J Anesth (2015) 29:426–432
DOI 10.1007/s00540-014-1951-2

ORIGINAL ARTICLE

Intravenous fenoldopam for early acute kidney injury after liver transplantation

Gianni Biancofiore · Maria L. Bindi · Mario Miccoli · Elisabetta Cerutti · Bruna Lavezzo · Laura Pucci · Massimo Bisà · Massimo Esposito · Luca Meacci · Roberto Mozzo · Chiara Stratta · Giuseppe Penno · Angelo Baggiani · Franco Filipponi

Received: 14 June 2014 / Accepted: 3 November 2014 / Published online: 30 November 2014

Abstract
Purpose Acute kidney injury remains a serious complication after orthotopic liver transplantation. To date, several 'renal-protective' agents have been explored in this setting but with conflicting and disappointing results. Therefore, our aim is to evaluate the effects of fenoldopam in liver transplant patients with an established renal injury.
Methods In this prospective study, intravenous fenoldopam 0.1 μg/kg/min was administered to consecutive liver transplant patients with postoperative (within 7 days from surgery) stage 2 acute kidney injury (AKI) according to the Acute Kidney Injury Network classification. Actual glomerular filtration rate (GFR; calculated by the iohexol plasma clearance), serum creatinine (SCr) and cystatin C (SCyC) were used to assess the effect of the medication on the patients.
Results During the study, 295 patients underwent liver transplant. Fifty-one patients (17.6 %) met the inclusion criteria and the data from 48 patients were analysed. SCr and SCyC levels decreased ($p < 0.001$ after 48 h; $p < 0.0001$ after 72 h) and GFR increased ($p < 0.001$ after 24 h; $p < 0.0001$ after 72 h). When compared to a cohort of comparable patients with AKI from our historical series, the patients in the present study showed better SCr and SCyC levels. It was not necessary to discontinue the infusion of fenoldopam in any patient because of the occurrence of adverse events potentially attributable to it.
Conclusion We showed that fenoldopam was capable of improving some renal function parameters in postoperative liver transplantation patients with on-going AKI. This preliminary study now sets the stage for a multicenter, randomized, placebo-controlled trial in order to provide definite evidence.

Keywords Fenoldopam · Liver transplantation · Acute renal failure · Complications · Postoperative · Prevention

Introduction

Although orthotopic liver transplantation (OLT) has proved highly successful for the management of acute and chronic end-stage liver diseases with thousands of procedures being performed each year, it remains a high-risk treatment due to its possible complications [1]. In particular, the incidence of acute kidney injury (AKI) has been reported to range between 17 and 95 % [2]. Different risk factors have been identified for post-OLT AKI with preoperative (advanced hepatic failure, hepatorenal syndrome, ascites), intraoperative (blood loss, hypotension, volume depletion) and postoperative (early graft dysfunction, sepsis, use of immune suppressive drugs and radiological contrast media, repeated surgeries) events being recognized as the most valuable [2–5]. Therefore, because of the numerous etiological factors,

G. Biancofiore (✉) · M. L. Bindi · M. Bisà · M. Esposito · L. Meacci · R. Mozzo
Liver Transplant Anaesthesia and Critical Care, P. Kaisserli ICU, Azienda Ospedaliera Universitaria Pisana, Ospedale Cisanello, 56100 Pisa, Italy
e-mail: g.biancofiore@med.unipi.it

M. Miccoli · A. Baggiani
Epidemiology and Biostatistics Unit, Department of Experimental Pathology, University School of Medicine, Pisa, Italy

E. Cerutti · B. Lavezzo · C. Stratta
Department of Anaesthesia and Critical Care, AOU Città della Salute e della Scienza, Turin, Italy

L. Pucci · G. Penno · F. Filipponi
Liver Transplant Unit, University School of Medicine, Pisa, Italy

it can be difficult not only to accurately identify but also to prevent what causes AKI in the early days after OLT. Moreover, a significant body of evidence shows that post-OLT AKI is not a transient phenomenon but a complication that may have implications on patients' outcome in the long term [2–7]. Therefore, there is a broad consensus on the fact that in post-OLT patients even small acute decreases in renal function should be considered important and that measures aimed at halting or improving the progression of the kidney dysfunction should be prompt and timely [2, 4–8]. Accordingly, several 'renal-protective' agents have been explored but, to date, the results have proved to be conflicting and sometimes disappointing [7]. We have previously studied the use of fenoldopam, a selective dopamine-1-receptor agonist exerting renal vasodilator effects at doses of ≥0.01 μg/kg/min, for the prevention of post-OLT AKI [8]. Therefore, in this preliminary observational study, we investigated this agent on a relatively restricted number of patients with an established renal injury in order to examine its effects before a future randomized trial.

