Original Article

Use of Intravenous vs. Intramuscular Hepatitis B Immunoglobulin in Prevention of Relapse of Hepatitis B in Post Liver Transplant Patients

Aftab Ahmed Siddiqui, Rakhshinda Jabeen, Moin Ahmed Ansari, Majid Ali Soomro, Saeed Ahmed, Masoud Bakheet Khashoub

ABSTRACT

OBJECT: To see the response of HBIg in post liver transplant patients in prevention of hepatitis B relapse by using two different routes of administration.
STUDY DESIGN: prospective comparative study.
PLACE AND DURATION OF STUDY: Sultan Qaboos University Hospital, Oman. From December 2001 – December 2007.
PATIENTS AND METHODS: Total 32 patients who underwent cadavaric liver-transplantation due to hepatitis B related end-stage liver disease were included in this study. Patients were divided into two groups by simple random technique. HBIg was administered through intravenous route to subjects of Group 1, whereas to subjects of Group II it was administered through intramuscular route. All patients received full recommended dose of HBIg with oral lamirudine for the prevention of relapse. Subjects were followed up for 30-months to record any event of relapse in both groups.
RESULTS: There were 24 (75%) males and 8 (25%) females, with median age of 37 years. Pretreatment HBV - DNA was detected in 28 (87.5%) and anti-HBS levels were <10-IU in all patients. During the course of treatment HBV-DNA found to be un-detectable and anti-HBS levels were maintained >100 in all patients. None of the study subjects in both groups had relapse of Hepatitis B.
CONCLUSION: Intramuscular route of administrating HBIg in post liver transplant cases secondary to hepatitis B was found to be as effective as intra venous route.

KEY WORDS: Liver transplantation, Hepatitis B, Hepatitis B immunoglobulin, intravenous, intramuscular, Lamivudine.

INTRODUCTIONS

After significant advancement in the treatment of chronic hepatitis B, liver transplantation remains the only hope and definite treatment for the treatment of end stage liver failure secondary to chronic liver disease. Initially when liver transplantation started in 60's the outcome was quiet disappointing because of graft rejection approaching up to 80-100%.[1] In the late 1980's, with the commencement of hepatitis B immunoglobulin[2] (HBIg) with addition of lamivudine[3] and adefovir,[4] in subsequent years the outcome was improved markedly. The overall survival rate increased up to 80% in one year and 65% at 3 years.[5] The cost and dose of HBIg required in intravenous (I/V) route is much higher as compared to intramuscular (I/M) route and if I/M route is as effective as I/V, this cost can be reduced[6].

The aim of the study was to compare the effectiveness of two different administration routes of HB1g, i.e. intramuscular (I/M) vs. intravenous (I/V), in post liver transplant Omani patients secondary to hepatitis B in preventing the relapse. This study can help in minimizing the cost of post liver transplant patient management.

PATIENTS AND METHODS

From December 2001 to December 2007, 32 patients with end stage liver disease due to HBV undergone cadavaric liver transplantation. They all had transplantation performed in Tianjin First Central Hospital, Tianjin, China. They all were received at Sultan Qaboos University Hospital (SQUH), Oman, within 1-3 months after the procedure.

Routine investigations were performed in all cases, which included complete blood count, coagulation profile, liver function test, urea, creatinine, electrolytes, blood sugar, glycosylated hemoglobin and tacrolimus level. Baseline investigations carried out were Magnetic Resonance Cholangio-pancreatography (MRCP), abdominal ultrasonography, cytomegalovirus (CMV) IgM, IgG and PCR CMV. Other investigations performed were anti-HBsAg and anti-HBC along with HBV DNA. All these investigations, except radiological procedure, were repeated every month, anti-HBs level was repeated every 6 months. All patients received tacrolinmus 1-3 mg throughout the follow-up period i.e. 30 months, mycophenolate mofetil 500-mg BD for one year, and steroids in a tapering dose for 3-6 months.

All patients who underwent liver transplantation secondary to hepatitis B related cirrhosis of liver with Child-Pugh score of 11-15/15 were selected for the study. Patients with any comorbid disease (like diabetes mellitus, hypertension) or hepatitis B and hepatitis C co-infection were excluded.

After obtaining informed consent the subjects were divided into two groups by simple random technique.

