Comparison of Efficacy of Hepatitis B Vaccination during Induction versus Maintenance Phase of Chemotherapy in Acute Lymphoblastic Leukemia: A Nonrandomized Clinical Trial

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Abstract

Background: Acute lymphoblastic leukemia (ALL) patients are susceptible to hepatitis B infection due to profound immunosuppression and repeated transfusions. However, the comparative effectiveness of hepatitis B vaccination in different phases of chemotherapy has not been studied. Aim: In this comparative interventional study (CTRI/2017/08/009402), vaccination in the induction phase (IP) was compared to that in the maintenance phase (MP). Materials and Methods: The participating ALL patients in both groups (29 per group) were vaccinated with double the dose of hepatitis B vaccine at 0, 1, and 2 months. The proportion of patients with seroprotective anti-hepatitis B surface titers (> 10 IU/ml) was compared between the two groups after each dose. Results: The seroprotection rates between both the phases were similar following the first (relative risk [RR] = 4, confidence interval [CI]: 0.47–33.65) and third (RR = 1.4, CI: 0.73–2.84) doses of vaccination, whereas following the second dose of vaccination, the seroprotection rate in IP was significantly higher than that of MP (RR = 1.9, CI: 1.07–3.35). Conclusion: This study concluded that a 0, 1, and 2 schedule of hepatitis B vaccination has similar efficacy in both the IP and the MP of chemotherapy in ALL patients. As the IP has a higher trend of seroprotection rates compared to MP, vaccination in IP followed by revaccination postchemotherapy may be preferred in countries with a high prevalence of hepatitis B infection.

Keywords: Accelerated vaccination schedule, acute lymphoblastic leukemia, controlled clinical trial, hepatitis B virus, vaccines

INTRODUCTION

The advent of modern chemotherapy regimens has improved the survival rates of acute lymphoblastic leukemia (ALL) patients drastically. However, hepatitis B is emerging as an important complication during chemotherapy in countries where it is highly prevalent.[1] The prevalence of hepatitis B in India is 2%–8%, making it a relevant problem during chemotherapy.[2] The reported prevalence of hepatitis B infection among ALL patients undergoing chemotherapy is very high, ranging from 16% to 45%.[3-6] This high susceptibility is the result of immunosuppression associated with chemotherapy and ALL, and large scale needs for transfusion support.[2] With a very effective vaccine in place, with seroprotection rates of over 96%, hepatitis B is a preventable complication.[7] The Advisory Committee on Immunization Practices (ACIP) recommends the completion of indicated inactive and subunit vaccines prior to initiation of chemotherapy whenever feasible. It also advises revaccination 3 months following chemotherapy if vaccination was carried out during chemotherapy. ALL is a medical emergency and it is not feasible to complete hepatitis B vaccination prior to chemotherapy initiation.[8] There are no clear guidelines in place regarding the timing of hepatitis B vaccination in ALL during chemotherapy. Majority of the patients acquire the infection during the induction phase (IP).[4] This highlights the need for vaccination during

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this phase. Cytotoxic chemotherapy results in CD4 T-cell depletion and poor response to vaccines. Intense multiagent chemotherapy comprising purine analogs, alkylating agents, and high-dose steroids results in profound immunosuppression in IP compared to the maintenance phase (MP). This can adversely affect the seroconversion rates in IP as documented by some studies. However, better seroconversion rates were apparent in MP. This creates the dilemma of whether hepatitis B vaccination should be given to the patients in IP or MP as data on their relative efficacy are lacking. This study was conducted to compare the seroprotection rates following hepatitis B vaccination during IP and MP in patients with ALL on chemotherapy.

**Materials and Methods**

**Study design and patient selection**

This study was a comparative nonrandomized interventional trial conducted outside in the departments of medicine and medical oncology on ALL patients from the outpatient department and inpatients of a tertiary care hospital in southern India from January 2015 to January 2017. Approval from the institute ethical committee (human studies) was obtained and it was registered in the Clinical Trials Registry of India (CTRI/2017/08/009402) prior to the study. It was carried out in accordance with the Helsinki Declaration of 1975, as revised in 2000. Signed informed consent was obtained from all the participants of the study (assent for participants between 12 and 18 years of age). In addition, informed consent was taken from the parents or legally accepted representative of participants below 18 years of age, following which they were screened based on the inclusion and exclusion criteria. Consecutive ALL patients either admitted or attending the outpatient department of the hospital, seronegative for hepatitis B virus surface antigen (HBsAg), and receiving chemotherapy (in either IP or MP) with anti-hepatitis B surface (HBs) titer <10 mIU/ml were included in the study. Patients with documented HIV positivity and currently receiving hepatitis B vaccine as a part of any other schedule were excluded. Consecutive patients in IP were included in Group I and those in MP were included in Group II. Group I and Group II were vaccinated exclusively in IP and MP, respectively.

