RESEARCH PAPER

Double Dose *Versus* Standard Dose Hepatitis B Vaccine in HIV-infected Children: *A Randomized Controlled Trial*

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Received: December 13, 2016; Initial Review: March 02, 2017; Accepted: July 25, 2017.

Objective: To compare the efficacy of double dose (20 µg) with standard dose (10 µg) of hepatitis B vaccine in HIV-infected children. **Methods**: Unvaccinated HIV-infected children were randomized to receive 3 doses of double dose (*N*=27) or standard dose (*N*=28) of recombinant Hepatitis B vaccine. Anti-HBs antibody titres were measured 3 mo after the last dose. An antibody titre ≥10 mIU/mL 12 weaks after the third dose was considered as serporotection. **Result**: Seroprotection was achieved by 17 (60.7%) children in standard dose group against 20 (74%) in the double dose group [RR (95%CI) 0.8 (0.17-1.7); *P*=0.29]. CD4 count < 500 cells/mm^3 was significantly associated with lower rates of seroprotection. **Conclusion**: Double dose of hepatitis B vaccine does not seem to provide any advantage when compared to standard dose in HIV-infected children.

Keywords: *Immunization, Immunodeficiency, Prevention, Vaccination.*

Trial Registration: CTRI/2016/01/006495

Published online: August 24, 2017. PII:S097475591600088

Co-infection with viruses like Hepatitis B and C is common in HIV-infected children [1]. All HIV-infected children must therefore be vaccinated against hepatitis B. Multiple factors lead to suboptimal response following vaccination in these children [2,3]. Even HIV-exposed but uninfected infants have been shown to have an altered immune response to vaccination [3,4]. This raises concern regarding the appropriate dose and schedule of vaccines to be administered to these children in order to achieve seroprotection. Numerous studies have shown a much lower level of seroprotection with Hepatitis B vaccine (HBV) in HIV-infected children and adults [5,6]. Various strategies to improve the seroconversion rates – like higher dose of the vaccine, additional doses of the standard dose or revaccination of the non-responders either by the double dose or standard dose [7,8] – have been tried. There is scarcity of data on seroconversion to HBV in HIV-infected Indian children on highly active antiretroviral therapy (HAART).

We conducted this study to compare the efficacy of double dose and standard dose of HBV in HIV-infected children.

METHODS

The study was a parallel group randomized controlled trial conducted at Anti retroviral therapy (ART) center of a tertiary level teaching hospital in Allahabad, UP, India from August 2014 to July 2015. The study was approved by the Institutional Ethical Committee (IEC). Written informed consent was obtained from the parents/ grandparents.

Accompanying Editorial: Pages 1001-03.

HIV-infected children in the age group between 18 months and 18 years fulfilling the following criteria were enrolled for the study: (*i*) Unvaccinated for Hepatitis B in the past and (*ii*) HBsAg negative. Children who were critically ill at the time of enrolment or anytime during the study were excluded from the study. The primary outcome measure was the Anti-HBs antibody titers 12 weeks after the 3rd dose of HBV.

All eligible children were randomized into Standard dose or Double dose groups with an allocation ratio of 1:1 using block randomization with blocks of 6 (*www.randomizer.org*). Children assigned to the standard dose group were given 0.5 mL (10 µg) of recombinant HBV deep intramuscular at 0, 1, 6 months. Children assigned to the double dose group were given 1 mL (20 µg) of HBV in the same schedule. Allocation was concealed in sequentially numbered, opaque and sealed envelopes, which were opened when a child was enrolled. All the children were thoroughly assessed before

enrolment and a detailed history was taken. The children were classified according to the revised World Health Organization (WHO) clinical staging and WHO immunological staging. The children received HAART according to the existing National AIDS Control Organization (NACO) guidelines. Anti-HBs antibody titres were estimated using enzyme linked immunosorbent assay (ELISA) (DS-EIA-ANTI-HBs) kit 12 weeks after the 3rd dose of HBV. Anti HBs titre ≥10 mIU/mL were considered as seroprotection.

Statistical analysis was done using Epi info 7 software. The data of the two groups were compared using the Chi square test, Student's t test or Mann-Whitney U test.

RESULTS

A total of 60 children were enrolled in the study with final analysis of 55 children (***Fig.* 1**). The baseline characteristics were comparable in both the groups **(*Table* I**). Seroprotection was achieved by 17 (60.7%) children in standard dose against 20 (74%) in double dose group but it was not statistically significant (***Table* II**). There was no difference in the seroprotective levels achieved when the children in both the groups were further stratified into two subgroups based on the CD4 counts at the time of enrolment; CD4 count <500 cells/mm^3 and CD count ≥500 cells/mm^3. CD4 count <500/mm^3 was independently associated with significantly lower rates of seroprotection irrespective of the dose of the vaccine (P=0.008) (***Table* II**). The coefficient of correlation (r) between the CD4 count and the Anti HBs titers achieved was 0.31 (P<0.001) showing a weak linear positive correlation.

