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ORIGINAL ARTICLE

Retrospective Study

Incidence and risk factors for early renal dysfunction after liver transplantation

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Abstract

AIM: To determine renal dysfunction post liver transplantation, its incidence and risk factors in patients from a Belgian University Hospital.

METHODS: Orthotopic liver transplantations performed from January 2006 until September 2012 were retrospectively reviewed (n = 187). Patients with no renal replacement therapy (RRT) before transplantation were classified into four groups according to their highest creatinine plasma level during the first postoperative week. The first group had a peak creatinine level below 12 mg/L, the second group between 12 and 20 mg/L, the third group between 20 and 35 mg/L, and the fourth above 35mg/L. In addition, patients who needed RRT during the first week after transplantation were also classified into the fourth group. Perioperative parameters were recorded as risk factors, namely age, sex, body

mass index (BMI), length of preoperative hospital stay, prior bacterial infection within one month, preoperative ascites, preoperative treatment with β-blocker, angiotensin-converting enzyme inhibitor or non steroidal anti-inflammatory drugs, preoperative creatinine and bilirubin levels, donor status (cardiac death or brain death), postoperative lactate level, need for intraoperative vasopressive drugs, surgical revision, mechanical ventilation for more than 24 h, postoperative bilirubin and transaminase peak levels, postoperative hemoglobin level, amount of perioperative blood transfusions and type of immunosuppression. Univariate and multivariate analysis were performed using logistic ordinal regression method. Post hoc analysis of the hemostatic agent used was also done.

RESULTS: There were 78 patients in group 1 (41.7%), 46 in group 2 (24.6%), 38 in group 3 (20.3%) and 25 in group 4 (13.4%). Twenty patients required RRT: 13 (7%) during the first week after transplantation. Using univariate analysis, the severity of renal dysfunction was correlated with presence of ascites and prior bacterial infection, preoperative bilirubin, urea and creatinine level, need for surgical revision, use of vasopressor, postoperative mechanical ventilation, postoperative bilirubin and urea, aspartate aminotransferase (ASAT), and hemoglobin levels and the need for transfusion. The multivariate analysis showed that BMI (OR = 1.1, P = 0.004), preoperative creatinine level (OR = 11.1, P < 0.0001), use of vasopressor (OR = 3.31, P = 0.0002), maximal postoperative bilirubin level (OR = 1.44, P = 0.044) and minimal postoperative hemoglobin level (OR = 0.059, P = 0.0005) were independent predictors of early post-liver transplantation renal dysfunction. Neither donor status nor ASAT levels had significant impact on early postoperative renal dysfunction in multivariate analysis. Absence of renal dysfunction (group 1) was also predicted by the intraoperative hemostatic agent used, independently of the extent of bleeding and of the preoperative creatinine level.

CONCLUSION: More than half of receivers experienced some degree of early renal dysfunction after liver transplantation. Main predictors were preoperative renal dysfunction, postoperative anemia and vasopressor requirement.

Key words: Liver transplantation; Acute kidney injury incidence; Perioperative complications; Acute kidney injury risk factors; Creatinine/blood; Severity renal failure

Core tip: One hundred and eighty-seven liver transplantations performed between 2006 and 2012 were retrospectively analyzed. Patients were classified into four groups according to their highest creatinine plasma level during the first postoperative week relying on sequential organ failure assessment renal classification. Perioperative parameters were recorded as risk factors. Univariate and multivariate analysis were performed. Fifty-eight percent of recipients experienced some degree of early postoperative renal dysfunction. The multivariate analysis showed that body mass index, preoperative creatinine level, use of vasopressor, hemostatic drug, postoperative bilirubin peak level and postoperative hemoglobin minimum level but not the donor status (cardiac dead or brain dead donor) were independent predictors of post-transplantation early renal dysfunction.

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INTRODUCTION

Renal failure is one of the main complications after orthotopic liver transplantation (OLT), with severe impact on early and long-term outcomes[1]. Renal function could even predict patients' survival before and after liver transplantation[2,3]. The prevalence of acute kidney injury (AKI) after OLT varies from 12% to 70% according to AKI definition[4-7]. Its pathogenesis is multifactorial and includes functional pre-renal hyperazotemia and acute tubular necrosis or apoptosis[4,8]. Highlighting AKI risk factors associated with OLT may help to reduce the prevalence of early renal dysfunction (and improve global outcome) via the development of therapeutic strategies aiming at reducing these risks.

Extensive research has suggested that many preoperative factors may favour the occurrence of AKI after OLT such as preoperative kidney dysfunction and hepatorenal syndrome (HRS), pre-OLT low serum albumin level, hypovolemia, ascites, concomitant chronic diseases leading to kidney injury (diabetes mellitus, hypertension), hepatitis C (which is associated with multiple glomerular diseases including membranous glomerulonephritis, mixed essential cryoglobulinemia and membranoproliferative glomerulonephritis[9,10]), Child-Pugh score and Meld score[10-14], all with conflicting evidence. During surgery, kidneys have to deal with further insults such as hypovolemia, inferior vena cava clamping and its associated increased pressure at the kidney level, hemorrhage and anemia, hemodynamic instability, blood transfusion, extended surgical procedure and some particular surgical techniques[9,15,16].

