCT, randomized controlled trial.

Table 2. Overview of studies and key references on mannitol, loop diuretics, and dopamine in kidney transplantation and in critically ill/major surgery.

	Kidney transplantation				Critically ill/major surgery			
Treatment modality	Study design	Parameter of efficacy	Outcome	Reference	Study design	Parameter of efficacy	Outcome	Reference
Use of mannitol	RCT	ARF need for dialysis	Beneficial effect	Weimar *et al.* [61]; Tiggeler *et al.* [106]; Van Valenberg *et al.* [107]	–	–	–	–
Use of loop diuretics	Observational study	Need for dialysis	No effect	Lachance *et al.* [109]	RCT	Recovery from ARF survival	No effect	Shilliday *et al.* [110]; Cantarovich *et al.* [114]
Use of renal dose dopamine	RCT	Need for dialysis	No effect	Grundmann *et al.* [120]; Kadieva *et al.* [122]	RCT	Prevention of ARF	No effect	Marik *et al.* [132]; Bellomo *et al.* [133]; Lassnigg *et al.* [115]
			Beneficial effect	Carmellini *et al.* [121]; Dalton *et al.* [124]*	Meta-analysis of RCTs			Kellum *et al.* [134]; Marik *et al.* [135]

RCT, randomized controlled trial; ARF, acute renal failure.
*Study solely investigating renal hemodynamics and functional parameters.

diuretics in extended dosages may even be harmful for the kidney [115], because they may disturb the protective corticomedullary redistribution of blood flow [116]. Thus, there are no indications for loop diuretics other than the removal of fluid overload that is contributing to organ dysfunction in the lung and heart.

Low-dose dopamine has been administered to increase renal blood flow, in the belief that this protects against renal failure. Studies on the efficacy of dopamine infusion in kidney transplantation are conflicting [117–119]. The majority of them failed to demonstrate any significant effect when dopamine was administered to the recipients following transplantation [120–123]. Low-dose dopamine given in the very early period after transplantation (3–6 h postoperatively) has recently been shown to significantly increase effective renal plasma flow, urine flow rate, creatinine clearance, and total urinary sodium excretion rate [124]. A persistent beneficial effect on kidney function could not be found for donors and recipients receiving dopamine during living donor nephrectomy [125]. Dopamine and chemically related catecholamines given to brain-dead organ donors to stabilize hemodynamics may improve the outcomes regarding acute rejection episodes, initial graft function, and graft survival [126–130]. Additionally, the antioxidant properties of catecholamines and chemically-related substances may protect endothelial cells from preservation injury during prolonged cold storage [131]. Nonetheless, the available evidence does not warrant the routine use of dopamine for perioperative care in kidney transplant recipients or in the critically ill with impending or overt renal failure. Dopamine has been administered in the belief that it reduces the risk of renal failure or ameliorates its severity and duration by increasing renal blood flow, but no clinical protection from this has been found [115,132,133]. It was concluded from meta-analyses that dopamine should not be given for these indications and should be eliminated from routine clinical use, given its potential side-effects [134,135] [Table 2].

Dialysis therapy and fluid overload

There is still an inadequate state of research on dialysis therapy before and after kidney transplantation. Before transplantation surgery, many patients present with a contracted volume, as they have been dialyzed to dry weight. It therefore seems reasonable to restrict fluid removal during preoperative dialysis to a target of 1–2 kg above the former dry weight. A Belgian case–control study [136] and a large American cohort investigation of nearly 23 000 transplant recipients [137] have shown that DGF occurs more frequently in hemodialysis patients than in those on peritoneal dialysis. Although the

causation could not be determined from the data, this finding can be taken as indicating that hypovolemia is a prerenal risk factor for DGF [9].

Post-transplant dialysis is required for transplant patients who develop DGF with oliguria. Hemodialysis is commonly preferred, but clinical criteria for the best use of dialysis after transplantation are not well established. Unlike for patients with acute ARF [138,139], studies investigating the effect of biocompatible dialysis membranes in DGF after transplantation failed to demonstrate any difference regarding the average number of hemodialysis treatment sessions, mean time to recovery, or graft outcomes [140–142] [Table 3]. Peritoneal dialysis can safely be continued in patients formerly on this treatment without major complications or increased frequency of peritonitis. Thus, the preference for hemodialysis post-transplant does not seem founded. Retrospective analyses of the existing clinical data on dialysis therapy after kidney transplantation could quickly illuminate this issue until more controlled prospective studies can be carried out.

