Acute Renal Failure in Liver Transplant Patients: Indian Study

Pradeep Naik · B. Premsagar · M. Mallikarjuna

Received: 10 September 2013 / Accepted: 11 November 2013 / Published online: 23 November 2013
© Association of Clinical Biochemists of India 2013

Abstract The acute renal failure is the frequent medical complication observed in liver transplant patients. The objective of this study was to determine the cause of acute renal failure in post liver transplant patients. A total of 70 patients who underwent (cadaveric 52, live 18) liver transplantation were categorized based on clinical presentation into two groups, namely hepatorenal failure (HRF, $n = 29$), and Hepatic failure (HF, $n = 41$). All the patients after the liver transplant had received tacrolimus, mycophenolate and steroids. We analyzed the modification of diet in renal disease, (MDRD) serum urea, creatinine and albumin before and after 5th and 30th day of liver transplant and data was categorized into survivors and non-survivors group. In HRF survivor group, serum creatinine, and urea levels were high and, albumin, MDRD were low in pre-transplant and reached to normal levels on 30th day of post transplant, and 79.3 % of patients in this group showed resumption of normal kidney function. On the contrary in HRF nonsurvivor group, we did not observed any significant difference and 20.7 % of patients showed irreversible changes after the liver transplant. In HF survivor group, 82.9 % of liver failure patients did not show any deviation in serum creatinine, urea, albumin and MDRD, whereas in HF non survivor group, 17.1 % of liver failure patients who had HCV positive before the transplant developed acute renal failure. The levels of creatinine, urea, albumin and MDRD were normal before the transplant and on day 30th, the levels of albumin and MDRD were significantly low whereas serum urea, creatinine levels were high. In conclusion, based on these

observations, an diagnosis and treatment of Acute renal failure is important among the liver transplantation cases in the early postoperative period.

Keywords Liver transplant · Acute renal failure · Immunosuppression · Hepatic failure

Introduction

Acute renal failure (ARF) is a frequent medical complication after the liver transplantation (LTx). Over the last two decades, progressively improving liver transplant survival rate has been instrumental in establishing the transplant surgery as a durable therapy for all the forms of end-stage liver disease [1]. Thus, focus has shifted to the quality of life after LTx, as well as prediction and management of conditions related to morbidity and mortality in long-term survivors [2]. The incidence of ARF is reported to range from 17 to 90 % in LTx patients [3–6]. It has been associated with an eightfold increase in mortality, prolonged stay in intensive care unit and a greater risk for infection-related complications [7].

Several factors have been explored the incidence of ARF in post LTx individuals. Some depend on the clinical state of the recipient before transplant and intra-operative vascular and metabolic dynamics and postoperative complications [6, 8, 9]. Patients awaiting liver transplantation may also have intrinsic renal disease, either in the form of pre-existing renal damage from diabetes mellitus or obstructive uropathy, or pre-existent end-stage renal disease (ESRD). In addition, acute tubular necrosis (ATN) may also develop as a result of hypotension, use of nephrotoxic drugs, or contrast media used in diagnostic studies. The glomerulonephritis may occur in patients with

P. Naik (✉) · B. Premsagar · M. Mallikarjuna
Department of Clinical Biochemistry, Global Hospitals,
Lakdikapool, Hyderabad 500004, India
e-mail: pradnaik408@yahoo.com

cirrhosis; most commonest form is a IgA nephropathy, which can produce mesangial deposits. Membrano-proliferative glomerulonephritis and post streptococcal glomerulonephritis have also been described in patients with liver disease. Hepatitis B is associated with various forms of renal diseases, the most common of which is membranous nephropathy, but membrano-proliferative glomerulonephritis and cryoglobulinemia have also been described. In addition, hepatitis B can cause kidney disease due to vasculitis in the form of polyarteritis nodosa, and similarly, hepatitis C infection has also been associated with an increased incidence of cryoglobulinemia [10–18]. During the initial days of post LTx, renal function deteriorates rapidly by nephrotoxic affects of immunosuppressive drugs. The immunosuppressive drug therapy immediately after transplantation influences the development of ARF, but declines slowly thereafter. This acute nephrotoxicity was highly reversible, responding to downward adjustments of tacrolimus dosage [19, 20]. The preventive measures such as careful adjustment of drug doses and of the hydro-electrolytic balance, together with the dialysis in the serious cases, are the most effective therapeutic modalities in the post LTx patients.