**Methodology**

After screening, 8 ml of blood was collected from consenting patients by venepuncture from the right cubital vein under strict aseptic precautions for testing anti-HBs titers, HBsAg, anti-hepatitis B core (HBc) total, and liver function test. Anti-HBs titers were measured using MBS HBsAb ELISA manufactured by MBS NEW S.R.L., Italy, HBsAg using HEPELISA by J. Mitra and Co. Pvt. Ltd., India, and anti-HBc total using Insight HBcAb rapid immunochromatographic assay by Tulip Diagnostics (P) Ltd., India. Subsequently, patients meeting the inclusion criteria were included in the study. Relevant history and baseline demographic data such as age, height, weight, history of prior vaccination, type of ALL, chemotherapy regimen, and laboratory parameters were collected. A detailed physical examination was performed and the first dose of hepatitis B vaccine was given intramuscularly. GeneVac-BTM (hepatitis B vaccine [rDNA] IP) manufactured by Serum Institute of India Pvt. Ltd. (212/2, Hadapsar, Pune, India) was used for vaccination. Patients included in Group I were vaccinated during the first 3 months of the IP of chemotherapy. Patients included in Group II were vaccinated during the initial months of MP of chemotherapy. A schedule of 0, 1, and 2 was followed, with patients receiving vaccination immediately after screening and 1 and 2 months following the first dose of vaccine. It was given intramuscularly into the deltoid of the right arm under aseptic precautions. Double the standard dose was used, i.e. 20 μg for children ≤10 years of age and 40 μg for those above 10 years of age. In cases of fever requiring antibiotics or thrombocytopenia below 5 × 10^9/L, the vaccination was deferred for a few days until recovery.

Anti-HBs titers and HBsAg were repeated 1 month after each dose of vaccination. Anti-HBs titer of 10 mIU/ml was considered protective based on the recommendations of the US ACIP and WHO. Seroprotection for a patient was defined when a patient has achieved protective anti-HBs titers as per laboratory. The seroprotection rate was calculated for each group a month following each dose of vaccination and then compared. Patients who died during the study period without receiving a full course of vaccination were excluded from the analysis. Patients who became HBsAg during the study period were excluded from receiving further doses of vaccine. Subgroup analysis was done between the groups to identify if type of chemotherapy regimen, tumor lineage, age (>10 years), and prior history of vaccination affected the difference in seroprotection rates between the two groups following the third dose of vaccination.

**Sample size calculation**

The seroprotection rates of 10.5% in IP and 46.2% in MP, as documented in previous studies, were used for the sample size calculation. To achieve a power of 80% with an alpha error of 5%, the sample size was calculated to be 58 (29 in each group).

**Statistical analysis**

All continuous data related to the patients’ clinical and biochemical parameters were expressed as mean with standard deviation or median with interquartile range based on the normality of data. The distribution of categorical data related to the patients such as gender, clinical characteristics, and primary outcome was expressed as frequency and percentage. The seroprotection rates were expressed as percentage of patients in both the groups with protective titers. The comparison of seroprotection rates between the two groups was carried out using the Chi-square test or Fisher’s exact test. Subgroup analysis was carried out using the Chi-square test or Fisher’s exact test adjusting for the variables: history of vaccination, age, tumor lineage, and type of chemotherapy to look for
confounding factors. \( P=0.05 \) was considered to be statistically significant for all comparisons.

**RESULTS**

Ninety patients were screened for the study, out of which a total of 58 patients completed the study with 29 patients in Group I and 29 patients in Group II. The screening and recruitment flow diagram [Figure 1] describes the recruitment process in detail. The baseline characteristics and laboratory parameters of the patients in Group I and Group II are represented in Table 1. Both the groups were similar with regard to the baseline characteristics such as age distribution, tumor lineage, and type of chemotherapy. A higher proportion of patients had a history of vaccination prior to initiation of chemotherapy and anti-HBc total positivity in Group II compared to Group I. Overall, 17.2% of the study population were detected to be anti-HBc total positive. None of the patients acquired HBsAg positivity during the study period. No injection site hematomas were observed.

Figure 2 shows a comparison of seroprotection titer rates between Group I and Group II following each dose of vaccination. It was found that following the first and third doses of vaccination, the seroprotection rates between both the groups were similar (relative risk [RR] = 4, confidence interval [CI]: 0.47–33.65; RR = 1.4, CI: 0.73–2.84), whereas following the second dose of vaccination, the seroprotection rate in IP was significantly higher than that of MP (RR = 1.9, CI: 1.07–3.35). In the subgroup analysis, the various parameters studied did not significantly alter the difference in seroprotection rates between the two groups following the third dose of vaccine [Figure 3]. However, parameters such as MCP841, B-cell ALL, and age <10 years seem to be improving the seroprotection rates in MP, albeit not significantly.