Moreover, it is reported that renal function relies on the liver graft quality. Renal prognosis is deemed to be worse with organs issued from cardiac death donors[17].

Postoperative additional factors such as radiological contrast media, sepsis and immunosuppressive drugs

(calcineurin inhibitors) promote renal failure[9,18].

The primary goal of our single center retrospective study was to estimate the incidence and severity of early postoperative renal dysfunction in OLT recipients and to highlight the perioperative AKI risk factors and their significance. The role of donation after circulatory death (DCD) was particularly looked into.

MATERIALS AND METHODS

Data were collected from a consecutive series of patients who underwent OLT at the University Hospital of Liege (Belgium) from January 2006 until September 2012. This analysis was limited to this time frame to avoid selection bias due to new recommendations in the handling of transplanted patients. We analyzed OLT patients developing acute renal failure (ARF) in the early postoperative course up to and including postoperative day 7 (primary outcome).

Data collection was based on a prospective clinical research database taking into account hospitalization data (preoperative hospital stay and infection occurrence), baseline demographic characteristics [age, gender, body mass index (BMI) and co-morbid conditions], preoperative clinical and biological data (urea, creatinine and bilirubin levels), perioperative septic status, ascites, previous treatment with β-*adrenoreceptor blockers*, angiotensin-converting enzyme inhibitors (ACEI) and *non-steroidal anti-inflammatory drugs (NSAIDs)*. We did not exclude patients with HRS pre-OLT from the study but we excluded patients who required preoperative renal replacement therapy (RRT).

A single surgical team, all members of which were specifically trained in OLT, performed all procedures. Intraoperative collected variables included liver graft source (cardiac dead or brain dead donor), need for surgical revision, need for transfusion [type of blood product administered: red cells concentrate (RCC), fresh frozen plasma (FFP) or platelet] and need for vasoactive drugs. Furthermore, we secondarily analysed the impact of the hemostatic agent used (aprotinin until October 2007, tranexamic acid later on - the only significant modification to protocol during the study period).

Post operative data during the first week were collected: need for transfusion (amount and type of blood product on days 0, 1 and 7), postoperative day 1 lactate peak level, minimum hemoglobin level, need for vasopressors, time to extubation, bilirubin peak level, aminotransferases peak levels, urea and creatinine peak levels, need for postoperative RRT and immunosuppressive drugs (tacrolimus, cyclosporine A or other immunosuppressive drug). The local triple immunosuppressive regimen consisted of a calcineurin inhibitor (cyclosporine or tacrolimus), an antiproliferative drug and a corticosteroid. Whole blood levels of calcineurin inhibitor were measured by chemiluminescence microparticle immunoassay (Architect® from Abbott).

We separated patients into four groups according to their renal function (relying on sequential organ failure assessment score stratification), based on the highest creatinine plasma level during the first postoperative week. The first group had a creatinine level below 12 mg/L, the second group between 12 and 20 mg/L, the third group between 20 and 35 mg/L, and the fourth above 35 mg/L. Patients who needed RRT during the first week after transplantation were also classified in the fourth group.

Statistical analysis

Statistical analysis was performed by the University's biomedical statisticians.

Univariate analysis was performed to identify variables associated with primary outcome as potential confounders. The results are presented as mean and standard deviation for normally distributed variables or median (interquartile range) for non-normally distributed variables. Several variables underwent a logarithmic transformation in order to standardize their distributions. Normality was checked by Shapiro-Wilk's test.

RRT: Comparisons between RRT and categorized variables were made by a χ^2 test whereas comparisons with continuous variables were made using logistic regression.

Comparisons between the 4 groups of renal dysfunction with categorized variables were made by a χ^2 test whereas comparisons with continuous variables were made using ANOVA or the Kruskal-Wallis' non-parametric test according to normality of variables. Ordinal logistic regression was performed in order to take the groups' order into account and hence renal dysfunction severity (group 4 "more severe" than group 3 "more severe" than group 2 "more severe" than group 1).

The results are considered as significant with an uncertainty level of 5% ($P < 0.05$). Statistical analyses were carried out using software SAS version 9.3.

Multivariate model

Variables included in the model are variables with a *P*-value lower than 0.10 in univariate analysis.

RESULTS

There were 78 patients in group 1 (41.7%), 46 in group 2 (24.6%), 38 in group 3 (20.3%) and 25 in group 4 (13.4%). Twenty patients required RRT: 13 (7%) during the first week after transplantation (group 4). There were 7 (3.7%) early deaths within 28 d after transplantation (Table 1).

