

Immune response to hepatitis B vaccine among patients on hemodialysis

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electronic systematic search of the published literature was carried and data on the immunological response to hepatitis B vaccination among hemodialysis patients was extracted from relevant studies. End stage renal disease patients on hemodialysis have a lower or an absolutely negative response to HBV vaccine. Several means have been tried to improve this response with some success, nevertheless none have been universally adopted. Genetic investigations are foreseen to make a break through concerning HBV vaccination.

Key words: Hemodialysis; Chronic kidney disease; Immune response; Vaccine; Adjuvant

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Core tip: This article discussed the history of immunological response to various types of Hepatitis B vaccines among patients on hemodialysis based on published findings of an array of studies up to this year. Moreover, it tackled the possible causes for such a response and possible future ways out of this dilemma.

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Abstract

Infection with hepatitis B virus (HBV) poses a major health threat worldwide, where the magnitude and overburden of chronic carrier state approaches 150 million chronic carriers. The prevalence of HBV is greater among dialyzed patients compared to the general population owing to their increased vulnerability to blood and its products, along with hazards posed by contaminated hemodialysis tools and devices. An

INTRODUCTION

Infection with hepatitis B Virus (HBV) poses a major health threat worldwide, where the magnitude and overburden of chronic carrier state approaches 150 million chronic carriers. The prevalence of HBV is greater among dialyzed patients compared to the general population, this could be attributed to the

fact they are needy for the blood and its products and thus more vulnerable, along with the jeopardy posed by contaminated hemodialysis tools and devices^[1]. Therefore HBV immunization is highly advised for patients suffering chronic kidney disease (CKD), whether pre-emptive or dialysis dependent, who are potential nominees for kidney transplant along with those on dialysis^[2]. In spite of this, surges of the aforementioned infection among patients on hemodialysis are persistently encountered even in advanced countries^[3-5].

The extent of renal failure has been described to determine the immunological riposte to hepatitis B immunization among this group of patients, where it has generally been reported to be suboptimal^[6-8]. The seroconversion rates and antibody titers among chronic renal disease patients has been shown to be less than the general population along with a shorter duration of seroprotection^[9]. The flawed effectiveness of HBV immunization among dialysis dependent patients can be justified by a group of determinants, noticeably the defective immunity owing to; azotemia, age^[10], sex^[11], body mass^[12], nourishment of such patients^[13], concomitant infection with HCV^[14] or HIV^[15], history of transfusion of blood or blood products^[16] and having the major histocompatibility complex also to be associated with this response^[17-19], along with failure to complete the full course of HBV vaccine^[20].

In order to enhance the riposte degree to hepatitis B immunization in end-stage kidney disease a group of strategies have been embraced and these are; building up the vaccine dose^[20], supplementary vaccine injections along with resorting to intradermal injections rather than the intramuscular in order to supplement the vaccination^[21]. Hepatitis B vaccination among pre-dialysis chronic kidney disease patients results in higher seroprotection rates when compared to those patients on dialysis^[22]. Adjuvants has been proposed to be of some help in raising the immunity, a good example for these adjuvants is levamisole, which is an antihelminthic with characteristics enabling it to stimulate suppressed T-cell action along with potentiation of B lymphocyte action^[23-25]. The target of this review is to discuss inadequate immunological riposte to hepatitis B immunization, its determinants and the possible solutions.

MANAGEMENT

Search strategy and data extraction

An electronic systematic search of the published literature was carried and data on the immunological riposte to hepatitis B vaccination among hemodialysis patients was extracted from studies of relevance. The databases were searched with the words "Hepatitis B immunization", "dialysis", "immunological riposte", "retarded riposte", "non-responders" and

"adjuvants" were used interchangeably in MEDLINE, Pubmed, MiPc library and Google.

