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Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose

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Abstract

Because HIV and hepatitis B virus share many common risk factors, it is important to try to vaccinate HIV patients against hepatitis B. There are numerous reports describing a variety of dose schedules, limited success and markers associated with impaired response to HBV vaccine in these individuals. All studies have been small in size making it difficult to draw conclusions within and between studies. The purpose of this study was to evaluate a double dose of hepatitis B vaccine under more definitive guidelines: double blinded, randomized, controlled, with numbers for statistical validity. Two hundred and ten HIV infected subjects received a standard dose (20 μg) or a double dose (40 μg) of recombinant hepatitis B vaccine IM 0, 1 and 6 months. Ninety-four receiving standard dose and 98 receiving double dose completed the study. The seroconversion rate (anti-HBs ≥ 10 mIU/mL) was 47 and 34% for double dose and standard dose, respectively ($p = 0.07$). A statistically significant higher seroconversion rate was associated with double dose comparing with standard dose for patients with CD4 cell counts ≥350 cells/mm^3 (64.3% × 39.3%; $p = 0.008$) but made no difference to seroconversion in those with CD4 <350 (23.8% × 26.3%; $p = 0.80$). Double dose also improved seroconversion comparing with standard dose for patients with HIV viral load <10,000 copies/mL (58.3% × 37.3%; $p = 0.01$) but made no difference to seroconversion in those with HIV viral load ≥10,000 copies/mL (16% × 17%; $p = 0.7$). Based on the results of this study, the best current strategy for hepatitis B vaccination in HIV patients would be to use a double dose as a primary series when the viral load is likely to be low and CD4 ≥ 350, when there is likely to be an adequate immune response.

Keywords: Hepatitis B vaccine; Human immunodeficiency virus (HIV); CD4 T lymphocyte count

1. Introduction

The human immunodeficiency virus (HIV) and hepatitis B virus (HBV) share many similar risk factors and routes of transmission, resulting in a high prevalence of co-infection [1–7]. In addition, HIV infection is associated with a greater chance of chronic HBV carrier state [8–10], a higher level of HBV replication [11–14], increasing its potential for transmission. Although there is a great need for HBV prevention in HIV infected patients, vaccine efficacy (as measured by seroconversion) has been poor, in HIV-infected children and adolescents [15–22] as well as in adults [9,23–33]. Currently, there are no data to determine the best HBV vaccine schedule for HIV-infected patients. The Advisory Committee on Immunization Practices (ACIP/CDCP) recommends that the anti-HBs response of HIV-infected patients should be measured post-vaccination, followed by one to three ad-

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ditional doses if antibody levels are low (≤10 mIU/mL). The immunogenicity of higher doses in a primary series is unknown, and recommendations cannot be made at this time [34]. Along similar lines, the European Consensus Group on Hepatitis B Immunity recommends double or additional doses of HBV vaccine for immunocompromised individuals who do not respond to standard schedules. There is an additional recommendation to administer the vaccine when patients' immune responses are likely to be high [35]. On the other hand, the World Health Organization, considers the data too limited to recommend the administration of additional doses of HBV vaccine to HIV-infected children [36]. The Brazilian Ministry of Health recommends doubling the primary dose of HBV vaccination for immunocopromized patients including those with HIV.

The purpose of this project was to design a large, double blind, randomized, controlled study to compare seroconversion rates of a double dose to a standard dose of HBV vaccine in HIV infected adult patients. As part of this evaluation, risk factors (such as CD4 counts and HIV viral load) of low response rates would be examined. A secondary objective was to evaluate the influence of the vaccine on CD4 cell counts and HIV viral loads.

2. Materials and methods

2.1. Study design and subjects

The project was approved by the Ethics Comission for Analysis of Research Projects (CAPPesq) of the University Medical School of Sao Paulo, Brazil. Patients positive for anti-HIV antibodies, greater than 18 years of age, negative for any HBV serological marker, without history of previous hepatitis B vaccine, without active opportunistic infection (at the time of admission) and willing to sign informed consent, were selected from HIV outpatient attending at University's clinic in Sao Paulo city, Brazil.