Kidney damage is usually ascertained from markers, most commonly albuminuria. Glomerular filtration rate (GFR) can be estimated using equations that incorporate serum creatinine, albumin and blood urea nitrogen (BUN) concentration with demographic and clinical variables such as age, gender, race, and body mass index (BMI). Determining the GFR provides a more accurate assessment of the level of kidney function than serum creatinine alone [21]. The most commonly used is the modification of diet in renal disease (MDRD) Study equation, and this formula was devised in an attempt to estimate GFR [22]. This study proposes the use of MDRD values as an outcome predictor for evaluation of ARF in post LTx recipients.

Materials and Methods

The study was conducted at Global Hospitals Hyderabad India, between the period 2005–2009. A total of 70 patients of which male 59 (mean $\pm$ SD Age in years 42 ± 16), female 11 (mean $\pm$ SD Age in years 37 ± 12) were enrolled in the study and were categorized into two groups. Hepatorenal failure (HRF) patients had both liver and renal failure ($n = 29$), and the other patients with Hepatic failure (HF) had liver failure with normal renal function ($n = 41$). The liver transplant included 52 cadaver and 18 live donors. Immediately after the transplant, all the patients were on immunosuppressive therapy (tacrolimus, mycophenolate and methylprednisolone), antiviral (ganciclovir), antiprotazoal, antibacterial and antifungal (fluconazole) as

per established clinical practices. We analyzed the rate of survivors and non- survivors in both the HRF and HF groups. Blood was collected in plain vacutainer from the patients before the transplant, fifth and thirtieth day of post liver transplant. Serum was separated and analyzed for urea, creatinine and albumin by using fully automated analyzer (Olympus AU 400) by using commercially available kits. Ethical clearance was obtained from the Institutional Ethical Committee of Global Hospitals, Hyderabad, India and the informed consent was obtained from all the subjects.

The MDRD was calculated as per the formula, MDRD: $GFR = 170 \times P_{Cr}^{-0.999} \times Age^{-0.176} \times BUN^{-0.170} \times Albumin^{0.318} \times 0.762$ (for women) $\times 1.180$ (for blacks).

Statistics

All values are expressed as mean $\pm$ SD. One-way ANOVA was done to compare the groups and significance among the groups was calculated by Student's *t* test. *p* value < 0.005 was considered significance. For the statistical analysis, Graph pad prism 6.02 software was used.

Results

As shown in Table 1, in HRF survivor group serum creatinine and urea were high, albumin and MDRD were low in pre-transplant, whereas immediately after the liver transplant, serum creatinine, urea, albumin and MDRD were reached to normal levels within 30 days after the transplant. In this group, 79.3 % of patients showed resumption of normal kidney function (Table 1). In HRF non-survivor group, we did not observe any significance difference in creatinine, urea, albumin and MDRD before and after the liver transplant. All the parameters remained high even after the liver transplant. In this group, 20.7 % of patients showed irreversible changes after liver transplant (Table 1).

In HF survivor group, 82.9 % of liver failure patients did not show deviation in serum creatinine, urea, albumin and MDRD (Table 1). On the other hand, in HF non-survivor group, 17.1 % of liver failure patients who had HCV infection before the transplant, developed acute renal failure after the transplant. The levels of urea, creatinine and MDRD were normal and albumin concentration was low before the transplant and on day 30th, the levels of albumin and MDRD were significantly ($p < 0.0001$) low and urea, creatinine were significantly ($p < 0.0001$) high (Table 1).

As shown in Table 1, 23 (79.3 %) patients had high urea and creatinine, and low MDRD. before LTx and were reversed to normal renal function after 30th day of post LTx. But, 6 (20.7 %) patients did not recover from acute