Methods

This study was approved by the local Investigational Review Board. Liver transplant recipients were considered eligible if aged >18 years and with a normal pre-OLT renal function, defined as glomerular filtration rate (GFR) >70 ml/min (estimated by the Modification of Diet in Renal Disease formula). Patients were enrolled if they (a) had signed an informed consent form, (b) were diagnosed with stage 2 AKI according to the Acute Kidney Injury Network (AKIN) classification (Table 1) during the first week after OLT [9], and (c) were hemodynamically stable (i.e., arterial mean blood pressure ≥65 mmHg during the 12 h before enrolment). Exclusion criteria were (a) expected survival (as judged by the attending physicians) <48 h, (b) a diagnosis of severe sepsis or septic shock, or (c) a need for high-dose furosemide (i.e., >200 mg in the 6 h before enrolment)

Patients were classified according to the Model for End-Stage Liver Disease (MELD), a scoring system for assessing the severity of chronic liver disease [10]. This score was initially developed to predict death within three months of surgery in patients who had undergone a transjugular intrahepatic portosystemic shunt procedure and was subsequently found to be useful in determining prognosis and prioritizing for receipt of a liver transplant. Today, the score is used by the United Network for Organ Sharing in the United States and Eurotransplant in Europe for prioritizing allocation of liver transplants instead of the older Child-Pugh score.

The native liver was removed with preservation of the inferior vena cava and a venovenous extracorporeal bypass was used in each patient during the anhepatic phase. At the end of surgery, all the patients were transferred to the Intensive Care Unit (ICU). Hemodynamic monitoring included invasive systemic arterial, pulmonary artery and capillary occlusion pressures and the measurement of cardiac performance by means of a pulmonary artery catheter (CCO/SvO2 Thermodilution Catheter; Edwards Lifesciences, Irvine, CA, USA). The patient's cardiovascular function was optimized targeting a cardiac index >3 L/min and a mean arterial pressure >65 mmHg. If urine output decreased to <1 ml/kg/h, furosemide IV 40 mg bolus was prescribed; if the goal was not reached, more furosemide was given up to a maximum dose of 500 mg. Fresh frozen plasma, fibrinogen and prothrombin complex concentrates were administered according to thromboelastography-guided coagulation management.

Study protocol

After enrolment, patients received a continuous intravenous infusion of fenoldopam 0.1 μg/kg/min. The result of the treatment was assessed by the measurement of serum creatinine (SCr) and cystatin C (SCyC) and calculating the patient's actual GFR at different time points. Blood samples for the determination of SCr and SCyC were collected immediately before (D0) and after 24 (D1), 48 (D2) and 72 (D3) h from the start of the treatment. If fenoldopam was administered for a longer period, the same parameters were measured daily until its discontinuation (end of treatment, EoT). The administration of fenoldopam was stopped when the patient's SCr returned to normal values. A patient's actual GFR was calculated using the iohexol plasma clearance (I-GFR) method at D0, D1, D3 and EoT time points.

Table 1 Classification/staging system for acute kidney injury according to the Acute Kidney Injury Network (AKIN) [22]

Stage	SCr criteria	Urine output criteria
1	Increase in SCr of ≥0.3 mg/dl (≥26.4 μmol/L) or increase to ≥150–200 % (1.5- to 2-fold) from baseline	<0.5 ml/kg/h for >6 h
2	Increase in SCr to >200 % to 300 % (>2- to three-fold) from baseline	<0.5 ml/kg/h for >12 h
3	Increase in SCr to >300 % (>3-fold) from baseline or SCr of ≥4.0 mg/dl (≥354 μmol/L) with an acute increase of at least 0.5 mg/dl (44 μmol/L)	<0.3 ml/kg/h for 24 h or anuria for 12 h

This methodology is based on the IV administration of 5 ml of Omnipaque 300 solution (Nycomed, Oslo, Norway) containing 647 mg/ml of iohexol (corresponding to 300 mg/ml of iodine); blood samples are taken immediately before (time 0) and at 5, 15, 60, 90, 180, 240, and 300 min after the injection [8, 11]. If the SCr level was ≥2 mg/dl, 2 further blood samples were taken at 360 and 420 min after the injection; if it was ≥5 mg/dl, a final sample was drawn after 1,440 min. Plasma iohexol concentrations were determined in the sampled blood in duplicate by means of high-pressure liquid chromatography (Waters Millipore, Milford, MA, USA) on a Bondapak C18 inverse phase column (Waters Millipore, Milford, MA, USA). The mobile phase consisted of a 96:4 solution of bi-distilled water and acetonitrile, pH 2.6. I-GFR was calculated using the formula I-GFR = injected iohexol dose/area under the plasma disappearance curve; the result was corrected by body surface area[11]. All of the samples for I-GFR determination were processed in the same laboratory.

