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Erythropoietin Use and Immunogenicity of Hepatitis B Virus Vaccine in Chronic Kidney Disease Patients: A Meta-Analysis

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Key Words
Recombinant human erythropoietin · Hepatitis B virus · Vaccine · Chronic kidney disease · Dialysis · Meta-analysis

Abstract
Background: It is known that the immunogenicity of hepatitis B virus (HBV) vaccine is lower in uremic patients than healthy subjects. Numerous inherited or acquired factors have been implicated in this lowered response, and the high frequency of recombinant human erythropoietin use among patients on maintenance dialysis has been suggested to play a pivotal role. However, the impact of therapy with recombinant erythropoietin on the immune response to HBV vaccine in patients with chronic kidney disease (CKD) is not appropriately detailed. ***Aim:*** To evaluate the influence of human recombinant erythropoietin therapy on the immunological response to HBV vaccine in CKD patients by performing a systematic review of the literature with a meta-analysis of clinical studies. ***Methods:*** We used the random-effects model of DerSimonian and Laird with heterogeneity and sensitivity analyses. The end-point of interest was the rate of patients showing seroprotective anti-hepatitis B titers at completion of a hepatitis B vaccine schedule among human erythropoietin users versus those who did not receive the drug in a CKD population. ***Results:*** We identified 11 studies involving 862 unique patients with CKD. Aggregation of study results did not show a significant increase in response rates among erythropoietin user versus non-user patients (pooled odds ratio = 1.431; 95% CI 0.954; 2.146), according to a random-effects model. No heterogeneity was found, the p value was 0.1 for our test of study heterogeneity ($Q = 14.147$). Stratified analysis in various subgroups of interest did not significantly change these findings. ***Conclusions:*** Our meta-analysis showed no link between immunological response to HBV vaccine and therapy with human recombinant erythropoietin among individuals on long-term dialysis. We suggest the use of recombinant vaccine towards hepatitis B in patients on regular dialysis irrespective of erythropoietin treatment.

Introduction

Control of the spread of hepatitis B virus (HBV) infection in dialysis units has been an important goal in the management of end-stage renal disease [1]. On a

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global basis, hepatitis B is one of the most important infectious diseases all over the world and patients on maintenance dialysis remain at an increased risk of exposure to HBV. If infected, patients on maintenance dialysis are at considerable risk of becoming chronic carriers due to poor cellular and humoral immune responses [1]. To prevent transmission of HBV in hemodialysis (HD) settings, numerous measures have been made including the screening of blood for HBV surface antigen (HBsAg), the decline in the number of blood transfusions received by dialysis patients because of recombinant human erythropoietin (rHuEPO) use, and the implementation of universal and specific measures within dialysis rooms, as recommended by the Centers of Disease Control and Prevention (CDC; Atlanta, Ga., USA) [2]. Hepatitis B vaccination is another factor responsible for the decline in HBsAg incidence rates among dialysis patients in recent years. However, recent data underline that the proportion of patients and staff within dialysis units who receive HBV vaccine on a routine basis is still low [3, 4].

Patients on maintenance dialysis typically show a suboptimal immune response to HBV vaccine compared with the non-uremic population (40–50 vs. >95%). In addition, anti-HBs titers in uremic patients are lower and decline faster [1]. The impaired immune response to HBV vaccination appears to extend to other vaccination schemes [5] and may help explain the high incidence of general infections in the dialysis population. Previous clinical studies have implicated a number of factors as predictors of seroconversion to HBV vaccine among patients on long-term HD [1], including rHuEPO which has been used widely in the treatment of renal anemia for two decades. The goal of this study was to investigate the available evidence on the relationship between erythropoietin use and immunological response to HBV vaccine in a long-term dialysis population by performing a systematic review of the literature with a meta-analysis of clinical studies.