Considering the 4 aforementioned groups, severity of renal dysfunction was correlated in univariate analysis

Table 1 Univariate analysis for severity of post orthotopic liver transplantation acute kidney injury

Variable	Whole group (*n* = 187)	Group 1 (*n* = 78)	Group 2 (*n* = 76)	Group 3 (*n* = 38)	Group 4 (*n* = 25)	*P* value between groups
Preoperative						
Age (yr)	56 ± 10	54 ± 10	56 ± 10	58 ± 9	57 ± 12	0.055
Sex (male)	147 (79)	61 (78)	32 (70)	33 (87)	21 (84)	0.410
BMI(kg/m²)	26 ± 4.5	25 ± 4	26 ± 5	26 ± 5	26 ± 5.0	0.055
Hospital stay (d)	3 ± 8	2.2 ± 4.8	4.2 ± 12.9	2.7 ± 7.9	6.4 ± 9.6	0.150
Bilirubin (mg/L)	25 (12-66)	17.4 (8.7-44.8)	23.2 (13.1-60.6)	32.3 (15.8-64.9)	56.3 (23.1-115.0)	< 0.0001
Creatinine (mg/L)	9.5 (7.4-12.3)	7 (6.6-9.3)	10.4 (8.0-12.7)	11.5 (9.3-14.5)	13.4 (6.6-16.0)	< 0.0001
Urea (g/L)	0.47 ± 0.35	0.34 (0.20-0.42)	0.40 (0.30-0.59)	0.42 (0.33-0.68)	0.64 (0.38-0.92)	< 0.0001
Ascites	138 (73)	50 (64)	37 (80)	30 (79)	21 (84)	0.015
β blockers	67 (37)	24 (31)	18 (39)	17 (46)	8 (33)	0.400
ACEI	18 (10)	8 (11)	4 (9)	4 (11)	2 (8)	0.770
NSAIDs	5 (3)	1 (1)	2 (4)	1 (3)	1 (4)	0.480
Prior bacterial infection	62 (33)	16 (20)	18 (39.1)	13 (34.2)	15 (60)	0.001
Intraoperative						
DCD	63 (34)	25 (32)	17 (37)	12 (32)	9 (36)	0.790
Infection	50 (27)	17 (22)	12 (26)	13 (34)	8 (32)	0.140
Vasopressors	86 (46)	18 (23)	25 (54)	25 (66)	18 (72)	< 0.0001
Surgical revision	45 (24)	12 (15)	12 (26)	11 (29)	10 (40)	0.009
Transfusion	169 (90)	66 (85)	44 (96)	37 (97)	22 (88)	0.060
Postoperative						
Lactates D1(mg/L)	434 ± 230	394 (270-509)	375 (279-484)	428 (283-527)	435 (334-711)	0.200
Minimum hemoglobin (g/dL)	8.0 (7.0-9.2)	8.9 (7.8-10.3)	7.7 (6.7-8.5)	7.55 (6.8-8.5)	6.7 (6.5-8.0)	< 0.0001
Bilirubin peak (mg/L)	40 (23-77.6)	37 (18-77)	32 (24-82)	51 (37-73)	60 (33-128)	0.006
ASAT (UI/L)	733 (372-1248)	554 (333-966)	804 (472-1988)	875 (399-1300)	822 (505-2458)	0.001
ALAT (UI/L)	617 (380-1068)	569 (332-941)	698 (399-1085)	546 (397-1113)	695 (407-1133)	0.260
Urea (g/L)	0.88 (0.6-1.3)	0.57 (0.46-0.69)	0.97 (0.80-1.14)	1.38 (1.21-1.64)	1.87 (1.52-2.18)	< 0.0001
Mechanical ventilation > 24 h	56 (30)	18 (23)	9 (20)	16 (42)	13 (52)	0.003
Mechanical ventilation days	1 (1-2)	1 (1-1)	1 (1-1)	1 (1-2)	2 (1-2)	0.001
RRT	20 (11)	4 (5)	2 (4)	1 (3)	13 (52)	< 0.0001
ICU stay (d)	3 (2-5)	2 (2-4)	3 (2-4)	5 (4-7)	6 (4-13)	0.005
Tacrolimus	177 (95)	77 (99)	43 (94)	35 (92)	22 (92)	0.089
Cyclosporin	21 (11)	5 (6)	7 (15)	6 (16)	3 (13)	0.170
Additional immunosuppressant	185 (98)	77 (99)	46 (100)	38 (100)	24 (96)	0.550
Transfusion RCC D0 (U)	1 (0-3)	0 (0-2)	2 (0-4)	2 (1-5)	2 (1-5)	0.001
Transfusion RCC D1 (U)	0 (0-1)	0 (0-0)	0 (0-1.5)	0 (0-2)	0 (0-4)	< 0.0001
Transfusion RCC D7 (U)	2 (0-5)	0 (0-3)	3 (1-6)	4 (2-7)	4 (2-12)	< 0.0001
Transfusion FFP D0 (U)	4 (2-6)	3 (0-6)	4 (2-7)	6 (3-9)	6 (3-8)	0.003
Transfusion FFP D1 (U)	0 (0-2)	0 (0-0)	0 (0-2)	2 (0-3)	2 (0-4)	< 0.0001
Transfusion FFP D7 (U)	6 (2-10)	4 (1-6)	6 (2.5-10)	8 (4-11)	8 (6-15)	< 0.0001
Transfusion platelets D0 (CUP)	1 (0-1)	0 (0-1)	1 (0-1)	1 (0-1)	1 (1-2)	0.001
Transfusion platelets D1 (CUP)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0.002
Transfusion platelets D7 (CUP)	1 (0-2)	0 (0-1)	1 (0-2.5)	1 (0-2)	2 (1-4)	< 0.0001

with patient BMI, ascites, prior bacterial infection, preoperative bilirubin, urea and creatinine levels, surgical revision, intraoperative vasopressor requirement, postoperative mechanical ventilation, postoperative urea, bilirubin, aspartate amino transferase (ASAT) peak levels and minimum hemoglobin levels, intensive care unit (ICU) length of stay and transfusion of each type of products (RCC, FFP and platelet cups).

