Original Article

Successful response of intradermal hepatitis B vaccine in nonresponders of intramuscular hepatitis B vaccine in general and hemodialysis population

Farina M. Hanif, Nasir Mehmood, Zain Majid, Nasir H. Luck, S. Mudassir Laeeq, Abbas A. Tasneem, Muhammad Manzoor ul Haque

Department of Hepatogastroenterology, Sindh Institute of Urology and Transplantation (SIUT), Karachi, Pakistan

Abstract

Background: Hepatitis B infection is one of the most common infections worldwide, with its vaccination being an effective preventive measure. Nonresponse to hepatitis B vaccination increases population susceptibility to virus dissemination along with detrimental complications. Despite twice intramuscular vaccination series, 14.3% in the general population and 50% in hemodialysis patients fail to mount a response against hepatitis B. We aimed to evaluate the effectiveness of intradermal (ID) vaccination in the nonresponders amongst the general and hemodialysis population.

Methods: A total of 5 doses of 10 μg of hepatitis B vaccine was given intradermally, 2 weeks apart, to both the study groups: patients who were on hemodialysis and the general population group who previously had failed to achieve satisfactory antibody titers with the IM administration of the vaccine. A hepatitis B surface antibody (HBsAb) titer of ≥10 IU/mL and ≥100 IU/mL were considered "responder" and "good responder," respectively.

Results: Out of a total of 95 participants, 49 (51.6%) were hemodialysis-dependent. Most of the participants were females 49 (51.6%). The mean age of all the participants was 39.02 ± 13.5 years (range: 18–70 years). Overall, 75.8% of the participants responded to the ID vaccination with a mean HBsAb titer of 263.5 ± 350.1 IU/L. Almost similar vaccination response was observed in both the hemodialysis and general population i.e., 75.5% and 76.1%, respectively ($P = 1.00$). In the hemodialysis group, the absence of hypertension ($P = 0.04$) and age ≥36 years ($P = 0.016$) were associated with an ID vaccination response.

Conclusion: For those not responding to the conventional IM route of the hepatitis B vaccine, the ID route is an effective way of immunization in this group and this approach would lead to a decrease in infection rates in the vulnerable population such as those on hemodialysis.

Keywords: Hemodialysis, hepatitis B vaccination, intramuscular route, intradermal route

Address for correspondence: Dr. Zain Majid, Department of Hepato-Gastroenterology, Dewan Farooq building, Sindh Institute of Urology and Transplantation , Chand Bibi Road, Karachi, Pakistan.
E-mail: zain88@hotmail.com

Submitted: 31-May-2020 **Revised:** 04-Jul-2020 **Accepted:** 05-Aug-2020 **Published:** 28-Oct-2020

Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/sjg.SJG_300_20

How to cite this article: Hanif FM, Mehmood N, Majid Z, Luck NH, Laeeq SM, Tasneem AA, *et al*. Successful response of intradermal hepatitis B vaccine in nonresponders of intramuscular hepatitis B vaccine in general and hemodialysis population. Saudi J Gastroenterol 2020;26:306-11.

INTRODUCTION

Hepatitis B infection, one of the most common infectious diseases, involves more than one-third of the world's population. The World Health Organization (WHO) has estimated that more than 350 million individuals are chronically infected with the hepatitis B virus (HBV) and 700,000 die annually.[1,2] The steady decline in the rates of new infection has been achieved due to an effective vaccine.[3]

Studies have shown that greater than 90% of the seroprotective response is achieved to three intramuscular (IM) doses of hepatitis B vaccination in the general population.[4,5] A poor or a failed response has been documented not only in patients having chronic diseases but also amongst the healthcare workers despite the administration of an additional fourth dose.[3,6] This unresponsiveness to hepatitis B vaccination makes the population vulnerable to virus dissemination and, in turn, could lead to detrimental complications. Thus, this led the researchers to propose new strategies of immunization to achieve "universal protection."[6] In individuals unresponsive to the first series of vaccines, three additional doses are recommended to complete a second series with a similar vaccine. Nonresponders to the second course should be evaluated for underlying chronic HBV infection. A novel approach to improve the effectiveness of vaccination is the intradermal (ID) route.[7]