Concomitant treatments

Standard perioperative anti-infective prophylaxis consisted of the administration of IV ampicillin-sulbactam 2 + 1 g for 2 days after OLT. Postoperative pain was controlled by intravenous morphine (1 mg/kg 40 min before the end of the procedure followed by a continuous infusion of 20–60 mg/day). The immunosuppressive protocol included oral cyclosporin A (Sandimmun Neoral®; Novartis Pharma SA, Huningue, France) titrated to maintain blood trough levels of 200–250 ng/dl or tacrolimus (Astellas Pharma SPA, Milan, Italy) titrated to maintain blood trough levels of 6–10 ng/ml. Basiliximab (Simulect®; Novartis Pharma SA) 20 mg IV on postoperative days 1 and 4, oral mycophenolate mophetil (Cellcept®; Roche Pharma SA, Milan, Italy) at a dose of 1 g twice a day and methylprednisolone (Solu-Medrol®; Pharmacia and Upjohn, Puurs, Belgium) at an intraoperative dose of 10 mg/kg, subsequently reduced by 50 % per day to a prednisolone dose of 20 mg/day, completed the immunosuppressive treatments. Patients with HCV-related cirrhosis did not receive steroids.

Statistical analysis

Data are reported as mean ± SD. The Kolmogorov–Smirnov test was performed to check normality of data and a post hoc statistical power analysis was performed. The $1 - \beta$ value was $p = 0.99$ indicating a low risk of type II error. In order to highlight the effects of fenoldopam on different levels of glomerular filtration, we compared our patients according to their I-GFR at the time of enrolment (higher or lower than the median value in the whole study population). The paired *t* test, the Mann–Whitney test and the chi-squared test were performed as appropriate; *p* values were determined with 95 % confidence intervals and the significance was set at $p < 0.05$. Data analysis was performed using the SPSS software (version 17.0, SPSS Inc, Chicago, USA).

Results

During the study period, 295 procedures were performed in 295 patients, all from cadaveric donors. Of them, 51 (17.6 %) were diagnosed with stage two renal injury according to the AKIN classification. Because 3 of them were excluded from analysis due to incomplete data collection, the study population consisted of 48 patients (30 males and 18 females). According to the AKIN classification, 38 patients were enrolled because of the SCr criterion and 10 for both the SCr and urine output criteria. Patients were aged 54.1 ± 6.8 years with a body mass index, at the time of the transplant, of 24.2 ± 2.3 kg/m^2. Post-viral cirrhosis (35 cases) was the most frequent cause leading to OLT; esotoxic cirrhosis (6 cases), liver cancer (4 cases) and sclerosing cholangitis (3 cases) were the remaining pathologies necessitating the transplant procedure. The MELD score for the patients was 21.4 ± 4. Twenty-seven patients received oral cyclosporin A and 21 received oral tacrolimus for immune system suppression. The trough blood levels of the two immunosuppressants at the time of enrolment were 175.1 ± 50.8 ng/dl and 4.6 ± 2.5 ng/ml, respectively. The administration of fenoldopam started at 47.2 ± 21.9 h from admission to the ICU and continued for 74.0 ± 30.3 h. In 3 cases (5.8 %) fenoldopam was discontinued because continuous renal replacement therapy (CRRT) was initiated. When fenoldopam was started, 3 patients (8.3 %) were receiving dopamine (8.1 ± 2.1 μg/kg/min) and 1 patient was receiving noradrenaline (0.05 ± 0.01 μg/kg/min). In the 12 h before the start of treatment, the urine output of the 48 studied patients was 537.0 ± 144.4 ml; all of them received furosemide at an average total dose of 101.1 ± 73.3 mg. At 24, 48 and 72 h from enrolment, 35 (41.0 ± 35.8 mg/day, $p < 0.0001$), 34 (23.7 ± 27.6 mg/day, $p < 0.0001$) and 28 (16.4 ± 20.6 mg/day, $p < 0.0001$) patients needed furosemide, respectively. At the end of treatment, 21 (11.9 ± 19.5 mg/day, $p < 0.0001$) patients were receiving furosemide. SCr and SCyC levels decreased and I-GFR increased throughout the study period (Table 2; Fig. 1). To assess whether the final outcome of the treatment depended on a possibly greater effect of fenoldopam in the less severe patients (i.e., those with higher greater baseline GFR) than in those with more severely compromised GFR, we compared our patients according to their I-GFR at the time of enrolment (higher or lower than the median value in the whole study population). In both the sub-groups, which were homogeneous with regard to the severity of their liver disease (MELD score 22.1. vs 21.2,