Material and Methods

Search Strategy and Data Extraction

We performed electronic searches of the National Library of Medicine's MEDLINE database, Current Contents, and manual searches of selected speciality journals to identify all pertinent literature. It has previously been demonstrated that an electronic search alone may not be sensitive enough [6]. Four MEDLINE database engines (Ovid, PubMed, Embase and GratefulMed) were used. The key words 'hepatitis B', 'vaccine', 'erythropoietin', and 'chronic kidney disease' (CKD) were used. Reference lists from qualitative topic reviews and published clinical trials were also searched. Our search was limited to human studies that involved individuals aged >19 years published in the English literature. All articles were identified by a search from January 1990 to November 2010. Data extraction was conducted independently by two investigators (F.F. and V.D.) and consensus was achieved for all data. Studies were compared to eliminate duplicate reports for the same patients, which included contact with investigators when necessary. Eligibility and exclusion criteria were prespecified.

Inclusion Criteria

We included studies evaluating patients with CKD. Studies restricted to students, military recruits or other cohorts that involved subjects <19 years of age were excluded. Many studies have identified an effect of erythropoietin therapy on response rate to hepatitis B vaccine. However, only studies that (i) specified either a relative risk and a measure of variance for vaccine response among CKD patients on rHuEPO therapy, compared with those who did not receive rHuEPO, or (ii) presented data in a form that could be used to construct a 2×2 contingency table were considered for final inclusion. Both randomized-controlled trials and observational studies were considered eligible for inclusion in the analysis. We included trials using plasma-derived or recombinant DNA hepatitis B vaccine. The decision as to inclusion or exclusion of clinical trials was not related to results. All dose schedules and routes of administration were included, as long as they involved primary vaccination regimens and not booster doses only. Patients who underwent a primary vaccination schedule (naive patients) or those who had failed to respond to a prior vaccine schedule (non-responder patients) against hepatitis B were enrolled.

Ineligible Studies

Studies were excluded if they reported inadequate data on measures of response, or included individuals with positive serology for HBsAg, antibodies to HBsAg (anti-HBs antibody) or human immunodeficiency virus (anti-HIV). Reports that were only published as abstracts or as interim reports were excluded; letters and review articles were not considered for this analysis. Studies that involved renal transplant recipients were excluded.

End-Points of Interest

We compared the seroprotection rate after completion of HBV vaccination schedule in CKD patients on rHuEPO therapy versus those who did not receive this drug. Patients vaccinated against HBV are considered immune if protective titers of anti-HBs antibody can be demonstrated after completion of vaccination. The level of antibody production that defines seroprotection was 10 IU/ml across the studies. These definitions were consistent with standards published in the scientific literature.

Statistical Methods

In all reports included in this analysis, data from patients who did not complete the vaccination schedule were excluded from the final analysis; thus, analysis was made by per-protocol, not by intention-to-treat. A summary estimate of the odds ratio (OR) for seroresponse after vaccination among CKD patients on rHuEPO therapy versus those who did not receive it was generated by use of a random-effects approach, as described by DerSimonian and Laird [7]. Cochrane's Q test was used for quantifying the heterogeneity [8]; the I^2 index, the percentage of total variation across studies due to heterogeneity rather than chance [9], was also used. The Galbraith plot was made to assess the heterogeneity and precision of single studies [10]. Pooled ORs were calculated in subgroups of clinical studies as sensitivity analyses. The publication bias assessment, i.e. the number of void or negative trials necessary to render the meta-analysis meaningless, was made according to the Klein formula [11]. The publication bias was also measured by the test of funnel plot asymmetry. The 5% significance levels were used for α risk. Every estimate was given with its 95% confidence Intervals (95% CI).

Results

Literature Review

Our electronic and manual searches identified 94 publications which were selected for full text review. 83 studies were excluded because they did not fulfill the inclusion criteria. A list of the 94 bibliographic references is available from the authors on request. Eleven papers [12–22], representing a total of 862 unique patients, were included in our meta-analysis. There was a 100% concordance between reviewers with respect to final inclusion and exclusion of studies reviewed based on the predefined inclusion and exclusion criteria.