Results are presented as mean ± SD if normal distribution, median (P25-P75) if non normal continuous variable, *n* (%) if categorical variable.

Using multivariate analysis, the ordinal multiple logistic regression analysis identified 5 independent predictors of increased postoperative creatinine peak level among our whole OLT population, namely BMI, preoperative creatinine level, use of vasopressor, postoperative bilirubin peak level and minimum postoperative hemoglobin level. It is to be noted that neither the donor status (cardiac death or brain death) nor transaminase levels were independent risk factor for AKI (Table 2).

Post hoc analysis of renal data into two chronological groups according to the hemostatic agent used showed that the occurrence of AKI (group 2, 3 and 4 together) was higher with tranexamic acid than with aprotinin, even when adjusting for preoperative creatinine (OR = 2.23, 95%CI = 1.13-4.41, *P* = 0.021) and regardless of the extent of bleeding (Table 3).

Table 2 Multivariate analysis for increased post orthotopic liver transplantation serum creatinine level

	OR	95%CI	*P* value
BMI (kg/m²)	1.10	1.03-1.18	0.0044
Preoperative increased creatinine (ln - mg/L)	11.07	5.28-23.23	< 0.0001
Vasopressors use	3.31	1.75-6.29	0.0002
Postoperative minimum Hemoglobin (ln - g/dL)	0.06	0.01-0.29	0.0005
Postoperative bilirubin peak (ln - mg/L)	1.44	1.01-2.05	0.044

BMI: Body mass index; ln: Natural logarithm.

Table 3 Post hoc multivariate analysis highlighting the effect of anti-hemorragic treatment strategy on acute kidney injury occurrence

Risk not being into the 1th group in multivariate analysis	OR	95%CI	*P* value
Antihemorragic treatment period	3.36	1.44-7.85	0.005
Preoperative increased creatinine (ln - mg/L)	1.36	1.20-1.54	< 0.0001
Bleeding (100 mL)	1.03	1.01-1.06	0.011

ln: Natural logarithm.

DISCUSSION

AKI remains a common disorder after OLT, despite advances in surgical technique, anesthesia, post-operative care and immunosuppressive therapy. We found 58% of OLT recipients to have some degree of renal dysfunction highlighted by an increase in serum creatinine level during the first postoperative week. The rate of AKI varies among studies. Cabezuelo *et al*[4] and Rymarz *et al*[19] observed an AKI prevalence of around 30% over the first week after surgery, while Junge *et al*[10] found only 12% patients developing AKI during the first week after OLT. The incidence of post-transplantation acute renal dysfunction is related to an increased mortality rate[20,21].

RRT requirement

When focusing on AKI severity, RRT requirement concerned 20 on 187 of our patients (11%), 13 (7%) of them within the first postoperative week. Likewise, in Faenza's study[22], 8% of OLT patients experienced ARF requiring RRT during the postoperative period. They found that ARF requiring RRT conferred an excessive risk of in-hospital mortality (n = 8, 40%). This increased risk cannot be explained solely by a more pronounced severity of illness and provides evidence that ARF is a specific, independent risk factor for a poor prognosis[22]. According to the literature, 3 to 20% of RRT-naïve patients who undergo OLT ultimately require postoperative RRT[23] with an associate increase in mortality rate[13,24].

Our results identified five parameters independently associated with a postoperative increased serum creatinine level.

Preoperative renal impairment

Some degree of preoperative renal impairment was a main factor highlighted by our study, as shown by others[4,10,12,19], especially since biological markers are delayed and reflect advanced renal damages[25]. Intrinsic chronic kidney disease predisposes patients with end-stage liver failure to acute renal dysfunction[26]. Furthermore, hemodynamic preoperative factors promote the risk of ARF in cirrhotic patients: kidney hypoperfusion is due to intravascular hypovolemia associated with parietal edema, hypoalbuminemia and hormone-induced vasodilatation of splanchnic circulation[26,27]. Renin angiotensin aldosterone axis is also disturbed. Edema of renal parenchyma itself can also play a role in this phenomenon[28].

A link between acute liver failure (ALF) and ARF is described in the literature. Seventy percent of patients with ALF developed AKI, and 30% received RRT. Patients with severe ARF had higher international normalized ratio values, more severe encephalopathy and shock than patients without renal dysfunction[29].

Vasopressor requirements

Like other authors, we observed an adverse role of vasoconstrictor therapy during surgery[13]. Nevertheless, maybe vasopressor requirement rather than vasopressor use is responsible for renal impairment. With cirrhosis, systemic arterial vasodilation is observed. Indeed, portal hypertension is associated with a release of vasodilatory substances (NO, prostacyclins). Moreover, vasodilation opens arteriovenous shunts. As a result, a hyperkinetic syndrome with an increase in the cardiac flow and a fall of the systemic blood pressure is observed in cirrhotic patients. During surgery, significant hemodynamic disturbances occur following liver mobilizations (dislocation), in addition to hepatomegaly in some cases, inducing a venous return decrease. Massive blood losses can occur especially in presence of adherences. Inferior cava vein clamping reduces once more venous return (up to 60%) and decreases cardiac flow (about 40% to 60%). Clamp withdrawal increases transient severe hypotension.