Table 1 Liver transplantation in cases due to hepato-renal failure and outcome

	Pre LTx	Post LTx (5th day)	Post LTx (30th day)
Creatinine (mg/dL) (NR: 0.5–1.5)			
HRF: survivor (<i>n</i> = 23)	2.2 ± 0.9	2.0 ± 0.54	0.9 ± 0.11 [#]
HRF: non-survivor (<i>n</i> = 6)	2.0 ± 0.2	2.1 ± 0.2	2.2 ± 0.3*
HF: survivor (<i>n</i> = 32)	0.8 ± 0.2	1.1 ± 0.41	0.9 ± 0.24
HF: non-survivor (<i>n</i> = 7)	0.9 ± 0.09	1.2 ± 0.15	2.5 ± 0.31
Albumin (g/dL) (NR: 3.5–5.0)			
HRF: survivor (<i>n</i> = 23)	2.3 ± 0.53	2.1 ± 0.39	3.9 ± 0.36 [#]
HRF: non survivor (<i>n</i> = 6)	2.1 ± 0.21	1.8 ± 0.12	2.1 ± 0.33*
HF: survivor (<i>n</i> = 34)	3.1 ± 2.5	2.3 ± 0.5	3.7 ± 0.41 [#]
HF: non survivor (<i>n</i> = 7)	2.9 ± 0.21	2.9 ± 0.15	2.3 ± 0.29 [#]
MDRD (ml/min) (NR > 90)			
HRF: Survivor (<i>n</i> = 23)	46 ± 11.2	39 ± 11.7	104 ± 21 [#]
HRF: non survivor (<i>n</i> = 6)	37 ± 8.2	33 ± 6.2	40 ± 12.1
HF: survivor (<i>n</i> = 34)	129 ± 91	109 ± 51	118 ± 15.9
HF: non survivor (<i>n</i> = 7)	122 ± 15.4	106 ± 15.3	45.4 ± 5.1*, [#]
Urea (mg/dL) (NR: 15–40)			
HRF: survivor (<i>n</i> = 23)	75.5 ± 22	57.5 ± 20.9	32 ± 6.0 [#]
HRF: non survivor (<i>n</i> = 6)	81.5 ± 18.1	84.6 ± 15	95 ± 11*
HF: survivor (<i>n</i> = 34)	25 ± 5.9	30.8 ± 7.0	29 ± 7.2
HF: non survivor (<i>n</i> = 7)	38 ± 5.9	59 ± 7.5	112.5 ± 13*, [#]

All values are expressed as mean ± SD

NR normal range, LTx liver transplant cases, HRF hepato-renal failure, HF hepatic failure, MDRD modification of diet in renal disease

* *p* < 0.001 survivors vs non survivors; [#] *p* < 0.001 pre-transplant versus 30th day of transplant

renal failure after LTx and all were expired in this group with pre LTx diagnosis history of End stage Liver Disease (ESLD) due to Non alcoholic fatty liver disease (NAFLD) and diabetes mellitus (DM) with NAFLD in HRF group. In HF group 34 (82.9 %) patients did not had any significant changes in creatinine, urea, albumin, MDRD before and after the liver transplant, whereas 7 (17.1 %) patients had high urea and creatinine and albumin and MDRD levels were low after LTx (Table 1) and all the patients in this group were expired with pre LTx diagnosis history of liver cirrhosis due to HCV Infection.

Discussion

However, despite the significantly improved surgical skills for LTx in recent years, operative complications are unavoidable. Hypotension from massive blood loss, circulatory instability duration of surgery, an-hepatic phase and many other intra-operative factors provide a well-recognized clinical environment for ischemic renal damage [23, 24]. Repeated rejection episodes [25] and postoperative volume depletion, severe infections, and the use of many potentially nephrotoxic drugs (tacrolimus, cyclosporine, mycophenolate), antibiotics, and antifungal agents

etc. [26–29] are some of the notable predisposing factors for ARF after the surgery [30]. Thomas et al. [26], demonstrated the elevated levels of urea before transplant and reached to normal range after 30th day of post LTx, similarly, creatinine clearance was low before the LTx and it reached to normal levels after 30th day of post LTx. These results are in agreement with our findings of the current study. We also observed 23 (79.3 %) patients had high creatinine and urea levels and low MDRD before the LTx and they were reversed to normal renal function after 30th day of post LTx. But the 6 (20.7 %) patients were not recovered from ARF after the LTx and expired with pre-LTx history of ESLD due to NAFLD, DM with NAFLD in HRF group. In HF group 34 (82.9 %) patients did not had any significant changes in creatinine, urea, and albumin, MDRD before and after the liver transplant. But, 7 (17.1 %) patients had high creatinine, urea, lower levels of albumin and low MDRD after LTx and these patients expired with pre-LTx diagnosis history of liver cirrhosis due to HCV Infection.

In the current study, we observed 17.1 % patients developed ARF after the LTx in hepatic failure group, which is slightly higher than 11.9 % as reported by Chuang et al. [31]. This may be due to nephrotoxic effects of tacrolimus and mycophenolate, and pre LTx diagnosis of HCV. Hence early

diagnosis and treatment of ARF is important among the LTx recipients in early period of post LTx.

Iwatsuki et al. [32] reported the renal recovery after LTx in 3 cases (their study had 3 cases) of hepatorenal failure patients, whereas we observed in 23 patients (79.3 %). On the other hand, Gonwa et al. [33] reported lower rate of survival in hepatorenal failure patients after the LTx. Studies have shown that preoperative hypoproteinemia and hypoalbuminemia are associated with greater incidence of post operative ARF [34]. In the current study, we observed 81.5 % of patients had hypoalbuminemia before the LTx. The presence of hypoalbuminemia in patients before the transplant may increase the risk of ARF, since it modifies Starlings forces in the systemic capillaries reduces the glomerular filtration, and alters the pharmacokinetics of potentially nephrotoxic drugs. Based on these findings, we may conclude that there is a relation between liver dysfunction and ARF in patients with post LTx.