Table 2 Renal function data

	Pre-OLT	D0	D1	D2	D3	EoT
SCr (mg/dl)	0.7 ± 0.3	1.7 ± 0.5*	1.6 ± 0.8	1.5 ± 0.9**	1.3 ± 0.8***	0.9 ± 03***
SCyC (mg/L)	=	2.0 ± 0.6	2.0 ± 0.7	1.8 ± 0.7**	1.7 ± 1.0***	1.2 ± 0.5***

I-GFR glomerular filtration rate GFR calculated through the iohexol plasma clearance

OLT orthotopic liver transplantation, *D0* enrolment, *D1* 24 h from enrolment, *D2* 48 h from enrolment, *D3* 72 h from enrolment, *EoT* end of treatment

* $p < 0.0001$ vs pre-OLT; ** $p < 0.001$ vs D0; *** $p < 0.0001$ vs D0

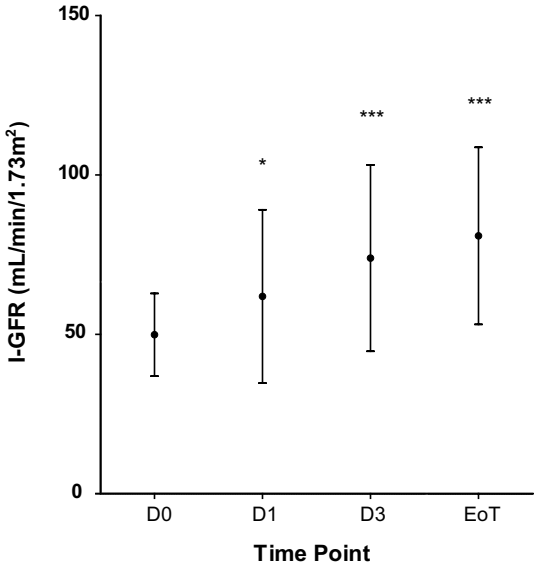

Fig. 1 I-GFR time course (whole study population). Data are reported as mean and SD. *D0* enrolment, *D1* 24 h from enrolment, *D3* 72 h from enrolment, *EoT* end of treatment. **$p < 0.001$ vs D0; ***$p < 0.0001$ vs D0