Table 1. Baseline characteristics of studies included in the analysis

Reference (first author)	Country	Patients n	Publication year
Sennesael [12]	Belgium	37	1991
Lombardi [13]	Italy	35	1992
Khan [14]	USA	97	1996
Navarro [15]	Spain	36	1996
Peces [16]	Spain	80	1997
Anandh [17]	India	77	2000
Hassan [18]	Israel	69	2003
DaRoza [19]	Canada	165	2003
Kara [20]	Turkey	15	2004
Chow [21]	Hong Kong	64	2006
Afsar [22]	Turkey	187	2009

Patient Characteristics

Some salient demographic characteristics of subjects enrolled in the included clinical trials are shown in table 1. The great majority (8 of 11, 73%) of studies were from centers in the developed world. There was 1 randomized clinical trial [17] and 10 cohort studies, 2 prospective [16, 19] and 2 retrospective [20, 21]. The design of the study (prospective or retrospective) remained unclear in 5 studies [12, 13, 15, 18, 22]. Khan et al. [14] collected prospectively data on HD and retrospectively on peritoneal dialysis (PD) patients.

Most (9/11 = 82%) reports concerned patients on maintenance dialysis; 2 addressed CKD patients at the pre-dialysis stage [18, 19]. Patients on PD and HD were included in 2 (22%) reports [14, 21]; 9 concerned patients on maintenance HD only. Overall, 99 (12%) patients were on PD, 234 (27%) did not yet require maintenance dialysis, and 529 (61%) were on maintenance HD. All PD patients received continuous ambulatory PD. Only naive patients were addressed in the studies included in our meta-analysis.

As listed in table 2, recombinant HB vaccine was administered by intramuscular route in most clinical studies. The mean age of subject cohorts ranged from 32 to 68 years (table 3). The gender distribution ranged from 35 to 87% male.

Summary Estimates of Outcome

Aggregation of study results did not show a significant increase in response rates among rHuEPO users versus those patients who did not use the drug, the pooled OR was 1.431 (95% CI 0.954; 2.146), according to a random-effects model. No heterogeneity was found, the p value was 0.1 for our test of study heterogeneity ($Q = 14.147$). I^2

Table 2. Vaccine schedules of studies included in the analysis

Reference (first author)	Vaccine route	Vaccine schedule months	Vaccine dose μg
Sennesael [12]	recombinant, IM	0, 1, 2, and 6	20
Lombardi [13]	Pasteur, IM	0, 1, 2, 3, 4, 5, and 6	5
Khan [14]	recombinant, IM	0, 1, 2, and 6	40
Navarro [15]	recombinant, IM	0, 1, and 6	40
Peces [16]	recombinant, IM	0, 1, 2, and 6	40
Anandh [17]	recombinant, IM (n = 41) recombinant, ID (n = 36)	0, 1, 2, 3, 4, 5, and 6* 0, 1, 2, 3, 4, 5, and 6**	20
Hassan [18]	recombinant, IM	0, 1, 3, and 6	40
DaRoza [19]	recombinant, IM plasma-derived, IM	0, 1, and 6 0, 1, 2, and 6	40
Kara [20]	recombinant, IM	0, 1, 2, and 6	40
Chow [21]	recombinant, IM	0, 1, and 6	20 (n = 14) 40 (n = 26) 80 (n = 24)
Afsar [22]	recombinant, IM	0, 1, 2, and 6	40

* Once a week. ** Twice a week.

Table 3. Baseline characteristics of studies included in the analysis

Reference (first author)	Age, years	Males, n (%)	Time on dialysis, months
Sennesael [12]	60.3 ± 10/55.3 ± 11*	16 (55)/9 (53)*	31 ± 30/30 ± 29*
Lombardi [13]	56 ± 14/68 ± 6*	22 (63)	not available
Khan [14]	48.7 ± 16/50.1 ± 16**	52 (54)	38 ± 58/35 ± 58**
Navarro [15]	not available	22 (61)	not available
Peces [16]	58.5 ± 1.5	36 (45)	61 (7–220)
Anandh [17]	32 ± 16/34 ± 11*	67 (87)	not available
Hassan [18]	59 ± 11/61 ± 10*	35 (51)	not applicable
DaRoza [19]	59.8 ± 14.9	106 (64)	not applicable
Kara [20]	51 ± 12/38 ± 14**	9 (60)	35 ± 15/24 ± 13**
Chow [21]	43 ± 12	33 (51)	8.5 (1–33)
Afsar [22]	45.1 ± 14/49.1 ± 8**	66 (35)	99 ± 66/80 ± 57**

* Values expressed as control and treatment groups. ** Values expressed as converter and non-converter patients.

was 36.4 (95% CI 74.7; 0.0). The test of funnel plot asymmetry was not significant [α = 2.21; 95% CI –0.39; 4.81 (p = 0.10)]. Figure 1 shows the test for asymmetry of the funnel plot related to cases in figure 2.