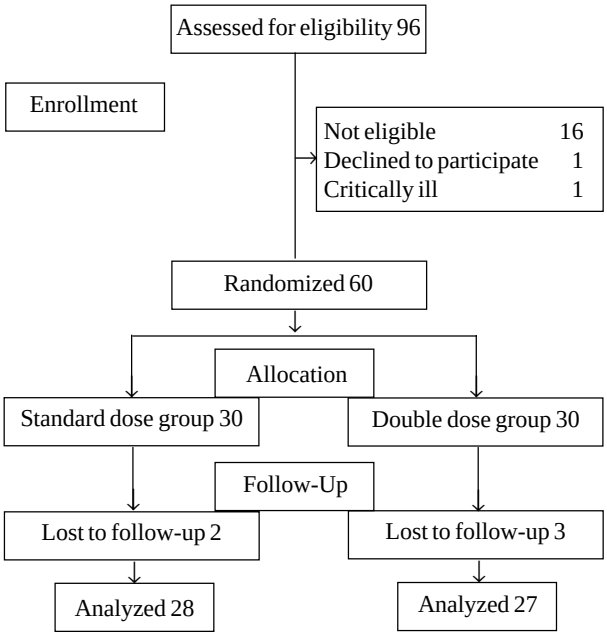

FIG.1 *Study flow chart.*

TABLE I BASELINE CHARACTERISTICS IN STUDY CHILDREN

	Standard dose (*n*=28)	*Double dose*(*n*=27)
M:F	3:1	2.3:1
Age (no.)		
18 mo - 5 y	3	1
5-10 y	12	15
10-18 y	13	11
Children on HAART	25%	22.2%
#*CD4 count (/mm^3)	719.8 (288.9)	730 (396.5)

**at enrolment*; *#values in mean (SD).*

DISCUSSION

In this study comparing the efficacy of double dose and standard dose HBV vaccine in HIV-infected children, the seroprotection rate in the double dose group was 74% compared to 60.8% of the standard dose group, but it was not statistically significant. The CD4 count at the time of enrolment was significantly associated with seroprotection with a linear positive relationship.

The limitation of the study is the small sample size because of the limited period of the study and single center-based enrolment. Only about one-fourth of these children were receiving HAART. Long-term follow-up for duration of seroprotection or development of hepatitis B infection was also not done in the present study.

Suboptimal immunological response to HBV in HIV-infected patients has been documented by numerous studies. A search for the ideal dose and schedule for the HBV in such individuals has not lead to a final consensus. Psevdos, *et al*. [9] studied the efficacy of double dose of HBV in HIV-infected individuals who failed to respond to standard dose vaccination. The double dose was compared with additional standard doses in non-responders. The response rate was significantly higher in the double dose group (85%) *vs.* additional standard doses (61%). Cornejo Juarez, *et al.* [10] conducted a randomized controlled trial comparing 10 µg dose with 40 µg dose and found no significant difference. Fonseca, *et al*. [11] found no significant difference in response to double dose of HBV in HIV- infected adults with seroconversion rates 47% compared to 34% in standard dose. However, double dose showed significantly higher response in individuals with CD4 ≥350 cells/mm^3 and HIV viral load <10,000 copies/mL. A meta-analysis by

TABLE II COMPARISON OF THE OUTCOMES IN STUDY GROUPS

	SD (*N*=28)	*DD* (*N*=27)	*RR* (95% *CI*)	*P Value*
Seroprotected, *N*(%)	17 (60.8%)	20 (74%)	0.8 (0.17,1.7)	0.29
CD4 <500/mm^3	3/8 (37.5%)	3/7 (42.8%)	0.87 (0.2, 3.0)	0.62
CD4 ≥500mm^3	14/20 (70%)	17/20 (85%)	0.8 (0.5, 1.1)	0.22
*Anti HBs titer (mIU/mL)	42.5 (7.5-335)	370 (9-1145)		0.09

**Median (IQR); SD standard dose; DD double dose.*

TABLE III CHARACTERISTICS OF SEROPROTECTED AND UNPROTECTED GROUP

	Achieved seroprotection	*Not achieved seroprotection*	*RR* (*95% CI*)	*P Value*
ART/No ART (N)	6/31	7/11	1.59 (0.8-2.95)	0.06
CD4 count, Mean (SD) (/mm^3)	788.02 (328.62)	596.16 (350.18)		0.05
CD4 count				
<500/mm^3 (*N*=15)	6 (40%)	9 (60%)	0.51 (0.27-0.98)	0.008
≥500/mm^3 (*N*=40)	31 (77.5%)	9 (22.5%)		

Ni, *et al.* [7] concluded that the response rates in the patients who received high dose was higher (OR 1.96; 95% CI 1.47, 2.61) [7].

A study by Pasricha, *et al.* [12] in India found significantly lower HBsAb levels in HIV-infected patients, especially those with a low CD4 count (<200 cells/mm^3), even with a double dose when compared to standard dose administered to healthy subjects. Bose, *et al.* [8] studied the immune response to 4 doses of double dose vaccine in HIV-infected children and found high (94%) seroconversion.

We found a CD4 count of <500 cells/mm^3 to be associated with significantly poor immune response. Other studies also found significantly suboptimal immune response in patients with a low CD4 count [13,14]. The use of ART did not significantly affect the immunological response of children in the index study. Cornejo-Juárez, *et al.* [9] found no association between type and duration of HAART and seroconversion but Psevdos, *et al.* [10] found use of HAART to be significantly associated with seroconversion.

We conclude that double dose of HBV does not seem to lead to higher seroprotection rate than standard dose in HIV-infected children. Further studies with a larger sample size and stratified according to age and CD4 counts will help us in understanding the need of modifying the dose of HBV in HIV-infected children in a better way.

Contributors: SAS, DKS: involved in designing the study, analysis of data and writing the manuscript; SAS, MM: involved in data collection and analysis; RR, AS: were involved in critical evaluation of the manuscript and analysis.
Funding: None; *Competing interests*: None stated.

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WHAT THIS STUDY ADDS?

- Three doses of 20 µg of hepatitis B vaccine do not seem to offer significantly higher rate of seroprotection than standard dose (10 µg) in HIV- infected children (aged >18 months) on anti-retroviral therapy.

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