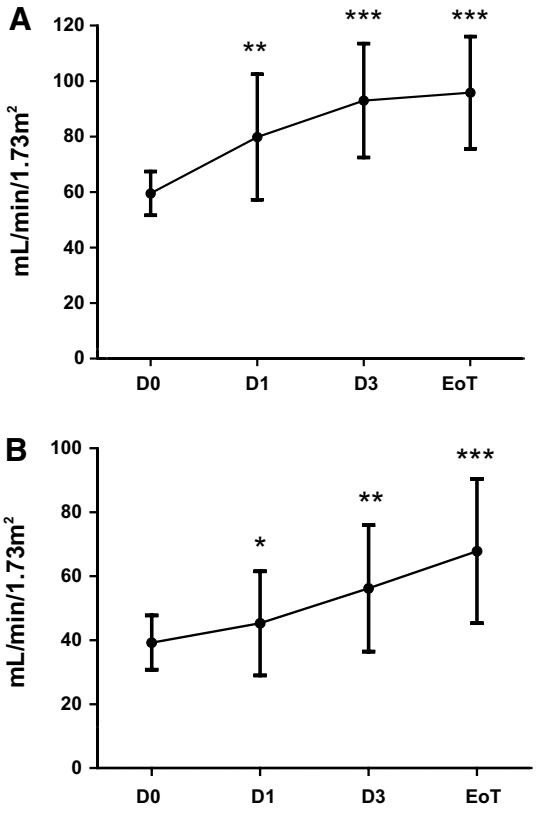

Fig. 2 I-GFR time course according to different I-GFR values at D0. Data are reported as mean and SD. **a** I-GFR in patients ($n = 25$) with a *baseline* (i.e., at enrolment) level >51.6 ml/min/1.71 m^2. **b** I-GFR in patients ($n = 23$) with a *baseline* (i.e., at enrolment) level <51.6 ml/min/1.71 m^2. *D0* enrolment, *D1* 24 h from enrolment, *D3* 72 h from enrolment, *EoT* end of treatment *$p < 0.05$ vs D0; **$p < 0.001$ vs D0; ***$p < 0.0001$ vs D0 (paired *t* test)

$p = 0.3$), I-GFR increased significantly (Fig. 2a, b). When compared to a cohort of comparable patients with AKI from our historical series, the patients in the present study showed better SCr and SCyC levels (Table 3).

Three patients (6.2 %) needed CRRT, a figure that is similar to that ($p = 0.1$) reported by our own group in a previous study where fenoldopam was used for preventing, instead of treating, AKI after OLT [8]. Two (4.1 %) of the 48 studied patients died in the ICU; both of them had AKI and were receiving CRRT. It was not necessary to discontinue infusion of fenoldopam in any patient because of the occurrence of adverse events potentially attributable to it.

Discussion

Here, we have provided preliminary evidence that fenoldopam may prove effective for the management of renal dysfunction in the early period after OLT. In our patients with AKIN stage 2 kidney injury (characterized by a 2- to 3-fold increase in SCr from baseline and/or a urine output <0.5 ml/kg/h for >12 h) SCr, SCyC and actual GFR significantly improved as the study progressed. This phenomenon was seen also in the subjects with lower baseline GFR levels. Unfortunately, we did not see a reduced need for CRRT compared to an historical cohort at our own institution.

Postoperative AKI in OLT recipients may lead to ominous consequences [2–4, 6, 12]. This explains the clinical

Table 3 Comparison between study and control (historical cohort) patients

	SCr (mg/dl)		SCyC (mg/L)	
	Fenoldopam, *n* 48	Control, *n* 48	Fenoldopam, *n* 48	Control, *n* 48
D0	1.7 ± 0.5	1.7 ± 0.3	2.0 ± 0.6	2.1 ± 0.8
D1	1.6 ± 0.8	2.2 ± 0.7*	2.0 ± 0.7	2.8 ± 0.9**
D2	1.5 ± 0.9	2.0 ± 0.8**	1.8 ± 0.7	2.4 ± 1.0***
D3	1.3 ± 0.8	1.7 ± 0.9***	1.7 ± 1.0	1.8 ± 1.1

D0 immediately before the start of the treatment, *D1* 24 h from the treatment, *D2* 48 h from the treatment, *D3* 72 h from the treatment

*$p < 0.05$ vs fenoldopam; **$p < 0.0001$ vs fenoldopam; ***$p < 0.01$ vs fenoldopam

attention and the research interest towards strategies aimed not only at its timely identification but also at preventing and reducing this complication. Unfortunately the pathophysiology of post-transplant AKI is complex and the results that have been achieved to date are limited. Therefore, the mainstay for the management of postoperative AKI is still represented by the adoption of universal strategies including knowledge of the risk factors, monitoring of fluids and electrolyte balance, maintenance of a mean arterial pressure >65 mmHg, avoidance of nephrotoxic drugs and adjustment of medication doses to the current renal function [2–4, 7]. Pharmacological interventions to manage post-OLT renal injury have been studied over the years with mixed results. Although widely used, furosemide proved inadequate for preventing and treating AKI with some evidence that it might even be harmful [2, 4]. Dopamine at 'renal' doses received most attention but it has been amply demonstrated to be ineffective [2, 4]. More recently, N-acetylcysteine (as an antioxidant), natriuretic peptides (as a renal vasorelaxating and natriuretic agent) and fenoldopam have been examined but their role is far from established. In fact, despite promising results of in vitro and experimental studies, it was impossible to prove the protective effect of N-acetylcysteine in the clinical setting of OLT [13]. A recent systematic review found natriuretic peptides were associated with a reduction in the post-surgery dialysis requirement and duration [014]. However, these findings are based on studies with suboptimal overall quality and power since only 3 of the 7 studies considered in this review concerned OLT patients (2 of them were performed before the year 2000) and the total number of treated patients was <50 [14]. Finally, few data are available about fenoldopam. It is important to outline that in previous studies, fenoldopam was mainly used in patients with near-normal renal function to prevent AKI rather than to treat an established injury, contrary to the present study [8, 15]. In the recent literature, mixed results can be found in other categories of patients about the possible role of fenoldopam in the management of postoperative AKI. A meta-analysis including 440 cardiac surgery patients suggests that fenoldopam reduces AKI [16]. In a single-center placebo-controlled pilot trial in septic patients, the reported incidence of AKI was significantly lower in the fenoldopam than in the placebo group [17]. In a randomized trial on newborns undergoing heart surgery, Ricci et al. found fenoldopam to be associated with lower postoperative urinary neutrophil gelatinase-associated lipocalin and SCyC concentrations compared with placebo suggesting some reno-protective effects [18]. Contrary to these positive findings, fenoldopam did not show any difference in the incidence of renal failure when it was compared to low-dose dopamine in 80 postoperative cardiac surgery patients. Furthermore, in a recent prospective, randomized, blinded, placebo-controlled study in 77 patients with a solitary kidney undergoing partial nephrectomy, its administration did not preserve renal function as evidenced by changes in the GFR or SCr [19]. It is necessary to find a way to interpret such conflicting data. As previously outlined, given the complexity of the pathogenesis of AKI, it may be simply naive to expect one single therapeutic intervention or agent to be successful [20]. Therefore, fenoldopam should not be regarded as yet another single 'magic bullet' against AKI but as a part of a multimodal clinical package.