All patients received tacrolimus 1-3 mg throughout the follow-up, mycophenolate mofetil 500-mg BD for one year, and steroids in a tapering dose for 3-6 months.

This study was conducted by the approval of ethical committee of SQUH.

We divided our patients in two groups, each group had sixteen patients. Group 1, included those patients who had received intravenous HBIg along with oral lamivudine; while group 2 consisted of the patients who had received intra-muscular HBIg and oral lamivudine. The initial standard protocol of giving the HBIg for the prevention of relapse of hepatitis B in both groups was started in china. Subsequently we monitored anti-HBS level every month and if anti-HBs level was found less than 100-IU/ml, we transfused HBIg along with lamivudine 100-mg once daily. Group 1 patients received intravenous HBIg (0.04-0.06 ml/kg), while group 2 patients received intra-muscular HBIg 2000 IU (5-6ml) in two divided doses in to the deltoid muscle to minimize the local side effects. Every patient was followed for minimum 30-months.

RESULTS

There were 24 (75%) males and 8 (25%) females with a median age of 37 years (range 21-53), **(Table I)**. The Pre-transplant characteristics of 32 study patients are shown in Table I. Twenty-two (68.75%) patients were HBeAg positive. The HBV-DNA was detected in 28 (87.5%). The anti-HBS levels were less than 10-IU in 32 (100%) patients. Majority of the patients was male and with detectable HBV-DNA levels.

The comparison of characteristics of two groups is shown in **(Table II)**.

There were 16 (50%) patients in group 1 (I/V immunoglobulin) and also 16 (50%) in group 2 (I/M immunoglobulin). In group 1 there were 14 male patients while group 2 had 10 male patients. Both groups were followed for a period of minimum 30 months. During this period HBV-DNA and anti-HBS were measured. HBV-DNA was un-detectable in all patients of both groups, and anti-HBS levels were maintained >100 in both groups by administration of HBIg by either route on monthly basis.

At the end of the follow up, none of our patients developed relapse of hepatitis B in both groups.

The cost of intramuscular HBIg per dose was approximately 675USD while the cost of intra-vascular HBIg per dose was 1,012 USD.

TABLE I: CHARACTERISTICS OF 32 PATIENTS PRIOR TO LIVER TRANSPLANTATION

Characteristics	No of Patients (%)
Male	24 (75)
Female	8 (25)
HBeAg (+)	22 (68.75)
HBV-DNA(+)	28 (87.5)
Anti-HBS(<10 IU/ml)	32 (100)

TABLE II: POST-TRANSPLANT COMPARISON OF CHARACTERISTICS BETWEEN TWO GROUPS

Characteristics	Group 1(n=16) IV Immunoglobulin	Group 2(n=16) IM immunoglobulin
Male	14 (87.5%)	10 (62.5%)
Female	2 (12.5%)	6 (37.5%)
Follow-up (months)	36 months	36 months
HBV-DNA by PCR	Undetected, 16 (100%)	Undetected, 16 (100%)
Anti-HBS>100 IU/ml	16 (100%)	16 (100%)
Cost per dose	1,012 USD	675 USD

DISCUSSION

Liver transplantation in patients with HBV cirrhosis is complicated by high recurrence rate. The nucleotide analogue lamivudine, given alone pre and post-transplant is associated with up to a recurrence rateof >50% due to induction of resistant strains[7]. Other nucleotides adefovir and famciclovir are not as effective or due to their nephrotoxicity are not used so widely as a first line therapy in liver transplant patients[8]. It has already been documented that HBV recurrence can be reduced with the use of alpha-interferon prior to transplantation and HBIg after transplantation[9]. Several studies demonstrated a reduction in re-infection in improved patients and graft survival after prophylaxis with HBIg[10]. The use of alpha-interferon is contraindicated in decompensated liver disease due to the deleterious side effects and it was not an option in our patients[11].

HBIg is a polyclonal preparation of human anti-HBs purified from pooled donor plasma. HBIg products provide passive immunization and significantly decrease HBV recurrence and increase in graft and pa-

tient survival in liver transplantation for hepatitis B related liver disease[12]. HBIg immmunoprophylaxis is based upon the rationale that administration of hepatitis B surface antibodies (anti-HBs) will bind and neutralize circulating virons and thus preventing HBV reinfection[13]. The clinical effectiveness of HBIg prophylaxis in the prevention of HBV recurrence following liver transplantation is dependent on the dose, length of administration and the viral replication status of the patients at the time of transplantation[14]. Serum HBV DNA level at the time of transplant is very important predictor of the half life of HBIg[15].