A surgical revision is needed when significant bleeding persists after correction of biological coagulation parameters, leading to anemia, hypotension, tissue hypoperfusion and cellular oxygen deprivation. These situations are associated with greater hemodynamic instability leading to renal hypoperfusion.

Sepsis-associated vasodilation further increases these circulatory derangements. Sepsis-related AKI doesn't seem to be related to renal global hypoperfusion but rather to renal hyperhemia with an intra-renal blood flow redistribution. The exact pathophysiology of sepsis-induced AKI is still not clear and seems multifaceted, with components of inflammatory

injury, ischemia-reperfusion injury, endothelial cell dysfunction, coagulation disturbance and apoptosis[30]. Moreover, recent findings suggest that pathophysiologic mechanisms of sepsis-induced AKI are different from non-septic AKI[31].

It is reported that vasoplegia-induced hypotension is correlated with progressive AKI during severe sepsis, relying on the Finnaki study's results[32]. On the other hand, generous fluid infusion and fluid overload in septic patients are also associated with progressive AKI[33,34].

Anemia and transfusion requirements

We found a significant impact of both postoperative anemia and transfusions on the incidence of early AKI. ARF severity was correlated to all transfused blood products in univariate analysis.

Data issued from literature are somewhat inconsistent regarding the effect of anemia and transfusion on renal function.

Villanueva *et al*[35] did not found any significant repercussion on the occurrence of acute kidney injury of different transfusion strategies with hemoglobin thresholds of 7 g/dL and 9 g/dL in 921 patients with upper gastro intestinal bleeding.

On the other hand, AKI is thought to happen when a combination of insults inducing renal hypoxia, inflammation and oxidative stress occurs in vulnerable patients[36,37]. Kidneys are known to be highly vulnerable to hypoxic injury in the setting of reduced oxygen delivery because of anemia[38,39]. Decreased renal oxygen delivery is due to hypotension, hemodilution and impaired renal blood flow.

On one hand, several studies have highlighted the harmful effect of the need for transfusion on renal function of liver recipient patients[11]. As a matter of fact, transfused erythrocytes may favour kidney injury because of the functional and structural alterations that they undergo during storage[40]. These include depletion of adenosine triphosphate and 2,3-diphosphoglycerate, loss of ability to generate nitric oxide, increased adhesiveness to vascular endothelium, release of pro-coagulant phospholipids, accumulation of pro-inflammatory molecules as well as free hemoglobin and iron[40,41]. Furthermore, erythrocytes undergo progressive structural changes during storage that lead a considerable proportion (up to 30%) of them to be rapidly removed from the circulation by macrophages[42], which may then release some of scavenged hemoglobin-iron complexes into circulation[43,44]. As a result, stored erythrocytes may, at least for a few hours after they are transfused, paradoxically weaken tissue oxygen delivery, enhance the inflammatory cascade, and worsen tissue oxidative stress[39,40,45,46]. Furthermore, a significant need for intraoperative transfusion of all type of blood products in previously non anaemic patient can be a reflection of either a more severe preoperative liver dysfunction with severe coagulation impairment, or a prolonged intervention with surgical difficulties and hemodynamic alterations. In contrast with what precedes, some authors even recommend an increased intraoperative vasopressor use aiming at reducing transfusion requirement. It is reported that norepinephrine can improve outcome and reduce mechanical ventilation duration without effect on renal function when comparing a restrictive fluid strategy and a liberal fluid strategy called placebo during OLT surgery[47].

Obviously, a particular attention must be paid for hemostasis and coagulation optimization.

Finally, there is a theoretical anti ischemic preconditioning effect of aprotinin, selective cyclooxygenase-2 inhibitors and oral anti-diabetics (sulfonylurea, glitazones) which inhibit potassium channels[48]. Aprotinin is not used anymore and has been replaced by tranexamic acid to limit blood losses. The unique major modification in intraoperative management of liver transplant recipients in our center is the discontinued use of aprotinin in October 2007 (it was pulled out from international market given the concern that aprotinin increased risk of complication and death in the intraoperative period). Paradoxically, when stratifying renal data in two groups according to the antihemorrhagic agent used, we observed that the occurrence of renal failure was higher with tranexamic acid than with aprotinin, even when adjusted for preoperative creatinine level. This effect was not in relation with an increased intraoperative bleeding.

Hyperbilirubinemia

Because of donors' paucity, sub optimal transplants coming from living donors, split or domino procedures and cardiac death donors often result in early hyperbilirubinemia, which is deemed to be due to suboptimal graft[49]. Hyperbilirubinemia is due to miscellaneous etiologies such as small for size syndrome and aged living donor, acute cellular rejection, graft preservation injury, surgical complications, sepsis or drug toxicity[50] with a higher prevalence in the context of living donors in the literature. Serum bilirubin level is a useful predictor of short-term (< 1 year) graft poor outcome[51].