Three pathophysiological considerations should be taken into account when considering the possible effects of fenoldopam in the setting of postoperative AKI. First, the recognition that the predominant etiology of AKI after OLT is an acute tubular necrosis due to hypoperfusion of the outer medulla [21]. Second, the acknowledgement that renal microcirculation is a key factor in the initiation and development of AKI and that ensuring an adequate perfusion and oxygenation of the kidney is central in the management prevention of AKI [4, 8, 20, 22]. Third, it has become evident that microcirculatory dysfunction interplays with the inflammatory response through the hypoxic insults resulting from the breakdown of the microcirculatory flow [22]. From this point of view, given its characteristics, fenoldopam might be an interesting pharmacological agent. In fact, it stimulates dopamine-1 receptors only (not dopamine-2), thus theoretically inducing greater vasodilation in the renal medulla than in the cortex [23]. Moreover, evidence is available from experimental studies that fenoldopam improves intrarenal hemodynamics, attenuates ischemia/reperfusion-induced inflammation and increases renal blood flow with better preservation of tubular histology [24–27]. Furthermore, in human studies, fenoldopam proved effective in increasing renal blood flow, and reducing the resistance of the renal circulation with a significantly higher GFR [28–30].

In the present study, despite the patients having some degree of renal injury, the non-ionic low-osmolar contrast medium iohexol was used to assess GFR. However, it is important to outline that the administered dose of iohexol was extremely low according to a well-established protocol at our institution [11, 31]. Morever, iohexol has become one of the most commonly used markers for assessing GFR in different clinical settings—liver dysfunction [32], established renal injury [33, 34], kidney transplantation [35], and critically ill patients with renal injury [36]. Our patients were not randomized and there was no blinding. Because of the absolute lack of specific data in the particular clinical setting of post-OLT AKI and the controversial results in this and other classes of patients where it was used, we intended to investigate fenoldopam with a preliminary experience characterized by (a) a well-identified and homogeneous group of patients (the largest where fenoldopam has been tested so far) where each one of them acted as the 'control' of him/herself; (b) a low type II error risk; and (c) a highly reliable methodology to assess a patient's GFR.

Our experience now provides a reliable data-set for setting-up a more complex randomized blinded study which hopefully will provide conclusive evidence.

In summary, we showed that renal-dose fenoldopam can improve GFR, ameliorate standard markers of renal function and increase urine output contemporarily reducing the need for diuretics in postoperative OLT patients with AKIN stage 2 kidney disease. However, it did not prove to be effective in decreasing the need for CRRT when compared to an historical cohort from our own institution. Because, as clinicians, our main target remains saving patients from dialysis or death and not from a reduced GFR or an elevated SCr, we think this study now sets the stage for a multicenter, randomized, placebo-controlled trial in order to provide conclusive evidence.