We made a stratified analysis in order to obtain more homogeneous subgroups of studies. Table 4 shows that pooled ORs did not significantly change and no significant heterogeneity occurred among various study subgroups. The test of funnel plot asymmetry was not significant in all study subgroups (data not shown).

Discussion

Several in vivo and in vitro experiments have shown specific and varied deficiencies in the immune response of patients with CKD, such as decreased immunoglobulin production, diminished interleukin-2 secretion by T lymphocytes, and impaired macrophage function [23, 24]. Many clinical factors may be responsible for the lower seroconversion rate to recombinant hepatitis B vaccine in patients with CKD including older age [25], nutrition-

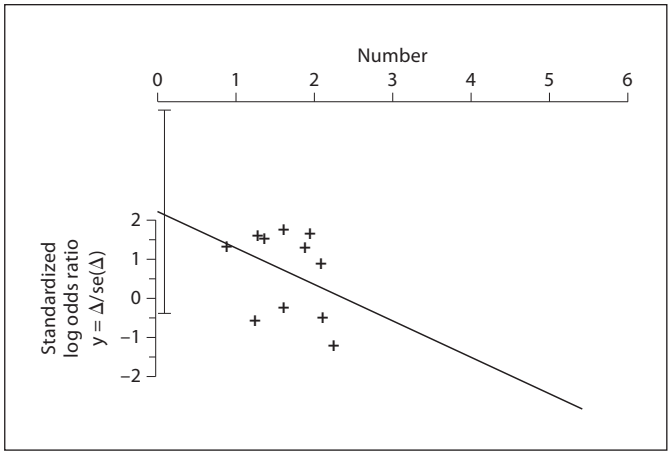

Fig. 1. Test of funnel plot asymmetry (primary analysis).

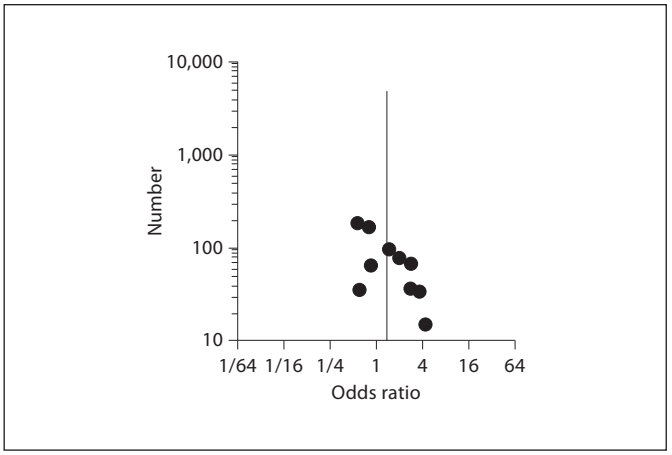

Fig. 2. Funnel plot (primary analysis).

Table 4. Pooled OR of failure to respond to vaccine (rHuEPO users vs. controls) in various subgroups of interest