Early postoperative hyperbilirubinemia can be considered as a sign of liver impairment from different causes (*i.e.*, surgical complications, infection or acute graft rejection) but it may in itself also potentiate other insults such as kidney failure[52]. When early hyperbilirubinemia is not an isolated phenomenon but presents with hepatocellular failure, *i.e.*, persistent coma, coagulopathy and elevated serum transaminase level, it is encompassed in the diagnosis of "primary non function" (or less severe early allograft dysfunction). In this particular situation, the patient also needs to be on prolonged mechanical ventilation and requires iterative transfusions. A rapid new liver transplantation is mandatory under these

circumstances. Primary non function is described as more frequent after "uncontrolled DCD donors" (*i.e.*, with a prolonged warm ischemia) and believed to be the consequence of severe I-R injury in relation with warm injury[53]. Delayed bilirubin increasing is often due to biliary complications (bile leakage and bile duct stricture).

Ischemia-reperfusion

Besides aforementioned hemodynamic phenomena, liver ischemia-reperfusion (I-R) injury occurs after liver transplantation and circulatory shock, leading to significant morbidity and mortality. There is substantial evidence towards hepatic I-R injury resulting in an intense inflammatory response initiated by oxidative stress in the liver parenchyma during reperfusion. Hepatic I-R injury is associated with a systemic inflammatory response syndrome through a combination of immunologic, toxic and inflammatory factors (cytokines release), which can cause AKI through hemodynamic mechanisms and direct tubular cell death[30,54-57].

Nevertheless, unlike previous studies[17,58,59], we did not find any significant relationship between DCD and renal dysfunction. In 2012, Leithead *et al*[58] published the results of a single-center study conducted on 88 consecutive DCD liver transplant recipients. During the immediate postoperative period, DCD liver transplantation was associated with an increased incidence of AKI compared with donation after brain death (DBD). Interestingly, increased perioperative peak ASAT, a surrogate marker of hepatic ischemia reperfusion injury, was the only significant predictor of renal dysfunction after DCD transplantation. Organs recovered from a DCD have some degree of oxygen deprivation during the time after the heart stops beating, which is called warm ischemia. One of the explanations of the lower impact of DCD on renal function in our data, in comparison with Leithead's studies, may be related to the differences in the legislation between the two countries. In the United Kingdom, discontinuation of therapy for DCD is carried out in the ICU, in the same condition than withdrawal of active treatment for a patient who is not a potential donor, *e.g.*, in the presence of the family. Organ donation may not be possible if the dying process is prolonged and may result in an unacceptable warm ischemic time[60]. Moreover, warm ischemia increases graft susceptibility to damages induced by cold injury.

The Belgian legislation authorizes treatment withdrawal (in the context of the DCD) within the operating theatre, which reduces considerably warm ischemia duration. Two minutes are awaited after circulatory arrest before establishing death followed by a 5-min "no touch" phase before skin incision[61]. This enables the warm ischemia time to be as short as possible.

Another sensitive ethical issue in DCD concerns organ preservation measures to protect organ viability until transplantation[62]. A tool to reduce I-R impact lies in preconditioning operations. Preconditioning consists of an improvement of the tolerance to ischemia (for 1 to 2 h) by brief episodes of flow occlusion or pharmacological means[63-65].

Preconditioning by halogenated anesthetics is related to several cellular mechanisms partially elucidated, such as the ATP dependant potassium channel opening (preserving mitochondrial function) and mitochondrial permeability transition pore closure [reducing the amount of radical oxygen species (ROS)][66-69]. These phenomena correspond to the early phase of the cellular protection; its duration is limited to 1-2 h. Preconditioning technique is possible only for a surgery where ischemia is programmed. Sevoflurane has also a protective effect on renal function (cystatine C) after coronary bypass surgery according to a double blinded multicenter study[67]. Pharmacological preconditioning by volatile anesthetics may protect non-cardiac organs against I-R[68,69].

Leithead *et al*[17] also showed an association between cold ischemic time (CIT) and perioperative AKI.

These findings strongly suggest that a sustained CIT is a causative factor for poor outcome (of the transplanted organ but also global) after DCD liver transplantation[70]. Cold ischemia duration corresponds to the time elapsed between infusion of preservation fluid and the moment when the graft is perfused in the receiver. Shorter the time, better the results of transplantation. Beyond 13 h of cold ischemia on a whole liver, the risk of primary non-function becomes important. In addition to its non-specific effects, cold ischemia enhances graft immunogenicity and host allo-responsiveness. The ischemic injury, a localized process of cellular metabolic disturbances, results from glycogen consumption, lack of oxygen supply and adenosine triphosphate (ATP) depletion[71]. Reperfusion abruptly reintroduces large amount of oxygen in the previously deprived cells. The mitochondrial respiratory chain, functionally damaged by ischemia, cannot accurately use this excess of oxygen. The reactivation of the ionic pumps rapidly corrects the acidosis, but at the cost of a sodium and calcium overload, potentially very harmful for the cell. Instead of synthesizing ATP, mitochondrion produces free ROS. It leads, by lipidic peroxidation, to cellular membranes damages (including mitochondrial membrane), but also to an indirect inflammation activation by leucocytes recruitment and by stimulating cytokines production, especially tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta[72-74]. Cytokines are mainly produced in the liver by the Kuppfer cells[75] but also by the extra-hepatic macrophages[76]. TNF-α propagates the inflammatory response[77]. Cytokines induce a local and general inflammatory syndrome followed by tissue edema. At reperfusion, body is flooded by degradation substances, such as lytic enzymes (ASAT, lactate

dehydrogenase), lactates, potassium, H+ ions… which can induce severe metabolic acidosis, renal failure, ARDS, heart failure or even multiple organ failure[78]. A similar situation is observed with the harmful remote effects of mesenteric I-R, where released mediators are involved in multi organ failure occurrence[79]. I-R phenomenon may clarify the stronger association we found between ASAT and AKI than between alanine amino transferase (ALAT) and AKI, even if ALAT is more liver specific than ASAT.

