Turk J Gastroenterol *2014; 25 (Suppl.-1): 26-31*

Evaluation of immunity status to routine vaccination in pediatric liver transplant candidates

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Original Article

ABSTRACT

Background/Aims: Generally, prevention of infections by vaccination is the least invasive and most cost-effective approach to reduce the incidence of infections and the morbidity and mortality in transplant recipients. Genetic diversity and different liver disease among patients contributes to variability in immune responses to vaccines and pathogens. The aim of this study was to evaluate immunity status to different vaccinated organisms in pediatric liver-transplant candidates.

Materials and Methods: The vaccination charts of 90 patients who were referred to Organ Transplant Center of Shiraz University of Medical Sciences were reviewed and compare with National Immunization Program recommendation, after that 10 mL blood was drawn from these patients for serologic studies by ELISA.

Results: Eighty percent of the patients had protective antibody titers for poliomyelitis, 65.6% for rubella, 62.3% for diphtheria, 60% for tetanus, 57.7% for pertussis, 55.5% for measles, 42.2% for hepatitis B and 36.7% for mumps.

Conclusion: Overall seroconversion rates were not satisfactory for many infections that may be due to lower rate of vaccination or even the underlying liver disease that interfere with optimal immunogenecity of vaccination. Therefore, vaccination charts should be periodically reviewed and updated, also repeated measurements of serum antibodies and appropriate revaccination if titers decline is recommended to prevent the vaccine-preventable disease in liver transplant candidates after transplant.

Keywords: Immunity status, vaccination, liver transplantation candidate, children

INTRODUCTION

Solid Organ transplant (SOT) recipients are at increased risk of bacterial infections (1). This has also been shown in pediatric SOT recipients, who (like their adult counterparts) require immunosuppressive medications to prevent graft rejection (2). Children face the additional burden of increased risk of infections because they may not have developed protective antibodies before transplantation was performed. Moreover, the effects of long-term immunosuppressive agents during critical time points of immune maturation in these children are not well understood (3). Generally, prevention of infections by vaccination is the least invasive and most cost-effective approach to reduce the incidence of infections and the morbidity and mortality in transplant recipients.

The adequate immunization of the transplant candidate, transplant recipient and transplant clinician should be a prominent goal of transplant centers in accordance with increasing emphasis on patient safety and adherence to existing guidelines (4). Also considering the young age of the transplant candidates and the urgency for transplantation, initiation of vaccine series earlier and shortening the intervals between the vaccine doses seems to be rational.

Genetic diversity among humans contributes to variability in immune responses to vaccines and pathogens; for example, some individuals do not respond to hepatitis B virus (HBV) vaccines despite no apparent immune defect (5).

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Received: March 07, 2013 **Accepted:** October 10, 2013
 • Available online at www.turkjgastroenterol.org • DOI: 10.5152/tjg.2014.5139

Post-transplantation immunosuppressive regimens interfere with the immune responses required for successful immunization in various ways (6). Immunosuppressive agents may influence the B-cell responses important for an effective response to immunization either directly, as a consequence of their antiproliferative potential, or via their impact on T-helper cells and relevant cytokines. Hence in SOT recipients, primary immunization should be undertaken before the start of the immunosuppression to permit the creation of a memory cell pool.

Although previous studies shows that immunization with live-attenuated vaccines are contraindicated in post-transplant children, Shinjoh et al. recommended that immunization using selected live-attenuated vaccines were safe and effective for post-transplant children who were not severely immunosuppressed (7). But other serologic studies shows that it is much more better to do so before transplantation rather than after that.

The aim of this study was to evaluate the immunity status to measles, rubella, mumps, tetanus, diphtheria, poliomyelitis, pertussis and hepatitis B in children who candidate for liver transplantation.

MATERIALS AND METHODS

All pediatric liver transplant candidates aged between 9 months and 18 years old, who were referred to Organ Transplantation Center of Nemazee Hospital, affiliated to Shiraz University of Medical Science, between May 2007 and June 2008 were invited to participate in this study. This tertiary care hospital is the only hospital in Iran in which pediatric liver transplantation is actively performed. Parents or legal guardians were instructed to bring the vaccination charts on the next out-patient appointment.

After giving written informed consent, parents or legal guardians were interviewed, and the vaccination charts were subsequently evaluated. Only charts that had been officially filled out with information about the vaccines were considered.

The vaccination status was considered appropriate according to the recommendation of the National Immunization Program (NIP), currently applied to all Iranian children (8). The recommended schedule by the NIP includes: BCG (Bacillus Calmette Guerin) vaccine, OPV (Oral Polio Vaccine), DTwP (Diphtheria, Tetanus, Pertussis) vaccine, MMR (Mumps, Measles, Rubella) vaccine and HBV vaccine. (Table 1) All of these programs are government sponsored.