In dialysis-dependent patients, the reported response is around 32% to 80% with the 1st series of IM vaccination.[4] Moreover, studies in the above-mentioned population documented that 50–60% respond with the repeated course.[3] Thus, a large number of such patients fail to achieve protection against HBV. Furthermore, a meta-analysis documented that 14.3% of the general population do not achieve adequate hepatitis B surface antibody (HBsAb) titer with repeated series.[5] Usually, vaccines are administered via the IM route, but the human muscle is a poor immunogenic organ in comparison to the skin, due to the presence of dendritic and Langerhans cells. They express high levels of class II major histocompatibility complex (MHC) and CD1 molecules. Due to the direct release of antigen to the skin immune system, via the ID route, T-cells are directly stimulated.[6]

The mechanism of nonresponse has been poorly defined. It is suggested that the defect in antigen presentation or CD4 T-cells' activation might be responsible for unresponsiveness to HBV vaccination.[3,5] Various studies have described nonresponders as "at-risk or vulnerable" population which includes patients with human immunodeficiency virus (HIV) infection, hepatitis C virus, celiac disease, diabetes mellitus (DM), inflammatory bowel disease, end-stage renal disease (ESRD), and/or hemodialysis (HD)-dependent population.[5,8] Furthermore, genetic predisposition, advanced age, and immunomodulatory medications have also been implicated in the blunted immune response.

In our study, we have evaluated both general and HD population nonresponders to two series of HBV vaccination administrated through the IM route. We aimed to evaluate and compare the effectiveness of HBV vaccine administrated via the ID route in these nonresponders.

METHODS

Study design

Study patients were prospectively recruited through consecutive sampling. Individuals who received two series of IM HBV vaccination and who had an HBsAb titers <10 IU/L, 6 weeks after last IM dose were labeled as nonresponder and were enrolled in the study. The study participants included both groups; general population and patients on maintenance hemodialysis. All study participants were negative for both anti-HCV and HBsAg by Micro Particle Enzyme Immunoassay (MEIA) ARCHITECT SYSTEM. Informed written consent was obtained from all the included patients and ethical approval was obtained from the institutional ethics committee.

A total of 5 doses of 10 μg of hepatitis B vaccine was given intradermally, 2 weeks apart, to the study population. The syringe used for ID injection was 1 mL tuberculin syringe with the permanently attached 27-gauge needle of half an inch with regular bevel. All patients were immunized with the recombinant hepatitis B vaccine (Engrex-B) with the purified surface antigen of the virus obtained by culturing genetically engineered Hansenula polymorpha yeast cells. The vaccine injection site was first spread taut, and the needle tip was inserted at a 10°–15° angle. The vaccine was injected slowly and "wheal" formation was documented. HBsAb titers were measured 6 weeks after completion of the vaccination. HBsAb titers were estimated by MEIA ARCHITECT SYSTEM and antibody titers ≥10 IU/mL were considered as "responders." The patients who achieved titers ≥100 IU/mL were labeled as "good responders." Patients with titers of <10 IU/mL were considered as nonresponders.

All participants' demographic and clinical data including age, gender, body mass index (BMI), comorbidity, duration of dialysis and HBsAb titer were recorded. The side effects at the

injection site were noted at the time of vaccination and 3 days afterward. Side effects known from ID vaccination, included pigmentation, skin nodules, and itching were recorded.

Statistical analysis

The analysis was performed using SPSS Statistics software (SPSS: An IBM Company, version 20.0, IBM Corporation, Armonk, NY, USA). The continuous variables were computed as mean ± standard deviation (SD) while categorical variables as frequency and percentage. For stratification, age was categorized based on the median value of 36 years. To document statistical significance between responders and nonresponders, unpaired student's *t*-test or Chi-square was used, as appropriate. Multivariate logistic regression analysis was carried out on variables found statistically significant on univariate analysis. A *P* value ≤0.05 was considered significant.

RESULTS

A total of 95 participants having a mean age of 39.02 ± 13.5 years (range: 18–70 years), were enrolled in this study. A comparison of the main demographic and clinical characteristics of the two groups of participants is shown in Table 1. All individuals received 5 doses of ID HBV vaccine and achieved a mean HBsAb titer of 263.5 ± 350.1 IU/L. The mean duration from IM vaccination to 1st dose of ID vaccination in the study population was 46 ± 6.3 days (range: 46–63 days). Overall, 75.8% of participants responded to vaccination among which 44.2% achieved good response i.e., more than 100 IU/L.