	Random-effects model OR (95% CI)	*Q* (p)	I^2
All studies (n = 11)	1.431 (0.954; 2.146)	14.147 (0.166)	36.4
Patients on dialysis (n = 9)	1.453 (0.924; 2.287)	11.3 (1.0)	38.3
Cohort studies (n = 10)	1.352 (0.873; 2.093)	13.065 (0.1)	38.8
Patients on HD (n = 6)	1.467 (0.765; 2.813)	9.245 (0.1)	56.7
Studies from the Western world (n = 8)	1.484 (0.97; 2.26)	7.206 (0.4)	16.7

al status [26], HIV infection [27], possession of the major histocompatibility complex haplotype HLA-B [28], and diabetes mellitus [29], among others. Controversial evidence exists about the effect of rHuEPO therapy on the outcome of the immune response to four doses of recombinant HBV vaccine in a CKD population. Recent data indicate that rHuEPO have humoral and cellular immunomodulating properties. As an example, rHuEPO increases immunoglobulin production and proliferation of human B cells and B-cell lines [30]. It increases significantly CD4 and CD8 cells without changing the CD4/CD8 ratio, decreases the number of natural killer cells and supports the impaired phagocytic activity among patients on long-term HD [31]. Finally, rHuEPO supports in vitro T-cell mitogenic proliferation in HD patients [32]. According to this evidence, the activity of rHuEPO on the immune response to recombinant HBV vaccine in the dialysis population through, at least, some of these immunomodulating properties has been suggested.

Sennesael et al. [12] were the first to observe higher antibody titers (HBsAb) after completion of a vaccine schedule in dialysis patients on rHuEPO than in those who did not receive it. A significant and positive relationship between anti-HBs titers and T4/T8 lymphocyte ratio was described. They suggested an influence of rHuEPO administration on antibody titers at completion of the vaccine schedule by affecting T-cell subsets.

Our meta-analysis determined that rHuEPO therapy has no impact on the immunological response to hepatitis B vaccine in a dialysis population. Our results were robust as no significant heterogeneity occurred in primary and stratified analyses. No publication bias was found and analysis of various subgroups yielded only minimal changes on the effect size.

Our findings are consistent with data from other sources. In their observational study on 105 patients on maintenance HD, Eardley et al. [33] observed no significant difference in mean rHuEPO dose between responder and non-responders dialysis patients after a primary

course of vaccine [6,495 vs. 6,171 IU/week (p = 0.66)]. Identical results were obtained by Kovacic et al. [34]. No link between seroresponse rate and rHuEPO therapy, as assessed by rate of rHuEPO administration between responder and non-responder patients, was noted after the HBV vaccine schedule in another cohort study [35]. Liu et al. [36] observed an increment of anti-HBs titers between the initial month and the seventh month, related to rHuEPO dosage, in the control group only.

This meta-analysis is potentially limited in a number of ways. First, the number of patients available for our analysis was not very large (n = 862). Secondly, we have made a meta-analysis of observational studies and it is well known that a meta-analysis of randomized clinical trials is provided with better accuracy and reliability [37]. Finally, the quality of the studies included in this systematic review was not high and there is increasing evidence showing that the quality of studies affect outcome estimates [37]. The minimal changes on the effect size (pooled ORs) obtained with stratified analysis, the complete absence of heterogeneity and publication bias strengthen our conclusions.

Various approaches have been suggested in order to improve the response rate to hepatitis B vaccine in dialysis populations including increased vaccine doses [35] or shots, or intradermal vaccine route [38, 39]. Higher immunogenicity has been observed when HBV vaccine has been given to CKD patients not yet requiring regular dialysis [19]. Numerous vaccine adjuvants have been recommended, such as interferon, interleukin-2, levamisole, thymopentin, and granulocyte-macrophage colony-stimulator factor [reviewed in 1]. The CDC currently recommend that HD patients receive by intramuscular route double doses (20 μg twice) at 0, 1, and 6 months [2]. The CDC suggest the deltoid as the preferred injection site. Adverse reactions are mild and largely confined at the site of injection; systemic reactions are uncommon. Regular monitoring of antibody levels to ensure that antibody concentrations remain above the protective level of 10 mIU/ml and booster vaccination whenever the levels of antibody against hepatitis B surface antigen (anti-HBs titers) fall below 10 mIU/ml have been recommended [40]. Vaccination with recombinant vaccine should be performed in patients on maintenance dialysis irrespective of rHuEPO administration.

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Disclosure Statement

The authors have no conflicts of interest to disclose.

References

1 Fabrizi F, Martin P: Hepatitis B virus infection in dialysis patients. Am J Nephrol 2000;20:1–11.

2 Centers for Disease Control and Prevention: Recommendations for preventing transmission of infections among chronic haemodialysis patients. MMWR 2001;50:1–43.