Yellow fever vaccine was not included in the current vaccination schedule because it is not endemic in Iran. Also Haemophilus influenza and conjugated Streptococcus pneumoniae and Varicella zoster vaccines are not parts of NIP. Patients, whose vaccination charts were not updated, were further referred to the Immunization Center for vaccination.

After interview with the parents, a blood sample of 7.5-10 mL was drawn from the children by parents' permission and send to microbiology lab for serologic studies. At laboratory bloods were centrifuged immediately and plasmas were separated and freezed in -70 degrees of centigrade. All instructions were followed as recommended by companies of the Kits provider.

Antibody levels against HBV were measured by ELISA (DIA.PRO Diagnostic Bioprobes Srl Milano-Italy). Anti-hepatitis B surface (anti HBs) antibody titers >10 WHO mIU/mL were considered protective (9). The diagnostic sensitivity of the tests was 100% with the specificity value >98%.

Antibody against mumps, measles and rubella were measured by ELISA (IBL Hamburg-Germany). Antibody titers against mumps were considered protective >10 IU/mL, against measles >255 mIU/mL (10). Anitibodies against rubella >15 IU/mL were considered protective, 10-15 IU/mL equivoval and <10 IU/mL non reactive (10), with sensitivity of 100% and specificity of >98.8%. Tetanus and diphtheria antitoxin values were determined by ELISA (DIA.PRO Diagnistic Bioprobes Srl Milano-Italy), values >0.1 and >0.01 IU/mL were considered protective respectively (11). Also antibody against pertussis was measured by ELISA and antibody concentration ≥1µg/mL was considered protective. Antibodies against polio virus were measured by ELISA (Demeditec Diagnostic GmbH-Germany) and values

Table 1. Vaccination protocol of Iran recommended by National Immunization Program

Vaccine	Description	Schedule	Comments
BCG	Bacille Calmette-Guérin vaccine	Birth	
DTwP	Diphtheria and Tetanus toxoid with whole cell Pertussis vaccine	2, 4, 6, 18 months; 6 years	
HBV	Hepatitis B vaccine	Birth; 2, 6 months	Also specified high risk group
MMR	Measles, Mumps, Rubella vaccine	12, 18 months	
OPV	oral Polio vaccine	Birth; 2, 4, 6, 18 months; 6 years	
Td	Tetanus and Diphtheria toxoid for older children/ adults		Rrepeated every 10 years

BCG: bacillus calmette guerin; HBV: hepatitis B virus; OPV: oral polio vaccine; DTwP: diphtheria; tetanus, pertussis; MMR: mumps, measles, rubella

>150 U/mL were considered positive, with sensitivity >99% and specificity value >98%.

Due to NIP in which protocols for all vaccines are completed at four years old and boosters are started next, the patients were divided into two different groups according to their age (less than four years of age and more than four years at the evaluation) and then the results of the antibody tests were gathered and compared with the history of vaccination documented in vaccination charts.

The study was performed in accordance with the principles of the Declaration of Helsinki 2000 and was approved by the local Ethics Committee of the Shiraz University of Medical science.

RESULTS

Ninety patients were participated in our study, the mean age was 8.9 years (range, 9 months-18 years) and 48 (53.3%) of candidates were boys.

Fifty-two patients (57.8%) had received complete doses of HBV vaccine and seventy-nine patients (87.8%) received complete doses of OPV.

Eighty-eight of patients (97.8%) received the single dose of BCG vaccine.

Fifty-eight of the patients (64.4%) received complete doses of DTwP according to NIP. Fifty (55.5%) of the patients received complete doses of MMR vaccines. Two (2.2%) of the patients had not received any vaccination.

Of these 90 children thirty-eight patients (42.2%) had protective antibodies against HBV, of whom fourteen patients (15.6%) were under four years old (13.3% received complete doses of HBV vaccine and 2.3% received only one dose of HBV vaccine) also twenty-four patients (26.6%) were older than four years old (15.6% received complete doses of HBV vaccine and 11% received only one dose of HBV vaccine), and fifty-one patients (56.7%) had no protective antibody against HBV, of whom 5.5% were under four years old with complete vaccination and 51.2% were older than 4 years old (17.8% received complete vaccination and 33.4% did not). Also one result (1.1%) was reported equivocal.

The rates of protective antibodies production in liver-transplant candidates with history of complete and incomplete vaccination are shown in Table 2.

Of 90 patients, seventy-two (80%) had protective antibodies against polio virus of whom twelve patients (13.3%) were under four years old who received incomplete doses of OPV vaccine. Sixty patients (66.7%) were older than four years old (53.3% received complete doses of OPV vaccine and 13.4% received only one dose of OPV vaccine, and seventeen patients (18.9%) had no protective antibody against OPV, of whom 5.6% were under four years old with history of incomplete vaccination and 13.3% were older than four year old (4.5% received complete vaccination and 8.8% did not). Also one result (1.1%) was reported equivocal.