The data were also stratified to compare responses between dialysis-dependent and the general population. A similar vaccination response was noted between hemodialysis and general population i.e., 75.5% and 76%, respectively (*P* = 1.00). To determine the predictive factor for response to vaccination, the data was stratified in individual group i.e., the general population and HD population

Of the 46 individuals in the general population, 35 (76%) achieved response after complete 5 ID doses of HBV vaccination. Among these, 18 (39.1%) achieved ≥100 IU/L HBsAb titer. The mean HBsAb titer achieved was 201.62 ± 287.10 IU/L. In total, only four individuals had DM. No statistically significant predictor of response was observed in the general population [Table 2].

Out of a total of 95 participants, 49 participants (51.6%) were on maintenance HD. In comparison to the general population, dialysis-dependent patients were of a younger age group and low BMI [Table 1]. Majority of patients were hypertensive (*n* = 28 [57.1%]) while 11 (22.4%) had DM.

Of 49 patients, 37 (75.5%) achieved a response to ID vaccination with a mean HBsAb titer of 321.7 ± 394.6 IU/L [Table 3]. Although the good response was observed more in HD patients (48.9%) than in the general population (39.1%), it was not statistically significant. (*P* = 0.41)

After stratification of data to observe the response of ID vaccination in dialysis-dependent population, absence of hypertension (HTN) (*P* = 0.02), and age ≥36 years was associated with statistically significant response (*P* = 0.01) Similarly, on multivariate regression analysis both HTN (*P* = 0.016) and age (*P* = 0.02) were also found to be significantly associated [Table 3].

DISCUSSION

Hepatitis B vaccination is an effective measure to prevent HBV-related morbidity and mortality.[5] Despite the accessibility and high efficacy of the HBV vaccine, around 5% of the immunocompetent population does

Table 1: Demographic and clinical characteristics of the study population (*n*=95)

	Dialysis-dependent (*n*=49)	General population (*n*=46)	*P*
Age, years, mean±SD	36.39±13.797	41.83±12.824	0.05
Age above 36 years, *n* (%)	22 (44.8)	29 (63)	0.83
Gender (female), *n* (%)	24 (48.9)	25 (54.3)	0.68
Height, cm, mean±SD	163.35±7.564	160.98±7.089	0.12
BMI, mean±SD	20.7211±4.92928	25.0959±5.04	<0.001
HTN, *n* (%)	28 (57.1)	4 (8.6)	<0.001
DM, *n* (%)	11 (22.4)	4 (8.6)	0.05
Response to intradermal HBV vaccination			
Responders, *n* (%)	37 (75.5)	35 (76)	1.0
Titer, IU/L, mean±SD	321.70±394.627	201.62±287.100	0.09
Good Response, *n* (%)	24 (48.9)	18 (39.1)	0.41
Weak Response, *n* (%)	13 (26.5)	17 (36.9)	0.377

BMI: Body mass index; DM: Diabetes mellitus; HTN: Hypertension; HBsAb: Hepatitis B surface antibody; Good response: HBsAbTiter >100 IU/L; Weak Response: HBsAbTiter 10-100 IU/L. *P*≥0.05 is considered significant

Table 2: Analysis of HBV intradermal vaccination response in the general population (*n*=46)

	Titer ≥100 IU/L (*n*=24)	Titer <100 IU/L (*n*=22)	*P*
Age, years, mean±SD	40.5±9.4	42.6±14.6	0.56
Age above 36 years, *n* (%)	10 (41.6)	19 (86.3)	1.00
Gender			
Male, *n* (%)	12 (50)	9 (40.9)	0.23
Female, *n* (%)	12 (50)	13 (59)	
Height, cm, mean±SD	162.6±7.8	164.0±7.3	0.51
BMI, mean±SD	21.2±5.2	20.1±4.6	0.44
HTN, *n* (%)	1 (4.1)	3 (13.6)	1.00
DM, *n* (%)	1 (4.1)	3 (13.6)	1.00

BMI: Body mass index; DM: Diabetes mellitus; HTN: Hypertension; HBsAb: Hepatitis B surface antibody. $P \leq 0.05$ is considered significant

not mount a protective immune response.[3] We observed, a similar efficacy of the ID route amongst nonresponders to the IM route i.e., more than 75% in dialysis-dependent and the general population. Moreover, we also found that hypertension and those with age less than 36 years were associated with nonresponse to the vaccine in HD population.