Postoperative hyperkalemia and fluid overload are prevalent indications for acute hemodialysis. Overzealous fluid administration may increase the demand on cardiac function, leading to myocardial dysfunction and associated morbidity. A more intense fluid regimen in the critically ill does not reduce mortality [143–145] and even precipitates noncardiogenic pulmonary edema [146,147]. A dose–response relation was observed between complications and increasing intravenous fluid volumes as well as increasing body weight [148]. In a prospective study of 48 consecutive postoperative patients admitted to a surgical ICU, mortality in the patients who gained more than 10% body weight was 31.6% as compared with 10.3% in the group that gained <10% body weight [149]. Elderly patients may have accumulated substantial co-morbidities during their life-time and in association with long-term dialysis [150,151]. They constitute a growing population of the dialysis patients entering the waiting lists for transplantation. Thus in contrast to recommendations from very early studies [58,59,65,152], a zealous fluid replacement regimen is no longer warranted, given the clinical outcomes and changing patient demographics.

Recent studies in gastrointestinal surgery advocate a more restrictive regimen for perioperative fluid administration [153]. A restricted intravenous fluid substitution predisposes the patient to less edema formation of the gut. This may shorten postoperative hypomotility of the bowel and may facilitate the onset of enteric alimentation. The potential for bacterial translocation and development of sepsis is also reduced. Reduced edema may improve tissue oxygenation and wound healing [154].

Table 3. Overview of studies and key references on the amount of volume substitution and renal replacement therapy in kidney transplantation and in critically ill/major surgery.

	Kidney transplantation				Critically ill/major surgery			
Treatment modality	Study design	Parameter of efficacy	Outcome	Reference	Study design	Parameter of efficacy	Outcome	Reference
Use of biocompatible membrane for hemodialysis	RCT	Recovery from DGF	No effect	Valeri *et al.* [140]; Romao *et al.* [141]; Woo *et al.* [142]	RCT	Recovery from ARF survival	Beneficial effect for biocompatible membranes	Hakim *et al.* [138]; Himmelfarb *et al.* [139]
Large volume therapy versus restricted volume therapy	Observational studies	Not well-defined: onset and extent of urine output	Beneficial effect for large volume therapy	Luciani *et al.* [152]; Dawidson *et al.* [58]; Willms *et al.* [59]; Dawidson *et al.* [65]	RCT	Survival	No effect or even adverse effect for large volume therapy	Hayes *et al.* [143]; Gattinoni *et al.* [144]
						Postoperative recovery	Adverse effect for large volume therapy	Lobo *et al.* [157]; Brandstrup *et al.* [148]

RCT, randomized controlled trial; DGF, delayed graft function; ARF, acute renal failure.

Retrospective analyses and prospective controlled clinical studies specifically addressing this issue have shown a clear benefit with regard to reductions of overall complications [148,155–157]. In particular, they have shown fewer pulmonary complications, a faster in-hospital recovery, and a trend towards a reduced perioperative mortality [148] [Table 3]. No deaths occurred in the fluid restricted group of the Danish multicenter RCT, whereas, four patients (4.7%) died in the standard group. The causes of death included pulmonary edema in two patients, pneumonia with septicemia, and pulmonary embolism [148]. Thus, simple clinical measures – such as fluid balance, arterial blood pressure, clinical assessment of peripheral edema, and carefully measured daily body weight – remain the key parameters for the monitoring of fluid therapy in surgery patients and transplant recipients.

Conclusions

Crystalloids without side-effects are the first choice for volume replacement in kidney transplantation. The routine use of various cocktails containing albumin, dopamine, and high dose diuretics is no longer warranted. Overzealous fluid administration should also be avoided, because it can be harmful or deadly. Adequate intravascular volume load should be maintained instead by restricted intravenous fluid substitution.

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