Fifty-six patients (62.3%) had protective antibodies against diphtheria of whom twelve patients (15.6%) were under four years old who received incomplete doses of diphtheria vaccine. Forty-two (46.8%) were older than four years old (20% received complete doses of diphtheria vaccine and 26.8% received incomplete doses of diphtheria vaccine, and thirty-four patients (37.7%) had no protective antibody against diphtheria, of whom 4.4% were under four years old with history of incomplete vaccination and 33.3% were older than four year old (20 % received complete vaccination and 13.3% did not).

Fifty-four patients (60%) had protective antibodies against tetanus toxoid of whom fifteen patients (16.7%) were under four years old who received incomplete doses of tetanus toxoid. Thirty-nine patients (43.3%) were older than four years old (22.2% complete doses of tetanus toxoid and 21.1% received incomplete doses of vaccine), and thirty-six patients (40%) had no protective antibody against tetanus toxoid, of whom 3.3% were under four years old with history of incomplete vaccination and 36.7% were older than four year old (17.7% received complete vaccination and 19% did not).

Fifty-two patients (57.7%) had protective antibodies against pertussis. None of whom was under four years old. Fifty-two patients (57.7%) were older than four years old (11% received incomplete doses of DTwP vaccines and 46.7% received complete doses of vaccine), and thirty-eight patients (42.3%) had no protective antibody against pertussis, of whom 20% were under four years old (12.3% with history of incomplete vaccination and 7.7% with history of complete vaccination), 22.3% were older than four year old (13.3% received complete vaccination and 9% did not).

Table 2. The rates of protective antibodies production (immune response) in liver-transplant candidates with history of complete and incomplete vaccination

Vaccine	Total (%)	Complete vaccination (%)	Incomplete vaccination (%)
HBV	42.2	62	28.5
Polio	80	92.3	75
Diphtheria	62.3	50	42.4
Tetanus	60	55.6	37.8
Pertussis	57.7	68.8	34.4
Mumps	36.7	35.2	40
Measles	55.5	68.1	51.4
Rubella	65.6	91	63.9

HBV: hepatitis B virus

Thirty-three patients (36.7%) had protective antibodies against mumps of whom six patients (6.7%) were under four years old who received incomplete doses of MMR vaccines. Twenty-seven patients (30%) were older than four years old (23.3% received incomplete doses of MMR vaccines and 6.7% received complete doses of vaccine), and fifty-seven patients (63.3%) had no protective antibody against mumps, of whom 13.3% were under four years old with history of incomplete vaccination and 50% were older than four year old (18.9% received complete vaccination and 31.1% did not).

Fifty patients (55.5%) had protective antibodies against measles of whom nine patients (10%) were under four years old who received incomplete doses of MMR vaccines. Forty-one patients (45.5%) were older than four years old (28.8% received incomplete doses of MMR vaccines and 16.7% received complete doses of vaccine), and forty patients (44.5%) had no protective antibody against measles, of whom 10% were under four years old with history of incomplete vaccination and 34.5% were older than four year old (7.8% received complete vaccination and 26.7% did not).

Fifty-nine patients (65.6%) had protective antibodies against rubella of whom two patients (2.2%) were under four years old who received incomplete doses of MMR vaccines. Fifty-seven patients (63.4%) were older than four years old (41.2% received incomplete doses of MMR vaccines and 22.2% received complete doses of vaccine), and twenty-four patients (26.7%) had no protective antibody against rubella, of whom 13.3% were under four years old with history of incomplete vaccination and 13.4% were older than four year old (2.2% received complete vaccination and 11.2% did not). Also seven results (7.7%) were reported equivocal. The rate of inadequate antibody titers in liver-transplant candidates with history of incomplete vaccination are shown in Figure 1.

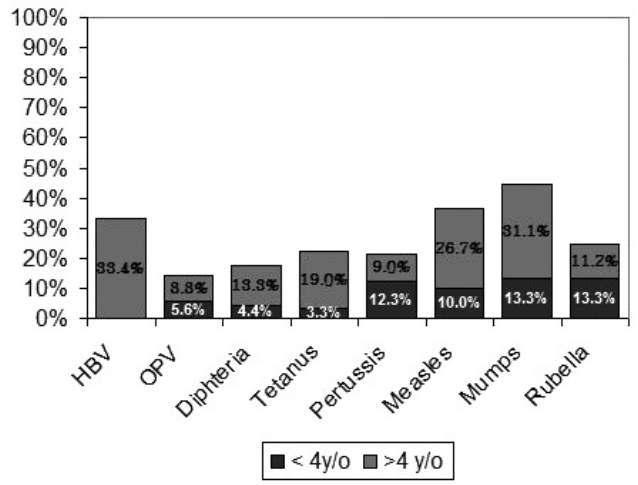

Figure 1. Rate of inadequate antibody titers in liver-transplant candidates with history of incomplete vaccination.