HBIg is most effective when administered in high doses and for longer duration of time[16]. The standard protocol for prevention of post-transplant hepatitis B consisted of HBIg as an intravenous dose of 35-ml (10,920 anti-HBs). The first dose should be administered at the time of hepatic transplantation (the anhepatic phase) with subsequent daily dosing from day 1 through day 7 post-operatively, followed by twice weekly dosing from day 14 to 3 months and there after, from month 4 onwards once monthly for six months[17]. All our patients received the initial dose of HBIg in China and then followed in SQUH as above protocol.

Anti-HBs level was monitored every month and if anti-HBs level was less than 100-IU, we transfused HBIg. Along with HBIg, lamivudine should be given daily and continued indefinitely[18]. The high dose of HBIg has stimulated studies evaluating strategies involving low dose HBIg with nucleoside analogue. Studies suggested use of low dose HBIg (400-800 IU daily for one week than monthly) intramuscularly along with same dose of lamivudine[19].

The aim of therapy is to maintain anti-HBs titre of at least 100 IU/L, which is considered as a protective dose. However some studies have suggested that the rate of re-infection can be further reduced by increasing titre above 500 IU/L[20].

In our study we used both intravenous and intramuscular routes, though the total dose and cost of HBIg in I/M group was much less as compared to intravenous group with similar efficacies. Such results have been described in other studies[21].

CONCLUSION

In conclusion, prevention of recurrence of hepatitis B in post liver-transplant patients can be achieved by HBIg and lamivudine. The dose and cost of HBIg can be reduced by using I/M route of administration, which is also safe and equally effective as I/V route. A larger study is recommended in similar population to validate our results.

REFERENCES

1. O'Grady JG, Smith HM, Davies SE, Daniels HM, Donaldson PT, Tan KC, et al. Hepatitis B virus reinfection after orthotopic liver transplantation. J Hepatol 1992;14:104-11.
2. Schilling R, Ijaz S, Davidoff M, Lee JY, Locarnini S, Williams R, et al. Endocytosis of hepatitis B immunoglobulin into hepatocytes inhibits the secretion of hepatitis B virus surface antigen and virons. J Virol 2003;77:8882-92.
3. Buti M, Mas A, Prieto M, Casafont F, González A, Miras M, et al. A randomized study comparing lamivudine monotherapy after a short course of hepatitis B immunoglobulin (HBIg) and lamivudine with long term lamivudine plus HBIg in the prevention of hepatitis B virus recurrence after liver transplantation. J Hepatol 2003;38:811-7.
4. Schiff ER, Lai CL, Hadziyannis S, Neuhaus P, Terrault N, Colombo M, et al. Adefovir dipivoxil therapy for lamivudine-resistant hepatitis B in pre- and post-liver transplantation patients. Hepatology 2003;38:1419-27.
5. Steinmüller T, Seehofer D, Rayes N, Müller AR, Settmacher U, Jonas S, et al. Increasing applicability of liver transplantation for patients with hepatitis B- related liver disease. Hepatology 2002;35:1528-35.
6. Han SH, Martin P, Edelstein M, Hu R, Kunder G, Holt C. Conversion from intravenous to intramuscular hepatitis B immune globulin in combination with lamivudine is safe and cost-effective in patients receiving long-term prophylaxis to prevent hepatitis B recurrence after liver transplantation. Liver Transpl. 2003;9:182-7
7. Perrillo R, Schiff E, Yoshida E, Statler A, Hirsch K, Wright T, et al. Adefovir dipivoxil for the treatment of lamivudine-resistant hepatitis B mutants. Hepatology 2000;32:129-34.
8. Angus PW, Patterson SJ, Strasser SI, McCaughan GW, Gane E. A randomized study to assess the safety and Efficacy of adefovir dipivoxil substitution for Hepatitis b immune globulin in liver transplantation Patients receiving long-term low dose Im hbig and lamivudine prophylaxis. Hepatology 2007;46(Suppl 1):238A.
9. Terrault N, Roche B, Samuel D. Management of the hepatitis B virus in the liver transplantation setting: a European and an American perspective. Liver Transpl 2005;11:716-32.
10. Marzano A, Salizzoni M, Debernardi-Venon W, Smedile A, Franchello A, Ciancio A, et al. Prevention of hepatitis B virus recurrence after liver transplantation in cirrhotic patients treated with lamivudine and passive immunoprophylaxis.