References

1. Klink JR, Pan LTT. Lessons from liver transplantation. Anaesthesia. 2012;67:1067–71.
2. Lewandowska L, Matuszkiewicz-Rowinska J. Acute kidney injury after procedures of orthotopic liver transplantation. Ann Transplant. 2011;16:103–8.
3. Karapanagiotou A, Kydona C, Dimitriadis C, Sgourou K, Giasnetsova T, Fouzas I, Imvrios G, Gritsi-Gerogianni N. Acute kidney injury after orthotopic liver transplantation. Transplant Proc. 2012;44:2727–9.
4. Saner F, Cicinnati V, Sotiropoulos G, Beckebaum S. Strategies to prevent or reduce acute and chronic kidney injury in liver transplantation. Liver Int. 2012;32:179–88.
5. Cabezuelo JB, Ramırez P, Rıos A, Acosta F, Torres D, Sansano T, Pons JQ, Bru M, Montoya M, Bueno FS, Robles R, Parrilla P. Risk factors of acute renal failure after liver transplantation. Kidney Int. 2006;69:1073–80.
6. Zhu M, Li Y, Xia Q, Qiu Y, Che M, Dai H, Qian J, Ni Z, Axelsson J, Yan Y. Strong impact of acute kidney injury on survival after liver transplantation. Transplant Proc. 2010;42:3634–8.
7. Phuong-Thu T, Phuong-Chi T. Wilkinson AH Management of renal dysfunction in the liver transplant recipient. Curr Opin Organ Transplant. 2009;14:231–9.
8. Biancofiore G, Della Rocca G, Bindi L, Romanelli A, Esposito M, Meacci L, Urbani L, Filipponi F, Mosca F. Use of fenoldopam to control renal dysfunction early after liver transplantation. Liver Transpl. 2004;10:986–92.
9. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A, The Acute Kidney Injury Network. Report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31–8.
10. Kamath PS, Kim WR. The model for end-stage liver disease (MELD). Hepatology. 2007;45:797–805.
11. Pucci L, Bandinelli S, Pilo M, NAnniepieri N, Navalesi R, Penno G. Iohexol as a marker of glomerular filtration rate in patients with diabetes: comparison of multiple and simplified sampling protocols. Diabet Med. 2001;18:116–20.
12. Camargo R, Rolim Ferraz L, Mies S, Martins Monte JC, Pavão dos Santos OF, Cendoroglo Neto M, de Oliveira Rodrigues CJ, Costa Batista M, Souza Durão M Jr. Impact of acute kidney injury exposure period among liver transplantation patients. BMC Nephrol. 2013;14:43.
13. Hilmi IA, Peng Z, Planinsic RM, Damian D, Dai F, Tyurina YY, Kagan VE, Kellum JA. N-acetylcysteine does not prevent hepatorenal ischaemia-reperfusion injury in patients undergoing orthotopic liver transplantation. Nephrol Dial Transplant. 2010;25:2328–33.
14. Nigwekar SU, Kulkarni H, Thakar CV. Natriuretic Peptides in the management of solid organ transplantation associated acute kidney injury: a systematic review and meta-analysis. Int J Nephrol 2013; epub ahead of print.
15. Della Rocca G, Pompei L, Costa MG, Coccia C, Scudeller L, Di Marco P. Fenoldopam mesylate and renal function in patients undergoing liver transplantation: a randomized, controlled pilot trial. Anesth Analg. 2004;99:1604–9.
16. Zangrillo A, Biondi-Zoccai GG, Frati E, Covello RD, Cabrini L, Guarracino F, Ruggeri L, Bove T, Bignami E, Landoni G. Fenoldopam and acute renal failure in cardiac surgery: a meta-analysis of randomized placebo-controlled trials. J Cardiothorac Vasc Anesth. 2012;26:407–13.
17. Morelli A, Ricci Z, Bellomo R, Ronco C, Rocco M, Conti G, De Gaetano A, Picchini U, Orecchioni A, Portieri M, Coluzzi F, Porzi P, Serio P, Bruno A, Pietropaoli P. Prophylactic fenoldopam for renal protection in sepsis: a randomized, double blind, placebo-controlled pilot trial. Crit Care Med. 2005;33:2451–6.
18. Ricci Z, Luciano R, Favia I, Garisto C, Muraca M, Morelli S, Di Chiara L, Cogo P, Picardo S. High-dose fenoldopam reduces post operative neutrophil gelatinase associated lipocaline and cystatin C levels in pediatric cardiac surgery. Crit Care. 2011;15:R160.
19. O'Hara JF Jr, Mahboobi R, Novak SM, Bonilla AM, Mascha EJ, Fergany AF, Campbell SC, Kaouk JH, Kaple KM, Gill IS, Ziegman SA, Sessler DI. Fenoldopam and renal function after partial nephrectomy in a solitary kidney: a randomized, blinded trial. Urology. 2013;81:340–5.
20. Jo SK, Rosner MH, Okusa MD. Pharmacologic treatment of acute kidney injury: why drugs haven't worked and what is on the horizon. Clin J Am Soc Nephrol. 2007;2:356–65.
21. Weber ML, Ibrahim HN, Lake JR. Renal dysfunction in liver transplant recipients: evaluation of the critical issues. Liver Transpl. 2012;18:1290–301.
22. Le Dorze M, Legrand M, Payen D, Ince C. The role of the microcirculation in acute kidney injury. Curr Opin Crit Care. 2009;15:503–8.