3 Jibani MM, Heptonstall J, Walker AM, Bloodworth LO, Howard AJ: Hepatitis B immunization in UK renal units: failure to put policy into practice. Nephrol Dial Transplant 1994;9:1765–1768.

4 Finelli L, Miller JT, Tokars JI, Alter MJ, Arduino MJ: National surveillance of dialysis-associated diseases in the United States, 2002. Semin Dial 2005;18:52–61.

5 Kruger S, Muller-Steinhardt M, Kirchner H, et al: A 5-year follow-up on antibody response after diphtheria and tetanus vaccination in hemodialysis patients. Am J Kidney Dis 2001;38:1264–1271.

6 Poynard T, Conn HO: The retrieval of randomised clinical trials in liver diseases from the medical literature: a comparison of Medlars and manual methods. Control Clin Trials 1985;6:271–279.

7 DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.

8 Petitti DB: Approaches to heterogeneity in meta-analysis. Statist Med 2001;20:3625–3633.

9 Higgins JPT, Thompson SG, Deeks JI, Altman DG: Measuring inconsistencies in meta-analysis. Br Med J 2003;327:557–560.

10 Galbraith RF: A note on graphical presentation of estimated odds ratios from several clinical trials. Stat Med 1988;7:889–894.

11 Klein S, Simes J, Blackburn GL: Total parenteral nutrition and cancer clinical trial. Cancer 1986;58:1378–1386.

12 Sennesael J, van Der Niepen P, Verbeelen D: Treatment with recombinant human erythropoietin increases antibody titers after hepatitis B vaccination in dialysis patients. Kidney Int 1991;40:121–128.

13 Lombardi M, Pizzarelli F, Righi M, Cerrai P, Dattolo P, Nigrelli S, Michelassi S, Sisca S, Alecci A, Di Geronimo P, Maggiore Q: Hepatitis B vaccination in dialysis patients and nutritional status. Nephron 1992;61:266–268.

14 Khan A, Bernardini J, Rault R, Piraino B: Low seroconversion with hepatitis B vaccination in peritoneal dialysis patients. Perit Dial Int 1996;16:370–373.

15 Navarro J, Teruel J, Mateos M, Marcen R, Ortuno J: Antibody level after hepatitis B vaccination in hemodialysis patients: influence of hepatitis C virus infection. Am J Nephrol 1996;16:95–97.