Epidemiology of HBV among hemodialysis

Hepatitis B infection has been declining in the last two decades in artificial kidney facilities, a status that mirrors the outcomes of efforts made in providing efficient prophylaxis measures^[26]. Variable prevalence of HBV infection among dialysis patients were reported from the different continents ranging between (6%), and (1.2%)^[27-29]. In a large scale study including 8615 adult dialysis patients from different dialysis facilities in the Western world, hepatitis B prevalence rates ranged from 0% to 6.6%^[5]. A principal determinant hindering the transmission of such an infection in artificial kidney facilities was the preservation of universal infection control measures. CDC guidelines advice segregation of patients who are antigen-positive, dedicating an independent nursing group and it further more prohibits sharing medicaments in artificial kidney facilities^[30]. Undiminished vulnerability percentages to hepatitis B infection were particularly observed in renal facilities dealing with HB (S) Ag carriers. Such vulnerability could be controlled by the strict cohesion to the global precautions; however causal incidences can to an outbreak the whole facility^[30,31]. History of immunization against hepatitis B targeting end stage renal disease sufferers started by the utilization of live attenuated virus derived from plasma, although it was initially reported to mount enough immunity, however, it was found later not to have induced a sufficient immunity. Currently supplied vaccines possess an outstanding safeness and immunogenicity account, providing protection rates falling just below 100% of the immunized group^[32]. However, some population subgroups, including some people of normal health and immune-deficient individuals, riposte inadequately to immunization. Part of such sets, are chronic kidney disease patients, including pre-emptive and dialysis patients, whom are regarded to have vulnerability to contract HBV owing to transmission to those on dialysis through surrounding surfaces, expendables, or apparatuses during hemodialysis^[33,34]. Hepatitis B vaccination, when combined with application of the other precautions, ended up in a definite and appreciable decline in new infections among hemodialysis patients and kidney facility personnel in Western countries^[35,36]. Despite the fact that the frequency of HBV is absolutely squatty, a big proportion of vulnerable chronic kidney disease sufferers have to get the vaccine. Regulations meant with control of transmission of infections in renal facilities gives a feeling of protection to working personnel, nevertheless, chronic kidney disease sufferers' vaccination is yet regarded a subsidiary and pricy procedure, there for resulting in

a greater proportion of unimmunized chronic renal disease sufferers in some countries. Hepatitis B poses an intimidation for chronic renal sufferers on hemodialysis, regardless of precautions secured, let alone meanwhile they are subjected to hemodialysis in their local facilities, but again meanwhile accommodated by other units when considering superior chronic kidney disease sufferers' acclimation, vacation enjoyment. During such plots, the susceptible chronic kidney disease sufferers' acts as a probable HBV infection aim (undertaking dialysis in machines, units dedicated for infected patients) moreover they act as a probable harbor for the disease taking it back to their local facilities^[37]. It should be noted that HBV can also be transmitted to dialyzed chronic kidney disease sufferers (as the rest of the general population) by other means known to transmit the disease (sexual route *etc.*). Those who caught the hepatitis infection can spread the disease in their home unit in turn, ahead of hepatitis B infection detection, unless active steps take place to protect patients from such an infection in terms of a fruitful immunization plan^[38]. A great proportion of hemodialyzed chronic kidney disease sufferers acquiring HBV have a tendency to progress to chronic hepatic disease (unable to eliminate their virus). Such chronic kidney disease sufferers are rendered to have greater vulnerability on attempting kidney transplantation, further more they pose a potential harbor for the disease to both other chronic kidney disease sufferers and non-immune working personnel^[39-41]. The aforementioned fact makes a comprehensively fruitful immunization plan imperative for chronic kidney disease sufferers and staff safeguard against this lifelong, enduring and possibly killing infection^[42].

BOOSTING THE IMMUNOLOGICAL RESPONSE TO VACCINATION

Evolution of the vaccine

Comparative to numerous other infections, immunization, as a protective strategy, performs a crucial role in limitation of the HBV infection and its consequences^[9]. Hitherto, there are triumvirate derivations of HBV vaccines. Saul Krugman's observation about immunogenicity of HBsAg and the immunizing properties of anti-HBs antibody facing HBV was a real breakthrough that resulted in producing the early vaccine derivation^[26] incorporating an inactive HBsAg extracted out of the plasma of the HBV carrier persons. Merck and Pasteur institute simultaneously produced the early vaccine derivation making use of aforementioned observation. Then, Food and Drug Administration of the United States of America approved it during 1981^[26]. The second derivation of HBV vaccine was engineered using recombinant DNA technology utilizing the yeast