Patients enrolled into the study were allocated in two groups: standard dose group – hepatitis B recombinant vaccine (Engerix-B, GlaxoSmithKline), was administered at the standard dose (20 μg of HBsAg) and double dose group – hepatitis B recombinant vaccine (Engerix-B, GlaxoSmithKline), was administered at double dose (40 μg of HBsAg), intramuscularly in the deltoid region, at 0, 1 and 6 months.

The eligible patients were interwied by the principal investigator and blood samples were collected at 0, 1, 6 and 7–8 months to evaluate anti-HBs, anti-HBc antibodies, CD4 cell counts and HIV viral load level. Samples were taken just prior to each dose then 1–2 months after the last dose.

With an estimated 50% seroconversion rate for the standard dose, an increase of 20% for the double dose was felt to be a clinically relevant difference. To detect this difference, 103 in each group was required ($\alpha = 0.05$ and $\beta = 0.20$, Epi Info 6). The number loss to follow-up was expected to be low since subjects were also patients being monitored through the HIV clinic. As subjects entered the study they were categorized to one of two "blocks" according to CD4 cell counts (CD4 <350 and ≥350 cells/mm^3). This cut-off value is one of the HIV criteria reported to the Brazilian Health Ministry. Within each block subjects were randomized (balancing every six subjects) to receive either the double dose or the standard dose of HBV vaccine. The pre-assigned randomization sequence was created by the principal investigator, using a random number table, then left with a special nursing team to prepare and administer the vaccine doses. Only this latter group had access to the study code. Subjects, investigators and laboratory staff remained blinded to the dose administered.

2.2. Laboratory methods

Testing for anti-HBs was done by semi-quantitative enzyme immunoassay (Microelisa system, Hepanostika® Anti-HBs New, Biomérieux bv, Boseind 15, 5281 RM Boxtel, The Netherlands) for some samples and by quantitative enzyme immunoassay (Microelisa system, IMx AUSAB®, ABBOTT, Abbott Park, IL, USA) for other samples (due to cost). Seroconversion was considered as post-vaccination titers equal or greater than 10 mIU/mL. Anti-HBc serological markers were determined by automatizeted qualitative microparticle enzyme assay tecnology (Imx Core, ABBOTT, Abbott Park, IL, USA) and by qualitative microparticle enzyme assay (Organon Tecknica bv NL-5281 RM Boxtel, The Netherlands). The absolute number of CD4 T lymphocytes was determined by a fluorescence-activated cell analyser, using monoclonal antibodies (FACSCount® System). The quantitation of HIV-1 RNA was measured by NASBA method (Nuclisens HIV-1 QT Organon Tecknica) and by AMPLICOR HIV-1 MONITOR® (version 1.5, ROCHE). The lower quantitation limit of NASBA was 80 HIV-1 RNA copies/mL. The limits of quantitation of the AMPLICOR HIV-1 MONITOR test was from 400 ($\log_{10} = 2.60$) to 750,000 ($\log_{10} = 5.87$) HIV-1 RNA copies/mL. To standardize the results we have utilizated the lower detection limit of AMPLICOR test (viral load = 400 copies/mL, $\log_{10} = 2.60$).

2.3. Statistical analysis

Data were recorded in Epi Info 6.04, analyses were done with STATA statistical software version 7.0. The criteria for statistical significance was $p \leq 0.05$. Chi-square tests and chi-square tests for tendency were used to compare standard and double dose groups for cathegoric variables and Student's *t*-tests were used for continuous variables. Univariate analysis was used to test for associations between independent and dependent (seroconversion) variables. A forward logistic regression model was constructed which included variables showing significance at $p \leq 0.20$ for univariate analysis. The coefficients of the logistic regression model were used to measure the associations of independent vari-