Our study indicate that ESLD due to NAFLD, DM and liver cirrhosis due to HCV may be a risk factor for ARF, because these are the factors involved in hemodynamic changes in the kidney. During hepatic failure, in cirrhotic patients it has been shown that plasma renin concentrations are high and that plasma concentrations of renin substrate, which is normally produced by the liver are low, and these results in vasoconstriction and flow redistribution within the kidney which might be affected [35–37]. Transient high blood levels of tacrolimus or cyclosporine may be also a risk factor for ARF. The fluid replacement therapy was the first choice for the majority of patients when ARF occurred in the early postoperative period after LTx. The limitation of the study is the small sample size.

Conclusion

Our findings indicate that patients with hepatic failure due to cirrhosis caused by HCV infection have higher mortality after the liver transplant. In HRF group, ARF was not recovered in patients had a history of liver cirrhosis due to NAFLD, NAFLD with DM. We suggest early diagnosis and treatment of ARF are important among the LTx cases in the early postoperative period.

Acknowledgments We thank the management and both medical and surgical gastroenterology team of Global Hospitals, Hyderabad, India for providing basic infrastructure for this study.

References

- Adam R, Hoti E. Liver transplantation: the current situation. *Semin Liver Dis.* 2009;29(1):3–18.
- Karam VH, Gasquet I, Delvart V, Hiesse C, Dorent R, Danet C, et al. Quality of life in adult survivors beyond 10 years after liver, kidney, and heart. *Transplantation.* 2003;76(12):1699–704.
- Fraley DS, Burr R, Bernardini J, Angus D, Kramer DJ, Johnson JP, et al. Impact of Acute renal failure on mortality in end-stage liver disease with or without transplantation. *Kidney Int.* 1998;54:518–24.
- McCauley J, van Thiel DH, Starzl TE, Puschett JB. Acute and chronic renal failure in liver transplantation. *Nephron.* 1990;55:121–8.
- Lima EQ, Zanetta DM, Castro I, Massarollo PC, Mies S, Machado MM, et al. Risk factors for development of acute renal failure after liver transplantation. *Ren Fail.* 2003;25:553–60.
- Bilbao I, Charco R, Balsells J, Lazaro JL, Hidalgo E, Llopart L, et al. Risk factors for acute renal failure requiring dialysis after liver transplantation. *Clin Transplant.* 1998;12:123–9.
- De Simone P, Precisi A, Petrucci S, Balzano E, Carrai P, Catalano G, et al. The impact of everolimus on renal function in maintenance liver transplantation. *Transplant Proc.* 2009;41(4):1300–2.
- Nuno J, Cuervas-Mons V, Vicente E, Turrión V, Pereira F, Mora NP, et al. Renal failure after liver transplantation: analysis of risk factors in 139 liver transplant recipients. *Transplant.* 1995;27:2319–20.
- Contreras G, Garces G, Quartín AA, Cely C, LaGatta MA, Barreto GA, et al. An epidemiologic study of early renal replacement therapy after orthotopic liver transplantation. *J Am Soc Nephrol.* 2002;13:228–33.
- Crawford DHG, Endre ZH, Axelsen RA, Lynch SV, Balderson GA, Strong RW, et al. Universal occurrence of glomerular abnormalities in patient receiving liver transplants. *Am J Kidney Dis.* 1992;19:339–44.
- Newell GC. Cirrhotic glomerulonephritis: incidence, morphology, clinical features and pathogenesis. *Am J Kidney Dis.* 1987;9:183–90.
- Eknoyan G. Glomerular abnormalities in liver disease. In: Epstein M, editor. *The kidney in liver disease.* Baltimore: Williams & Wilkins; 1988. p. 154–81.
- Blaker F, Hellwege HH, Kramer V, Thoenes W. Membranous nephropathy and hepatitis B antigen. *Lancet.* 1975;2:955.
- Levo Y, Gorevic PD, Kassab HJ, Zucker-Franklin D, Franklin EC. Association between hepatitis B virus and essential mixed cryoglobulinemia. *N Engl J Med.* 1977;296:1501–4.
- Prince AM, Trepo C. Role in immune complexes involving SH antigen and pathogenesis of chronic active hepatitis and polyarteritis nodosa. *Lancet.* 1971;1:1309–10.
- Patek HA Jr, Ceegal D, Bevans M. The coexistence of cirrhosis of the liver and glomerulonephritis: report of 14 cases. *Am J Med Sci.* 1951;221:77–84.
- Rai GS, Hamlyn AN, Dahl MGC, Morley AR, Wilkinson R. Primary biliary cirrhosis, cutaneous capillitis, and IgM associated membranous glomerulonephritis. *Br Med J.* 1977;1:817–8.
- Moroz SP, Cutz E, Butle JW, Sas-Kortsak A. Membranoproliferative glomerulonephritis and childhood cirrhosis associated with alpha1 antitrypsin deficiency. *Pediatrics.* 1976;57:232–4.
- McCauley J, Fung JJ, Todo S, Jain A, Deballi P, Starzl TE, et al. Changes in renal function after liver transplantation under FK 506. *Transplant Proc.* 1991;23:3143–5.
- Porayko MK, Textor SC, Krom RAF, Hay JE, Gores GJ, Richards TM, et al. Nephrotoxic effects of primary immunosuppression with FK-506 and cyclosporine regimens after liver transplantation. *Mayo Clin Proc.* 1994;69:105–11.
- Stevens LA, Coresh J, Amy E, Deysher PE, Feldman H, et al. Evaluation of the modification of diet in renal disease study equation in a large diverse population. *J Am Soc Nephrol.* 2007;18:2749–57.
- Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of diet in renal disease study group. *Ann Intern Med.* 1999;130:461–70.