16 Peces R, de la Torre M, Alcazar R, Urra JM: Prospective analysis of the factors influencing the antibody response to hepatitis B vaccine in hemodialysis patients. Am J Kidney Dis 1997;29:239–245.
17 Anandh U, Thomas P, Shastry J, Jacob CK: A randomised controlled trial of intradermal hepatitis B vaccination and augmentation of response with erythropoietin. J Assoc Physicians India 2000;48:1061–1063.
18 Hassan K, Shternberg L, Alhaj M, Giron R, Reshef R, Barak M, Kristal B: The effect of erythropoietin therapy and hemoglobin levels on the immune response to Engerix-B vaccination in chronic kidney disease. Ren Fail 2003;25:471–478.
19 DaRoza G, Loewen A, Djurdjev O, Loce J, Kempston C, Burnett S, Klaii M, Taylor P, Levin A: Stage of chronic kidney disease predicts seroconversion after hepatitis B immunization: earlier is better. Am J Kidney Dis 2003;42:1184–1192.
20 Kara I, Yilmaz M, Suner A, Kadiroglu A, Isikoglu B: The evaluation of immune responses that occur after HBV infection and HBV vaccination in hemodialysis patients. Vaccine 2004;22:3963–3967.
21 Chow K, Law M, Leung C, Szeto C, Li P: Antibody response to hepatitis B vaccine in end-stage renal disease patients. Nephron Clin Pract 2006;103:c89–c93.
22 Afsar B, Elsurer R, Eyileten T, Yilmaz M, Caglar K: Antibody response following hepatitis B vaccination in dialysis patients: does depression and life quality matter? Vaccine 2009;27:5865–5869.
23 Girndt M, Kohler H: Hepatitis B virus infection in hemodialysis patients. Semin Nephrol 2002;22:340–350.
24 Pesanti EL: Immunologic defects and vaccination in patients with chronic renal failure. Infect Dis Clin North Am 2001;15:813–821.
25 Fabrizi F, Martin P, Dixit V, Bunnapradist S, Dulai G: Meta-analysis: The effect of age on immunological response to hepatitis B vaccine in end-stage renal disease. Aliment Pharmacol Ther 2004;20:1053–1062.
26 Fernandez E, Betru MA, Gomez R, Montoliu J: Response to the hepatitis B virus vaccine in haemodialysis patients: influence of malnutrition and its importance as a risk factor for morbidity and mortality. Nephrol Dial Transplant 1996;11:1559–1563.
27 Ahuja TS, Kumar S, Mansoury H, Rodriguez H, Kuo YF: Hepatitis B vaccination in human immunodeficiency virus-infected adults receiving haemodialysis. Kidney Int 2005;67:1136–1141.
28 Pol S, Legendre C, Mattlinger B, Berthelot P, Krein H: Genetic basis of nonresponse to hepatitis B vaccine in hemodialysis patients. J Hepatol 1990;11:385–387.
29 Alavian SM, Tabatabaei S: The effect of diabetes mellitus on immunological response to hepatitis B virus vaccine in individuals with chronic kidney disease: a meta-analysis of clinical trials. Vaccine 2010;28:3773–3777.
30 Kimata H, Yoshida A, Ishioka C, Masuda S, Sasaki R, Mikana H: Human recombinant erythropoietin directly stimulates B cell immunoglobulin production and proliferation in serum free medium. Exp Immunol 1991;85:151–156.
31 Huraib S, Abu Aisha H, Al Momen A, Al Wakeel J, Memon N, Al Tuwaijri A: Effect of recombinant human erythropoietin on lymphocyte phenotyping and phagocyte activity in hemodialysis patients. Am J Kidney Dis 1997;29:866–870.
32 Shurtz Swirski R, Kristal B, Shkolnik T, Weissman I, Shapiro G, Shasha SM: Short-term effect of erythropoietin on T-cell mitogenic proliferation in chronic renal failure patients. Nephron 1996;72:27–29.
33 Eardley K, Jones H, Osman H, Smith S: Efficacy of the accelerated hepatitis B vaccination schedule used in haemodialysis patients post-exposure to virus: a single-centre experience. Nephrol Dial Trasplant 2002;17:1982–1987.
34 Kovacic V, Sain M, Vukman V: Efficient haemodialysis improves the response to hepatitis B virus vaccination. Intervirology 2002;45:172–176.
35 Fabrizi F, Di Filippo S, Marcelli D, Guarnori I, Raffaele L, Crepaldi M, Erba G, Locatelli F: Recombinant hepatitis B vaccine use in chronic hemodialysis patients. Nephron 1996;72:536–543.
36 Liu J, Liu Y, Lin H, Yang Y, Kuo H, Lin P, Huang C: Intravenous iron attenuates post-vaccination anti-HBsAg titers after quadruple hepatitis B vaccination in dialysis patients with erythopoietin therapy. Int J Clin Pract 2009;63:387–393.
37 Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP: Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses? Lancet 1998;352:609–613.
38 Waite M, Thomson L, Goldstein M: Successful vaccination with intradermal hepatitis B vaccine in hemodialysis patients previously nonresponsive to intramuscular hepatitis B vaccine. J Am Soc Nephrol 1995;5:1930–1934.
39 Marangi A, Giordano R, Montanaro A, De Padova F, Schiavone MG, Dongiovanni G, Basile C: Hepatitis B virus infection in chronic uremia: long-term follow-up of a two-step integrated protocol of vaccination. Am J Kidney Dis 1994;23:537–542.
40 Rangel M, Coronado V, Euler G, Strikas R, for the Advisory Committee on Immunization Practices and the American Academy of Pediatrics: Vaccine recommendations for patients on chronic dialysis. Semin Dial 2002;13:101–107.