The standard vaccination schedule for the hepatitis B vaccine comprises three IM doses of 20 μg each in the general population, while for the immunocompromised or the high-risk group a higher dose (40 μg each) in a four-dose schedule is recommended. Serum HBsAb titer is measured at 4 to 6 weeks after the vaccination schedule to determine the immune response. Participants having HBsAb titer of more than 10 IU/L are considered as responders. The subgroup of the vaccinated populations who do not respond to standard regimen along with additional booster dose or repeated vaccination course is considered as a true " nonresponder."[3,9]

Hypertension, either primary or secondary to classical autoimmune diseases, has a strong association with immune activation. It is postulated that mechanical and oxidative damage to vessels and organs by activation of the renin-angiotensin-aldosterone system and sympathetic nervous system leads to the formation of danger-associated molecular patterns (DAMPs) and neoantigens which, in turn, activate the innate and adaptive immune system.[10,11] This possible modification of the immune system can be attributed to our finding of poor response to HBV vaccination in our study population. DM is associated with poor immune to HBV vaccination.[3,5] R van de Berg *et al*.[12] has documented less than 20% response in HIV patients with diabetes. Reduced seroprotection rate (41.8% vs. 16% in healthy controls) for HBV infection was also observed in diabetic children following IM administration by Leonordi *et al*.[13] A meta-analysis of 193 nonresponder diabetic patients has documented a 67.5% response with repeated vaccine course.[5] We documented a higher response of 86.6% in our 15 adult diabetic participants with the majority achieving an HBsAb titer between 10–100 IU/L (46.7%). The difference can be attributed to the mode of vaccination i.e., IM in the former and also the small sample size. Studies in chronic kidney disease patients and HD-dependent have documented DM as a predictor of poor response.[14,15] Majority of our dialysis-dependent patients were diabetic but the association was not statistically significant with vaccine response. It can be attributed to the fact that our study population was nonresponder to repeated vaccination series while studies have documented poor response after primary vaccination.

Studies have documented conflicting associations of age on HBV vaccination response.[16] Similar to Chin[14] and Waite *et al*.,[17] we have also observed a statistically significant association of age with HBV response but only in our HD study population ($P = 0.02$). Although IM vaccination is the recommended and simple mode of vaccine delivery, this method can be less efficacious due to the low infiltration of antigen-presenting cells in striated muscle. On the other hand, the dermis is infiltrated by Langerhans cells thus activation with antigen might lead to robust cell-mediated and humoral immune response. Furthermore, it is proposed that the ID administration may lead to longer trapping of antigen in comparison to the IM route.[4,6] Gonzalez *et al*.,[18] and Brink *et al*.,[19] comparing lower dose of ID vaccination

Table 3: Analysis of HBV intradermal vaccination response in dialysis-dependent population (*n*=49)

	Titer ≥100 IU/L (*n*=24)	Titer <100 IU/L (*n*=25)	Univariate analysis *P*	Multivariate analysis
Age, years, mean±SD	36.04±13.6	36.7±14.2	0.86	
Age above 36 years, *n* (%)	20 (83.3%)	22 (88%)	0.04	0.029
Gender				
Male, *n* (%)	12 (50%)	13 (52%)	1.00	
Female, *n* (%)	12 (50%)	12 (48%)		
Height, cm, mean±SD	162.6±7.8	164.09±7.3	0.51	
BMI, mean±SD	21.2±5.2	20.1±4.6	0.44	
HTN, *n* (%)	10 (41.6%)	18 (72%)	0.04	0.016
DM, *n* (%)	5 (20.8%)	6 (24%)	1.00	
Dialysis <5, years, *n* (%)	14 (58.3%)	10 (40%)	0.12	