J Hepatol 2001;34:903-10.
11. Perrillo R, Tamburro C, Regenstein F, Balart L, Bodenheimer H, Silva M, et al. Low-dose, titratable interferon alfa in decompensated liver disease caused by chronic infection with hepatitis B virus.. Gastroenterology 1995;109(3):908-16.
12. Roche B, Samuel D. Liver transplantation for hepatitis B virus related liver disease: indications, prevention of recurrence and results. J Hepatol 2003;39:S181-9.
13. Samuel D, Muller R, Alexander G, Fassati L, Ducot B, Benhamou JP, et al. Liver transplantation in European patients with hepatitis B surface antigen. N Eng J Med 1993;329:1842-7.
14. Tchervenkov JI, Metrokas P, Deschenes M, Alpert E, Tector AJ, Cantarovich M, et al. Decreasing viral load pre transplant and passive immunoprophylaxis with hepatitis B immunoglobulin post transplant prevents hepatitis B virus recurrence after liver transplantation: an 8-year single-centre experience. Transplant Proc 2001;33(1-2):1514-5.
15. Marzano A, Gaia S, Ghisetti V, Carenzi S, Premoli A, Debernardi-Venon W, et al. Viral load at the time of liver transplantation and risk of hepatitis B virus recurrence. Liver Transpl 2005;11:402-9.
16. Wong SN, Chu CJ, Wai CT, Howell T, Moore C, Fontana RJ, et al. Low risk of hepatitis B virus recurrence after withdrawal of long-term hepatitis B immunoglobulin in patients receiving maintenance nucleos(t)ide analogue therapy. Liver Transpl 2007;13:374-81.
17. Kim WR, Poterucha JJ, Kremers WK, Ishitani MB, Dickson ER. Outcome of liver transplantation for hepatitis B in the United States. Liver Transpl 2004;10:968-74.
18. Kim KM, Chol H, Hwang S. Efficacy of combination prophylaxis with short term HBIg and long-term lamivudine in preventing de novo hepatitis B infection in orthotopic liver transplant recipients HBcAb positive donors. Hepatology 2000;32:292 A.
19. Gane EJ, Angus PW, Strasser S, Crawford DH, Ring J, Jeffrey GP,. Lamivudine plus low-dose hepatitis B immunoglobulin to prevent recurrent hepatitis B following liver transplantation. Gastroenterology 2007;132:931-7.
20. Terrault NA, Zhou S, Combs C, Hahn JA, Lake JR, Roberts JP,. Prophylaxis in liver transplant recipients using a fixed dosing schedule of hepatitis B immunoglobulin. Hepatology 1996;23:1327-33.
21. Yao FY, Osorio RW, Roberts JP, Poordad FF, Briceno MN, Garcia-Kennedy R. et al. Intramuscular hepatitis B immune globulin combined with lamivudine for prophylaxis against hepatitis B recurrence after liver transplantation. Liver Transpl Surg. 1999;5(6):491–496.

AUTHOR AFFILIATION:

Prof. Aftab Ahmed Siddiqui *(Corresponding Author)*
Head, Department of Medicine
Liaquat College of Medicine and Dentistry/
Darul-Sehat Hospital
Karachi, Sindh-Pakistan.

Dr. Rakhshinda Jabeen
Assistant Professor of Medicine
Liaquat College of Medicine and Dentistry/
Darul-Sehat Hospital
Karachi, Sindh-Pakistan.

Dr. Moin Ahmed Ansari
Consultant Psychiatrist
Liaquat National Hospital
Karachi, Sindh-Pakistan.

Dr. Majid Ali Soomro
Lecture Department of Medical Education
Liaquat University of Medical and Health Sciences
Jamshoro, Sindh-Pakistan.

Dr. Saeed Ahmed
Registrar Gastroenterology/Medicine
Sultan Qaboos University Hospital
Al-Khod Muscat Oman.

Dr. Masoud Bakheet Khashoub
Sr. Consultant Gastroenterology/Director General
Sultan Qaboos University Hospital
Al-Khod Muscat Oman.