23. Gainza FJ, Valdivieso A, Quintanilla N, Errazti G, Gastaca M, Campo M, et al. Evaluation of acute renal failure in the liver transplantation preoperative period: incidence and impact. *Transplant Proc.* 2002;34(1):250–1.
24. Jindal RM, Popescue I. Renal dysfunction associated with liver transplantation. *Post grad Med J (Engl).* 1995;71:513.
25. Dibona GF. Renal neural activity in hepatorenal syndrome. *Kidney Int.* 1984;25:841–53.
26. Thomas G, Kelly D, Norris S, Crosby O, Hegarty J, Crowley K, McEntee G, et al. Acute renal failure in orthotopic Liver transplantation. *Irish J Med Sci.* 1996;165:271–3.
27. Starzl TE, Todo S, Fung J, Demetris AJ, Venkataramanan R, Jain A, et al. FK 506 for human liver, kidney and pancreas transplantation. *Lancet.* 1989;2:1000.
28. Platz KP, Mueller AR, Blumhardt G, Bachmann S, Bechstein WO. Nephrotoxicity following orthotopic liver transplantation. A comparison between cyclosporine and FK506. *Transplantation.* 1994;58(2):170–8.
29. Chen CL, Chen YS, De Villa VH, Wang CC, Lin CL, Goto S, et al. Minimal blood loss living donor hepatectomy. *Transplantation.* 2000;69:2580.
30. Alvares-da-Silva MR, Waechter FL, Francisconi CF, Barros E, Thome F, Traiber C, et al. Risk factors for postoperative acute renal failure at a new orthotopic liver transplantation program. *Transplant Proc.* 1999;31:3050–2.
31. Chuang FR, Lin CC, Wang PH, Cheng YF, Hsu KT, Chen YS, et al. Acute renal failure after cadaveric related liver transplantation. *Transplantation Proc.* 2004;36:2328–30.
32. Iwatsuki S, Popovtzer MM, Corman JL, Ishikawa M, Putnam CW, Katz FH, et al. Recovery from hepato renal syndrome after orthotopic liver transplantation. *Med J (Engl).* 1973;289:1155–9.
33. Gonwa TA, Mai ML, Melton LB, Hays SR, Goldstein RM, Levy MF, et al. Renal replacement therapy and orthotopic liver transplantation: the role of continuous veno-venous hemodialysis. *Transplantation.* 2001;71:1424–8.
34. Cabezuelo JB, Ramirez P, Rios A, Acosta F, Torres D, Sansano T, et al. Risk factors of acute renal failure after liver transplantation. *Kidney Int.* 2006;69:1073–80.
35. Schroeder ET, Eich RH, Smulyan H, Gould AB, Gabuzda GJ. Plasma renin level in hepatic cirrhosis: relation to functional renal failure. *Am J Med.* 1970;49:186–91.
36. Berkowitz HD, Miller LD, Itskovitz HD. Liver disease, renal function, and the renin-angiotensin system. *Surg Forum.* 1968;19:391–2.
37. Ayers CR. Plasma renin activity and renin-substrate concentration in patients with liver disease. *Circ Res.* 1967;20:594–8.