**DISCUSSION**

In the present study, similar seroprotection rates were noted following both the first and third doses of hepatitis B vaccination in IP and MP of chemotherapy in ALL patients. However, a higher seroprotection rate was observed in IP following the second dose of vaccination. A similar outcome was noted across all subgroups.

The seroprotection rate following vaccination in MP is well documented. On the other hand, in studies where vaccination was carried out in the IP, the seroprotection rates were measured in the MP following a booster dose. To the best of our knowledge, neither has any study measured the seroprotection rates at the end of IP nor has the comparison between the two phases been attempted.

The seroprotection rates of 10.5% and 18.9% had been documented following vaccination in IP using a vaccination schedule of 0, 1, and 2 with a booster given 1 year later and another schedule of 5 primary doses of vaccine given 1 month apart with a booster 1 year later, respectively.\[^{4,5}\] However, the measurement of seroprotection rate was not carried out at the end of IP but in the MP of chemotherapy following the administration of booster dose. In contrast to this, in the present study, it was measured at the end of IP resulting in a significantly higher seroprotection rate of 44%. An accelerated schedule of vaccination (0, 1, and 2 months) may have an advantage over the regular schedule (0, 1, and 6 months) during the IP of chemotherapy where protective titers need to be achieved faster.

The seroprotection rate of 38.6% was achieved using five doses of 20 \( \mu \)g GenHevac B (0, 1, 6, 12, and 15) in MP. An accelerated schedule of 20 \( \mu \)g Engerix B at 0, 1, and 2 months followed by two boosters at 6 and 12 months yielded 32% seroprotection rates with 26% seroconversion rates noted at the end of the third dose.\[^{10}\] Patients aged 1–16 years only were included in this study. Baytan et al. (2008) explored seroconversion rates in children following an accelerated schedule (0, 1, and 2 months) using 40 \( \mu \)g (four times the standard dose) of vaccine starting in the 3rd month of MP when the lymphocyte count was more than 3000/mm\(^3\).\[^{11}\] The seroprotection rates in the groups with and without evidence of prior hepatitis B infection were 100% and 33%, respectively. However, the results from the group...
Table 1: Baseline characteristics of patients in Group I and Group II

| Characteristic                                      | Group I (Intensive phase, \( n = 29 \)) | Group II (Maintenance phase, \( n = 29 \)) |
|-----------------------------------------------------|----------------------------------------|------------------------------------------|
| Age (years)*                                        | 12 (5-25)                              | 11 (4.5-22)                              |
| Sex                                                  |                                        |                                          |
| Male                                                 | 17 (58.6)                              | 21 (72.4)                                |
| Female                                               | 12 (41.4)                              | 8 (27.6)                                 |
| Height (cm)*                                        | 132 (28.4)                             | 130 (30.5)                               |
| Weight (kg)*                                        | 35.0 (19.7)                            | 33.6 (22.6)                              |
| Prior history of vaccination*                        | 10 (34.5)                              | 15 (51.7)                                |
| Mediastinal mass present*                           | 4 (13.8)                               | 7 (24.1)                                 |
| Pallor*                                              | 20 (69)                                | 22 (75.9)                                |
| Lymphadenopathy*                                    | 17 (58.6)                              | 18 (62.1)                                |
| Hepatomegaly*                                       | 12 (41.4)                              | 16 (55.2)                                |
| Splenomegaly*                                       | 16 (55.2)                              | 1 (44.8)                                 |
| BCR-ABL positive*                                   | 2 (6.9)                                | 0 (0)                                    |
| CNS involvement*                                    | 3 (10.2)                               | 1 (3.4)                                  |
| Type of ALL*                                        |                                        |                                          |
| T-cell                                              | 7 (24)                                 | 10 (34)                                  |
| B-cell                                               | 22 (76)                                | 19 (66)                                  |
| Type of chemotherapy*                               |                                        |                                          |
| GMALL                                                | 4 (10)                                 | 6 (21)                                   |
| MCP841                                               | 21 (72)                                | 18 (62)                                  |
| BFM95                                                | 3 (14)                                 | 4 (14)                                   |
| Laboratory parameters                               |                                        |                                          |
| Hemoglobin (g/dL)*                                   | 7.2 (2.3)                              | 7.5 (3.1)                                |
| Total leukocyte count (cells/mm\(^3\))*             | 7,970 (2,960-37,745)                   | 10,090 (3,250-32,645)                    |
| Platelets (cells/mm\(^3\))*                         | 53,000 (21,500-6,000)                  | 41,000 (30,500-79,000)                   |
| Total bilirubin*, mg/dL                             | 0.7 (0.5-0.8)                          | 0.6 (0.6-0.8)                            |
| Aspartate aminotransferase (units/l)*                | 33 (23-57)                             | 32 (21-49)                               |
| Alanine aminotransferase (units/l)*                 | 32 (18-54)                             | 21 (16-38)                               |
| Alkaline phosphatase (units/l)*                     | 325 (205-485)                          | 271 (189-406)                            |
| Total protein*, g/dL                                | 6.6 (6.1-7.2)                          | 6.8 (6.2-7.1)                            |
| Albumin*, g/dL                                      | 3.6 (3.4-3.9)                          | 3.6 (3.1-3.8)                            |
| Anti-HBc total positivity*                          | 2 (6.9)                                | 8 (27.6)                                 |