BMI: Body mass index; DM: Diabetes mellitus; HTN: Hypertension; HBsAb: Hepatitis B surface antibody. $P \leq 0.05$ is considered significant

to regular dose IM route documented 78.1% and 81% seroconversion in the general population, respectively. Henderson *et al*.,[20] documented higher efficacy of the ID HBV vaccine as compared to the IM route. While Playford *et al*.,[21] documented 90% response with ID vaccination in healthcare workers nonresponders to the primary IM route. We achieved a 76.1% response in general population nonresponder to primary vaccination series. The difference in response rate can be attributed to the differences in the vaccine dose and population sample size. Dialysis is a major risk factor for HBV infection. Achieving protective antibodies is of utmost importance to prevent nosocomial HBV transmission along with the patient's morbidity and mortality.[4] Uremia induced impaired phagocytosis, antigen presentation, T-cell activation, and antibody production contributes to the lower immune response from conventional HBV vaccination in chronic kidney disease patients.[4,22] The degree of immune response correlates with the degree of renal failure.[4,23] Barraclough *et al*.,[4] reported better seroconversion rates in dialysis patients vaccinated with ID route as compared to IM i.e., 79% vs 40%, respectively. The study also documented a higher HBsAb titer of 239 IU/L with ID administration in comparison to the IM route. Similarly, Al Saran *et al*.,[16] reported an 80% response rate in 15 hemodialysis Saudi patients who were nonresponder to two courses of IM vaccination. We also documented 75.5% seroconversion in our 49 HD patients with HBsAb titer of 321.70 ± 394 IU/L. Despite the documented evidence of effective protection with ID route, it is not widely practiced due to technical difficulties, fear of inadvertent subcutaneous administration, and a lack of knowledge regarding this mode of vaccination. We had our staff trained for 1 day and documented well-tolerated and effective ID vaccine administration in both HD-dependent and the general population.[4] The known, self-limited, side effects of the ID vaccine of mild erythema and nodule formation at the injection site were rarely seen in our study.[4,22]

We have documented for the first time effective and equal efficacy of HBV vaccination via ID route in general and HD-dependent population, nonresponders to primary two series of IM vaccination. Although the majority of the HD-dependent population had better ID response with HBsAb titer >100 IU/L, it was not statistically significant. We have also observed an association of hypertension and age with poor vaccination response in HD population.

Our study has some limitations. The long-term effect of HBV vaccination has not been studied; however, Barraclough *et al*.,[4] and Fabrizi *et al*.,[24] have documented a longer duration of HBV protection after ID route of administration. Although, absence of hypertension was a better predictor of immune response we did not document the antihypertensive taken by the participants and its probable effect on the immune response. We did not explore the role of human leukocyte antigen (HLA) on the negative response of the HBV vaccine. This needs to be explored further in the future.

Based on these results, we recommend that further large-scale studies are warranted on this topic to further corroborate these findings and to revisit the current guidelines regarding hepatitis B vaccination in nonresponders to conventionally administered IM vaccine.

CONCLUSION

In hepatitis B vaccination nonresponders, the ID route is an alternative, effective, and safe way of immunization to decrease infection rates especially in the vulnerable population such as hemodialysis patients.

Declaration of patient consent

The authors certify that all participants of this study had given informed written consent.The form includes not only their biological data but also their laboratory parameters, imaging and other relevant clinical information that might be useful for the principal investigator. Furthermore, the participants agreed to the publication of their information without disclosing their demographic details to be reported in any journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Aljarbou AN. The Emergent Concern of Hepatitis B globally with special attention to Kingdom of Saudi Arabia. Int J Health Sci (Qassim) 2013;7:333-40.
2. Harkisoen S, Arends JE, van Erpecum KJ, van den Hoek A, Hoepelman AI. Hepatitis B viral load and risk of HBV-related liver disease: From East to West? Anna Hepatol 2012;11:164-71.
3. Walayat S, Ahmed Z, Martin D, Puli S, Cashman M, Dhillon S. Recent advances in vaccination of non-responders to standard dose hepatitis B virus vaccine. World J Hepatol 2015;7:2503-9.
4. Barraclough KA, Wiggins KJ, Hawley CM, van Eps CL, Mudge DW, Johnson DW, *et al*. Intradermal versus intramuscular hepatitis B vaccination in hemodialysis patients: A prospective open-label