DISCUSSION

This study reports a low incidence of adequate immunization for some vaccines (HBV, DTwP and MMR) in liver transplant candidates compare to normal children although the incidence of immunization is good for others (BCG and OPV).

In serologic studies we observed that the rate of protective antibodies are highest for polio and is lowest for mumps. This was not expected for us because due to high incidence of mumps in our country and also high rate of subclinical infection, we expected to notice higher rate of protection for this organism even in the absent of immunization. Also due to world wide eradication program for polio the rate of protective antibody is relatively good and highest compare to others. The rates of protective antibodies in our patients are significantly lower than the other studies; Balloni et al. found rates of 86.2% for diphtheria and 100% for tetanus in their study (12). Also Kano et al. found the rates of seroconversion against measles, rubella, and mumps after pre-transplantation vaccination 82%, 100% and 95% respectively (13). Worns et al. documented that seventy-six percent of the vaccinated patients with autoimmune liver disease (against HBV vaccine) developed anti-HBs antibody (14).

The actual immune level of the patients depends on several factors: natural disease, natural booster, immunization, and host-related factor. As we see in this study for some infections (polio, rubella, diphtheria and tetanus), there is a relatively higher rate of protective antibodies.

Immunogenecity of vaccination in chronic liver disease patients may be barrier to optimal protection and some children with chronic liver disease may not respond optimally to primary vaccination producing lower serum antibodies (15). Also immunosuppressive therapy for underlying liver disease may interfere with immunogenecity of the vaccines (12). This was seen in our study for some vaccines such as HBV vaccine, tetanus toxoid, diphtheria vaccine, mumps, measles and rubella (MMR) vaccines, that there is low rate of protective antibody even in patients with history of complete vaccination. This can be overcome in some patients by repeated vaccination with increasing dose, e.g. in case of hepatitis B (16) or by some special vaccination programs recommended by some authors (17,18). Our study revealed that the rates of protective antibodies are higher for patients with more than four years of age at the time of study especially in patients who had history of complete vaccination. This may be due to repeated vaccination episodes in this group of the patient according to older age.

The rates of inadequate antibody titers are high for HBV, measles, mumps, and pertussis; these show that immunization for these common infections should be considered more strongly.

There are many guidelines for vaccination of SOT candidates (18) and Kano et al. (13) proved the efficacy and safety of im-

munization for pre- and post- liver transplant children, but larger studies are needed to establish the efficacy and safety of immunization after transplantation.

Overall, seroconversion rates were not satisfactory for many infections that may be due to lower rate of vaccination or even the underlying liver disease that interfere with optimal immunogenecity of vaccination.

As antibody titers reflect the immediate immune response to a vaccine, they are only surrogate markers for potential long-term protection. Titers considered to be protective for healthy children may not prevent infections in children with chronic liver disease or in immunocompromised children after transplantation.

Therefore, achievement of antibody titers does not always correlate with true protection from infection, for these reasons one should remain vigilant.

The vaccination charts should be periodically reviewed and updated specially by family physicians and primary health care providers where these children are visited more often so as to prevent the vaccine-preventable disease in liver-transplant candidates before transplantation and also repeated measurements of serum antibodies and appropriate revaccination if titers decline (19).

Because of the young age of many of the transplant candidates and the urgency of transplantation, they may require initiating vaccine series earlier and with shorter intervals between the vaccine doses than the program routinely recommended by NIP.

Although Haemophilus influenza and Streptococcus pneumoniae and Varicella zoster virus are major cause of infections and morbidity in pediatric age group with more emphasis in immunocompromised children such as post SOT children, these vaccine are not included in our NIP (19). It is recommended to add these vaccines at least to vaccination program of such high risk patients. It remains unclear whether liver transplant recipients are at an increased risk of meningococcal disease. However, the meningococcal polysaccharide vaccine might be recommended for all candidates (4).

Tetanus, diphtheria and pertussis immunization is part of the routine vaccination series for infants and young children, but until recent years adolescents and adults received only booster doses of tetanus-diphtheria (Td) vaccine. In accordance with Advisory Committee on Immunization Practices (ACIP) guidelines for the general public, it would make sense to vaccinate transplant candidates with TdaP during the pre-transplant evaluation when the clinician would otherwise administer a Td booster (4).

Another sources of infection in these patients are infectious disease in family members therefore it is recommended to also follow vaccination program of family members of such high risk patients to optimize vaccination status in family members and prevent vaccine-preventable disease in family and therefore in the patients.

Conflict of Interest: No conflict of interest was declared by the authors.

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