Saccharomyces cerevisiae resulting in the formulas; Engerix B along with Recombivax HB. Both vaccine formulas encompass HBsAg. Nevertheless, the third vaccines derivation mounts an appreciably greater protection if compared to HBsAg owing to the use of pre-S1 along with pre-S2 immune triggers; however, their availability is yet limited. Recombinant DNA technology has also been used to produce the third generation vaccines by mammalian cells^[26,43]. Different American, European and Asian states adopted The WHO recommendation 1991 concerning large-scale HBV immunization by year 1997. Therefore there is an appreciable drop in pervasiveness of the HBV infection^[43,44], and its complications including HCC and fulminating hepatitis^[44].

Adjuvants

Several methods have been suggested to potentiate the outcome of HBV immunization and its riposte among chronic kidney disease sufferers on hemodialysis. Use of adjuvants was suggested to potentiate the riposte to immunization. Examples for such adjuvants are; high thymopentin doses^[45]. Levamisole is another adjuvant that has been suggested to improve vaccination results among such patients. It is probable that it can also be efficient in boosting HBV vaccination riposte among HD dependent patients^[46], however in terms of taking a rather mature decision it is prudent to conduct further research in this field in order to now the pros and cons of such agents. Fabrizi *et al.*^[47] found in their meta-analysis that a better immune response is mounted when GM-CSF is added as an adjuvant to HBV vaccine. Polymethylmethacrylate is another adjuvant that has been proposed to improve the immunity post vaccination^[48]. HBV-AS04 encompassing the synergist 3-O-desacyl-40-monophosphoryl lipid A that is consistent with Engerix B customary, is a further adjuvant improving the immune response^[26]. A Recent research conducted by Saade *et al.*^[49] has found that Advax (a polysaccharide adjuvant) induces a potent humoral and cellular induced immunity with minimal reactions in the preclinical phase. Yet most of the studies in this context have some methods limitation such as lack of randomization^[50]. Thus a long term data about the sustainability of the effect of these adjuvants is to be verified.

Changing the route of administration and booster doses

Currently, HBV vaccinations, particularly the second derivation, are administered through the intramuscular (deltoid) route three times (on 0, 1 and 6 mo's period). Antibodies' to Anti-HBs titers above 10 IU/L are deemed effective. Considering revaccinating subjects or boosting a currently administered vaccine is required in situations where

the titers level falls beneath 10 IU/L such as time linked falls in titers, or those seen among high risk groups such as immunosuppressed, smokers, obese persons, kidney failure patients and those suffering hepatic disease^[9,43].

Currently, administration of HBV immunization through either the intradermal and intramuscular injection routes is under evaluation in chronic kidney disease sufferers who undergo HD. Short term follow up, reflected that the former route of HBV immunization can mount a more potent immune riposte if compared to the later route^[26]; nevertheless, such a believe has been refuted by long term follow up.

FUTURE PROSPECTS

Genetic investigations might help in the improvement of hepatitis B vaccines and there for it may lead to reduction in the proportion of vaccine failures^[51]. Increased interferon (IFN)-gamma production was shown to be associated with positive response to vaccines^[52,53]. As IL-18 is involved in IFN-gamma production^[54-57], it was used as adjuvant to DNA vaccines against HBV^[53,57,58]. Channarong *et al*^[57] has devised a recombinant plasmid bearing a gene encoding HBsAg combined to DNA segment encoding full-length murine IL-18. All immunized mice showed a remarkable serum anti-HBsAg IgG response following two intramuscular injections of the vaccines on comparison to the level of mice vaccinated with the vaccine devoid of the DNA segment encoding IL-18. Recently Hu *et al*^[59] found on animal experiments that adding calcineurin B subunit to Engerix mounted an higher hepatitis B antibodies both in dose and time dependent manner through promoting an inflammatory response where IFN- γ , IL-6, TNF- α are produced^[59]. It is probable that in the near future all people throughout the world will be vaccinated on the mandatory basis.

CONCLUSION

Chronic kidney disease patients on hemodialysis tend to have no or at most a lower response to HBV vaccine. Several means have been tried to improve this response with some success, nevertheless, absolutely none have been universally adopted. Genetic investigations are foreseen to make a breakthrough concerning HBV immunization.

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