randomized controlled trial in nonresponders to primary vaccination. Am J Kidney Dis 2009;54:95-103.
5. Yanny B, Konyn P, Najarian LM, Mitry A, Saab S. Management approaches to hepatitis B virus vaccination nonresponse. Gastroenterol Hepatol (N Y) 2019;15:93-9.
6. Filippelli M, Lionetti E, Gennaro A, Lanzafame A, Arrigo T, Salpietro C, *et al*. Hepatitis B vaccine by intradermal route in non responder patients: An update. World J Gastroenterol 2014;20:10383-94.
7. Tajiri K, Shimizu Y. Unsolved problems and future perspectives of hepatitis B virus vaccination. World J Gastroenterol 2015;21:7074-83.
8. Leonardi S, Del Giudice MM, Spicuzza L, Spina M, La Rosa M. Hepatitis B vaccine administered by intradermal route in patients with celiac disease unresponsive to the intramuscular vaccination schedule: A pilot study. Am J Gastroenterol 2010;105:2117-9.
9. Danziger-Isakov L, Kumar D, Practice AICo. Vaccination of solid organ transplant candidates and recipients: Guidelines from the American society of transplantation infectious diseases community of practice. Clin Transplant 2019;33:e13563.
10. Drummond GR, Vinh A, Guzik TJ, Sobey CG. Immune mechanisms of hypertension. Nat Rev Immunol 2019;19:517-32.
11. Harrison DG, Vinh A, Lob H, Madhur MS. Role of the adaptive immune system in hypertension. Curr Opin Pharmacol 2010;10:203-7.
12. Van den Berg R, van Hoogstraten I, van Agtmael M. Non-responsiveness to hepatitis B vaccination in HIV seropositive patients; possible causes and solutions. AIDS Rev 2009;11:157-64.
13. Leonardi S, Vitaliti G, Garozzo MT, Miraglia del Giudice M, Marseglia G, La Rosa M. Hepatitis B vaccination failure in children with diabetes mellitus? The debate continues. Hum Vaccin Immunother 2012;8:448-52.
14. Chin AI. Hepatitis B virus vaccine response in hemodialysis: Baseline patient characteristics. Hemodial Int 2003;7:296-303.
15. Lacson E, Teng M, Ong J, Vienneau L, Ofsthun N, Lazarus JM. Antibody response to Engerix-B and Recombivax-HB hepatitis B vaccination in end-stage renal disease. Hemodial Int 2005;9:367-75.
16. Al Saran K, Sabry A, Ismail M, El Halwany Z, El Sayed N, Farouk N. Intradermal hepatitis B vaccine in hemodialysis patients previously non-responsive to intramuscular hepatitis B vaccine route. ARC J Nephrol 2016;1:5-10.
17. Waite NM, Thomson LG, Goldstein MB. Successful vaccination with intradermal hepatitis B vaccine in hemodialysis patients previously nonresponsive to intramuscular hepatitis B vaccine. J Am Soc Nephrol 1995;5:1930-4.
18. Gonzalez ML, Usandizaga M, Alomar P, Salvá F, Martín F, Erroz MJ, *et al*. Intradermal and intramuscular route for vaccination against hepatitis B. Vaccine 1990;8:402-5.
19. Brink NS, Murray AB. Intradermal vaccination against hepatitis B in a group of medical students. S Afr Med J 1991;79:653-4.
20. Henderson EA, Louie TJ, Ramotar K, Ledgerwood D, Hope KM, Kennedy A. Comparison of higher-dose intradermal hepatitis B vaccination to standard intramuscular vaccination of healthcare workers. Infect Control Hosp Epidemiol 2000;21:264-9.
21. Playford EG, Hogan PG, Bansal AS, Harrison K, Drummond D, Looke DF, *et al*. Intradermal recombinant hepatitis B vaccine for healthcare workers who fail to respond to intramuscular vaccine. Infect Control Hosp Epidemiol 2002;23:87-90.
22. Jhorawat R, Shah P, Beniwal P, Agarwal D, Nijhawan S, Malhotra V. Comparison of intradermal route and dose of Hepatitis B vaccine administration in chronic dialysis patients: A pilot study. Saudi J Kidney Dis Transpl 2018;29:376-80.
23. Janus N, Vacher LV, Karie S, Ledneva E, Deray G. Vaccination and chronic kidney disease. Nephrol Dial Transplant 2008;23:800-7.
24. Fabrizi F, Andrulli S, Bacchini G, Corti M, Locatelli F. Intradermal versus intramuscular hepatitis b re-vaccination in non-responsive chronic dialysis patients: A prospective randomized study with cost-effectiveness evaluation. Nephrol Dial Transplant 1997;12:1204-11.