Eurotransplant is responsible for allocation of donor organs in Belgium. A match list is generated by a computer algorithm that takes into account all medical and ethical criteria. Another potential explanation of the difference between Leithead's report and our data perhaps relies on the policy of preferential allocation by Eurotransplant of an organ coming from a DCD to the donor's transplantation center (to reduce cold ischemic duration in those organs which have already experienced warm ischemia).

The recipient selection is also important since organs coming from a DCD are selectively reserved to uncomplicated cases to ensure short cold ischemic time (by avoiding cases with extensive history of abdominal surgery or portal-vein thrombosis)[53].

Likewise in our study, a recent meta-analysis focusing on post OLT complications also failed to detect a significant difference in complication rates (including renal failure) in the subgroup of cardiac death donors[80].

Immunosuppressive drugs

Unexpectedly, we did not found any significant impact of immunosuppressive drugs on early AKI. Nevertheless, nephrotoxicity associated with calcineurin inhibitors (CNI), *e.g.*, cyclosporine and tacrolimus, is common and occurs either acutely or after chronic use. Acute injury is believed to be dose and concentration-dependent. However, it may be observed in patients with therapeutic blood concentrations. CNI-induced AKI is believed mainly to come from afferent glomerular arteriolar vasoconstriction, reduced renal blood flow and ultrafiltration coefficient and, as a result, decreased glomerular filtration rate. This may be attributable to an increased production of vasoconstrictive factors (such as thromboxane A2 and endothelin) together with a decrease in renal vasodilatory prostaglandins and inhibition of nitric oxide[9,18,81-84]. CNI-associated AKI may develop early in therapy. It can occur within a few days after the initiation of either cyclosporine or tacrolimus. Early CNI-induced AKI generally improves once the cyclosporine or tacrolimus dose is reduced or discontinued. In contrast, late CNI-induced chronic renal failure is associated with interstitial nephritis and is usually irreversible[18-82].

In our institution, usual immunosuppressive therapy is based on low dose tacrolimus (serum target of 5-8 ng/mL), mycophenolic acid and steroids. It corresponds to the renal sparing immunosuppression regime in other studies[17,58,59,85], where renal sparing immunosuppression could significantly reduce early kidney dysfunction in comparison with their standard immunosuppressant treatment with CNI (serum tacrolimus target of 8-10 ng/mL), azathioprine and decreasing dose of steroids.

Limitations

Serum creatinine is the most established, simple, and inexpensive estimation of renal function. It is the primary method of detection of all forms of renal failure. Usually, monitoring renal function mostly relies on the results of the serum creatinine level and the estimated glomerular filtration rate calculated with the use of Levey's modification of diet in renal disease and Cockcroft-Gault formulas with an additional monitoring of diuresis. Relying on the Risk Injury Failure Loss and End-stage renal disease (RIFLE) classification introduced in 2002, modified as AKI network (AKIN) classification since 2005, the AKI term currently integrates a wide range of renal dysfunctions, starting with a very early and slight renal dysfunction with minimal changes in the serum creatinine level (stage 1, risk), through moderate changes (stage 2, injury), to an advanced renal failure (stage 3, failure).

One limitation of the study is the lack of use of the RIFLE, AKIN or more recent Kidney Disease Improving Global Outcomes criteria to define the degree of acute kidney injury. Moreover, as well in our study than in all the AKI definitions mentioned above, the use of serum creatinine (sCr) as renal dysfunction marker is also questionable in the context of liver failure.

Even if sCr remains the most practical biomarker and the most commonly used for renal function evaluation, it presents many weaknesses in clinical practice since it is influenced by body weight, muscle mass, race, age, gender, protein intake and muscle metabolism. Body weight and muscle mass probably explain why BMI is an independent significant factor of postoperative increased creatinine level. In the particular case of a cirrhotic patient, it is also affected by a decreased formation of creatinine from muscles (due to muscle waste)[86], a decreased hepatic capacity to produce creatinine, an increased renal tubular secretion of creatinine[87], a low dietary protein intake to avoid hyperammonemia[7], an impairment of creatinine dosage with bilirubin high level[88] and an increased volume of distribution responsible for dilution of sCr. As a consequence, measurements of sCr in patients with cirrhosis overestimate glomerular filtration rate (GFR) or kidney function. Even more, creatinine is not an early reflection of GFR variations (substantial rises in serum creatinine are often not witnessed until 48-72 h after the initial kidney insult[89,90]) and rapid deterioration of renal function can be underestimated in the first days. In addition, significant renal disease can exist with minimal or

no change in creatinine because of renal reserve or enhanced tubular secretion of creatinine[91,92]. On the other hand, slight modifications of serum creatinine level can be due to variation of body water content, corresponding to a false positive elevation. Although a decreased urinary output is the second criteria used in all those scores, it is admitted that use of urinary output in patients with cirrhosis and ascites is inadequate since these patients suffer from sodium retention and often present oliguria, even if they have a relatively preserved GFR[93]. Moreover urinary output is frequently artificially enhanced by use of diuretics.