23. Carey RM, Siragy HM, Ragsdale NV, Howell NL, Felder RA, Peach MJ, Chevalier RL. Dopamine-1 and dopamine-2 mechanisms in the control of renal function. Am J Hypertens. 1990;3:59S–63S.
24. Aravindan N, Samuels J, Riedel B, Shaw A. Fenoldopam improves corticomedullary oxygen delivery and attenuates angiogenesis gene expression in acute ischemic renal injury. Kidney Blood Press Res. 2006;29:165–74.
25. Aravindan N, Cata JP, Dougherty PM, Shaw AD. Effect of fenoldopam on ischemia/reperfusion-induced apoptosis. Ren Fail. 2006;28:337–44.
26. Aravindan N, Natarajan M, Shaw AD. Fenoldopam inhibits nuclear translocation of nuclear factor kappa B in a rat model of surgical ischemic acute renal failure. J Cardiothorac Vasc Anesth. 2006;20:179–86.
27. Miller Q, Peyton BD, Cohn EJ, Holmes GF, Harlin SA, Bird ET, Harre JG, Miller ML, Riley KD, Hogan MB, Taylor A. The effects of intraoperative fenoldopam on renal blood flow and tubular function following suprarenal aortic cross-clamping. Ann Vasc Surg. 2003;17:656–62.
28. Meco M, Cirri S. The effect of various fenoldopam doses on renal perfusion in patients undergoing cardiac surgery. Ann Thorac Surg. 2010;89:497–503.
29. Teirstein PS, Price MJ, Mathur VS, Madyoon H, Sawhney N, Baim DS. Differential effects between intravenous and targeted renal delivery of fenoldopam on renal function and blood pressure in patients undergoing cardiac catheterization. Am J Cardiol. 2006;97:1076–81.
30. Mathur VS, Swan SK, Lambrecht LJ, Anjum S, Fellmann J, McGuire D, Epstein M, Luther RR. The effects of fenoldopam, a selective dopamine receptor agonist, on systemic and renal hemodynamics in normotensive subjects. Crit Care Med. 1999;27:1832–7.
31. Biancofiore G, Pucci L, Cerutti E, Penno G, Pardini E, Esposito M, Bindi L, Pelati E, Romanelli A, Triscornia S, Salvadorini MP, Stratta C, Lanfranco G, Pellegrini G, Del Prato S, Salizzoni M, Mosca F, Filipponi F. Cystatin C as a Marker of renal function immediately after liver transplantation. Liver Transpl. 2006;12:285–91.
32. Swan SK, Halstenson CE, Kasiske BL, Collins AJ. Determination of residual renal function with iohexol clearance in hemodialysis patients. Kidney Int. 1996;49:232–5.
33. Frennby B, Sterner G. Contrast media as markers of GFR. Eur Radiol. 2002;12:475–84.
34. Gaspari F, Perico N, Remuzzi G. Measurement of glomerular filtration rate. Kidney Int. 1997;63:S151–4.
35. Castagnet S, Blasco H, Vourc'h P, Benz-De-Bretagne I, Veyrat-Durebex C, Barbet C, Alnajjar A, Ribourtout B, Buchler M, Halimi JM, Andres CR. Routine determination of GFR in renal transplant recipients by HPLC quantification of plasma iohexol concentrations and comparison with estimated GFR. J Clin Lab Anal. 2012; 26:376–83.
36. Erley CM, Bader BD, Berger ED, Vochazer A, Jorzik JJ, Dietz K, Risler T. Plasma clearance of iodine contrast media as a measure of glomerular filtration rate in critically ill patients. Crit Care Med. 2001;29:1544–50.