*Values are expressed as median (interquartile range), †Values are expressed as mean (SD), ‡Values are expressed as frequency (%). SD=Standard deviation, CNS=Central nervous system, ALL=Acute lymphoblastic leukemia, HBc=Hepatitis B core

Figure 3: Forest plot of relative risk of protective titers following the third dose of vaccine by subgroups
with prior evidence of infection are limited by a small sample size (n = 6). In contrast to the above studies, the population in the present study were older (included adults above 16 years) and double the standard dose of vaccine was used. Despite these differences, the seroprotection rate observed in the MP following an accelerated vaccination schedule in the present study (31%) is similar to the above-mentioned studies.

It is of interest to note that the seroprotection rates obtained following two doses of vaccine in IP (66.5%) are comparable to the seroprotection rates reported in the general population (76%).[10‑18] As IP involves more aggressive chemotherapy, it is only logical to assume that the immunosuppression during this phase would be much more profound compared to MP. This should lead to a better seroconversion rate following vaccination in MP compared to IP, but the results from this study stand in contrast to this general notion. The seroprotection rates in induction were found to be higher compared to MP even though this difference was not statistically significant. The plausible reason could be that the patients are not immunosuppressed enough during the initial 1–2 months of induction chemotherapy as compared to the latter part of induction. With the development of profound immunosuppression, there is a probable loss of protective titers among patients who had achieved it previously. It is well documented that patients with a prior history of vaccination lose their protective titers following an intensive phase of chemotherapy.[10,16‑18] The low seroprotection rates in MP could be attributed to the fact that the immune system takes 6–12 months for reconstitution after stopping chemotherapy. [16,19] This might explain the better seroconversion response attained with vaccination in IP after the second dose of vaccine. As profound immunosuppression sets in, this response is lost resulting in fall in seroprotection rates over time. Even so, the presence of protective titers during the IP should be beneficial as the risk of hepatitis B transmission is highest during the IP of chemotherapy.

In subgroup analysis, parameters such as MCP841, B-cell ALL, and age <10 years seem to demonstrate a trend toward better seroprotection rates in MP but not significantly. It is quite possible that the effect of these parameters is not significant because of the low sample size. Even though the groups differed in terms of anti-HBc total positivity in baseline characteristics, anti-HBc total positive patients could not be included in the subgroup analysis as the numbers were too low in both of the groups. However, a trend toward better seroprotection rates was noted among anti-HBc total positive patients in both IP and MP in the current study. In the subgroup analysis, a prior history of vaccination did not alter the seroprotection rates between the groups. One would have expected a better response to vaccination in MP due to the higher number of previously vaccinated patients in the maintenance group. This is probably because both ALL disease pathology and chemotherapy have been shown to affect memory cell function and booster response.[17]

One major limitation of the study was the nonrandomized design. Randomization of the patients would have improved the reliability of the results obtained, but due to practical difficulties, it was not possible to randomize the patients. Another limitation is the small sample size and short follow-up period. The trend in seroprotection rates over a period of time could have provided better insight into long-term outcomes. The lack of data on absolute lymphocyte count and immunoglobulin levels which could have provided an insight into the degree of immunosuppression and its effect on the response to vaccination is another limitation of the study.

Conclusions

The seroprotection rates following a 0, 1, and 2 schedule of hepatitis B vaccination in IP was similar to that of MP 1 month after the third dose. The seroprotection rates following hepatitis B vaccination in IP are significantly higher compared to that of MP following the second dose of vaccine, but it was not sustained. Hence, the 0, 1, and 2 schedule of hepatitis B vaccination has similar efficacy in either the IP or the MP of chemotherapy in ALL patients. As the IP has a higher trend of seroprotection rates compared to MP, vaccination in IP followed by revaccination postchemotherapy may be preferred over the latter for the schedule of vaccination in countries with a high prevalence of hepatitis B infection.

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Conflicts of interest

There are no conflicts of interest.

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