A "troponin-like" biomarker of AKI that is easily measured, unchanged by other biological variables, and capable of both early detection and risk stratification would considerably help for the diagnosis of AKI. It has been proposed that new biomarkers of renal function may be added to the diagnosis of AKI[94]. Nevertheless, recent studies focusing on critical patients have shown disappointing conclusions regarding the impact of routine use of neutrophil gelatinase-associated lipocalin (NGAL) analysis[95-97].

Anyway, by using serum creatinine evolution for 7 d after transplantation, we estimated that a perioperative event would be emphasized by an increase in creatinine level, even with a 48 h delay in comparison with other biomarkers such as NGAL[98]. The aim of this study was not here to detect a renal damage as quickly as possible but to highlight all the perioperative factors which may affect kidney function.

On the other hand, we only excluded from our analyses patients with previous renal failure requiring RRT (but not patients with moderate renal dysfunction). Even if it is easily conceivable that a kidney with less reserve will be more prone to functional deterioration compared to a healthy kidney, our study design reflects more real life situation in ICU management of AKI post OLT, taking into account that patients without previous oliguria or elevated serum creatinine could indeed have lost a substantial number of nephrons.

In conclusion, our study demonstrated that AKI after liver transplantation is a common complication since more than half of liver transplanted patients experienced some degree of early renal dysfunction after transplantation. BMI, hyperbilirubinemia, preoperative renal dysfunction, peroperative circulatory instability requiring the use of vasopressor and postoperative anemia are independent predictors of AKI occurrence.

Despite the reputable poor quality of the graft in DCD, neither comparison between DCD and DBD, nor ASAT level were associated with post-OLT AKI by multivariate analysis.

Besides targeting improvement of graft quality, a particular attention must be paid to avoid preoperative additive kidney damages, to optimize intraoperative hemodynamics and to consider treatment in order to reduce transfusion requirements.

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COMMENTS

Background

Acute renal dysfunction is a frequent complication in the perioperative period of liver transplantation, with an impact on renal and vital outcomes in some cases. Moreover, acute renal failure has multifactorial etiologies with possible complex interactions.

Research frontiers

Since acute renal failure is frequent and may result from multiple etiologies with additional extra renal confounding factors and, moreover, is delayed from its cause, there is no unique treatment to prevent or resolve renal dysfunction. Highlighting significant risk factors of renal dysfunction should allow focusing on these parameters and reducing their impact in the future.

Innovations and breakthroughs

The authors found a high prevalence of perioperative renal dysfunction after liver transplantation. Previous studies evaluated the late renal impact after liver transplantation and prolonged immunosuppressive treatment, but few of them focused on the perioperative period to highlight renal repercussions at that time-limited but crucial period. Among studies focusing on renal function during early postoperative period, organs from donation after cardiac death (DCD) seemed to be associated with more renal dysfunction than with liver from brain dead donors. The authors did not find the same association. It seems extremely important since donor shortage will lead to an increasing proportion of transplantations from DCD rather than from donation after brain death.

Applications

The authors observed that preoperative renal dysfunction, body mass index (BMI), vasopressor, postoperative low hemoglobin and high bilirubin levels were independent risk factors for developing renal dysfunction. While it seems difficult to act on BMI or on previous renal function, optimizing hemodynamics and coagulopathy management appears useful.

Terminology

Acute renal dysfunction is defined as a sudden reduction in renal filtration ability, induced by one or more harmful phenomena. It leads to serum ions imbalance, blood accumulation of waste substances, fluid retention and metabolic acidosis. Acute renal failure can be fatal and requires intensive treatment. Nevertheless, it may be a reversible condition. Early postoperative period is defined in this study as the first week following liver transplantation. When focusing on renal function, since usual (bio)markers of renal failure are delayed, this period reflects hemodynamic and metabolic changes encountered just before, during and immediately after surgical intervention (early surgical complications). Donation after cardiac/circulatory death and donation after brain death: Donation after circulatory death is a donor in refractory cardiac arrest or suffering from devastating and irreversible organ injury (usually brain injury) and awaiting cardiac arrest, but who does not meet formal brain death criteria. In these later cases, it is decided to withdraw care. When the patient's heart

stops beating, the organs are harvested in the operating room. Organs from a cardiac dead donor have some degree of oxygen deprivation during warm ischemia, *i.e.*, the time after the heart stops beating. Donation after brain death occurs when a person has a disastrous and irreversible brain injury, which causes total cessation of all brain function (including upper brain structure and brain stem). Brain death is not a coma nor a vegetative state but a real dead condition where cardio respiratory function is sustained by artificial devices (*e.g.*, mechanical ventilation).

Peer-review

The manuscript is a single center retrospective study that aims at estimating the incidence and severity of early postoperative renal dysfunction in orthotopic liver transplantation recipients and at highlighting the perioperative acute kidney injury risk factors and their significance, with particular attention to the role of DCD. The manuscript is well-written and deserves publication, as it carries a useful message to the clinicians involved in transplantation.

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