Intramuscular vs intradermal route for hepatitis B booster vaccine in celiac children

Salvatore Leonardi, Andrea Domenico Praticò, Elena Lionetti, Massimo Spina, Giovanna Vitaliti, Mario La Rosa

Salvatore Leonardi, Andrea Domenico Praticò, Elena Lionetti, Massimo Spina, Giovanna Vitaliti, Mario La Rosa, Department of Pediatrics, University of Catania, 95100 Catania, Italy

Author contributions: All authors equally contributed to the realization of the research project and the writing of the paper.

Correspondence to: Salvatore Leonardi, MD, Department of Pediatrics, University of Catania, Via S. Sofia 78, 95100 Catania, Italy. leonardi@unict.it
Telephone: +39-953-782764 Fax: +39-953-782385
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Abstract

AIM: To compare intradermal (ID) and intramuscular (IM) booster doses, which have been used in healthy and high risk subjects, such as healthcare workers, haemodialysis patients, human immunodeficiency virus patients, and renal transplant recipients unresponsive to initial hepatitis B vaccination, in celiac individuals.

METHODS: We conducted our study on 58 celiac patients, vaccinated in the first year of life, whose blood analysis had showed the absence of protective hepatitis B virus (HBV) antibodies. All patients had received the last vaccine injection at least one year before study enrolment and they had been on a gluten free diet for at least 1 year. In all patients we randomly performed an HBV vaccine booster dose by recombinant hepatitis B vaccine (Engerix B) 2 μg by the ID route, while 28 celiac patients were revaccinated with Engerix B 10 μg by the IM route. Four weeks after every booster dose, the anti-hepatitis B surface (HBs) antibody titer was measured by an enzyme-linked immuneadsorbent assay. We performed a maximum of three booster doses in patients with no anti-HBs antibodies after the first or the second vaccine dose. The cut off value for a negative anti-HBs antibody titer was 10 IU/L. Patients with values between 10 and 100 IU/L were considered "low responders" while patients with an antibody titer higher than 1000 IU/L were considered "high responders".

RESULTS: No significant difference in age, gender, duration of illness, and years of gluten intake was found between the two groups. We found a high percentage of "responders" after the first booster dose (ID = 76.7%, IM = 78.6%) and a greater increase after the third dose (ID = 90%, IM = 96.4%) of vaccine in both groups. Moreover we found a significantly higher number of high responders (with an anti-HBs antibody titer > 1000 IU/L) in the ID (40%) than in the IM (7.1%) group, and this difference was evident after the first booster dose of vaccination (P < 0.01). No side effects were recorded in performing delivery of the vaccine by either the ID or IM route.

CONCLUSION: Our study suggests that both ID and IM routes are effective and safe options to administer a booster dose of HBV vaccine in celiac patients. However the ID route seems to achieve a greater number of high responders and to have a better cost/benefit ratio.

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Key words: Hepatitis B virus; Non responders; Intradermal route; Intramuscular route; Celiac disease

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INTRODUCTION

In literature there are several reports describing a non-responsiveness to hepatitis B vaccine in celiac patients,[1-4], although the pathogenic mechanism is still unclear. As a matter of fact it seems that this failed response could be linked to the "major histocompatibility complex" (MHC) and human leucocyte antigen (HLA)-II pattern characterizing the disease,[5-7] while other studies indicate that gluten intake at the time of vaccination could influence the vaccine-induced immune response.[8]

However it is not completely understood whether the unresponsiveness to hepatitis B vaccine in celiac patients is also linked to a weakened immune response in healthy older people or to a physiological loss of humoral immunity with the flow of time.[9] Fisman et al.[10] published a meta-analysis on the increased risk of unresponsiveness to hepatitis B vaccination in older subjects, finding a low response even in 30-year-old patients.

An important consideration is that the titer of anti-hepatitis B surface (anti-HBs) antibodies that should be considered as cut-off for "non-response" to hepatitis B virus (HBV) vaccine is < 10 IU/L, when the measurement is performed a long time after the vaccination. The responsiveness to hepatitis B vaccine should usually be determined by antibody measurement within 2-6 mo after the third vaccine dose. In those patients with anti-HBs < 10 IU/L a booster vaccine schedule should be proposed, but until now there is no consensus on this kind of management.

In the present study we administered a vaccine booster dose against HBV by the intradermal (ID) or intramuscular (IM) route in celiac patients, whose antibodies levels against the HBV were low after the first regimen of hepatitis B vaccine performed in the first year of life.

The aim of our study was to evaluate the possibility to provide a satisfactory immune response against HBV by these procedures, comparing their efficacy.

MATERIALS AND METHODS

Our study was a prospective, randomized study, conducted on 58 celiac patients (age, mean ± SD, 9.8 ± 6.2 years) of 116 celiac subjects (age, mean ± SD, 10.2 ± 5.7 years) referred to our Pediatric Department, University of Catania, Italy, whose blood analysis showed the absence of protective HBV antibodies (anti-HBs). In all included patients, the diagnosis of celiac disease was made after one year of age, based on clinical signs and standard serological markers (antigliadin IgA and IgG, tissue trans-glutaminase IgA antibody, anti-endomysial antibody) and on typical histological findings on small bowel biopsies (vilous atrophy with crypt hyperplasia and increased intraepithelial lymphocytes).

All patients received the anti-HBV vaccine at 3, 5 and 11 mo of age by IM injection on the front-lateral area of their quadriceps muscle (10 μg of Engerix B, GlaxoSmith and Kline, Belgium), as planned by the Italian standard vaccination schedule.

All patients had received the last vaccine injection at least one year before the study enrolment and they had been on a gluten free diet for at least 1 year. None of the patients had ever been affected by HBV infection.

In all patients we randomly performed an HBV vaccine booster dose by the ID or IM route. Thirty celiac patients were revaccinated by the ID route with a 2 μg dose of recombinant hepatitis B vaccine (Engerix B) administered on the flexor surface of the forearm, using a 1 mL syringe and 26-gauge needle. In all the patients a visible skin weal was noticed as evidence of the ID inoculation.

Twenty-eight celiac patients were revaccinated by the IM route with a 10 μg dose of Engerix B administered in the lateral region of their deltoid muscle, using a 5 mL syringe and 26-gauge needle.

Four weeks after every booster dose, the anti-HBs antibody titer was measured by enzyme-linked immune-absorbent assay (hepanostica anti-HBs, bioMerieux, Netherlands). We performed a maximum of three booster doses in patients with no anti-HBs antibodies after the first or the second vaccine dose. The cut off value for a negative anti-HBs antibody titer was 10 mIU/mL. Patients with values between 10 and 100 IU/L were considered "low responders" while patients with an antibody titer higher than 1000 IU/L were considered "high responders".[11]

Statistical analysis

The Mann-Whitney U-test was performed to compare age, duration of illness, years of gluten intake and HBs antibody titer between the two groups of patients. The Fisher exact test was used to compare the gender, the number of non responders, low responders and high responders between the ID and IM groups. P value < 0.05 was considered statistically significant.

RESULTS

The main features of the two groups of patients are reported in Table 1. No significant difference of age, gender, duration of illness, and years of gluten intake was found between the two groups.

The number and the percentage of responders to ID and IM hepatitis B vaccination after every dose injection are reported in Table 2, together with the mean and SD of the anti-HBs titer in the two groups after the first and the third booster.

Both groups of patients showed a similar percentage of responders after the first dose of vaccine (ID = 76.7%, IM = 78.6%) and a major increase after the third dose (ID = 90%, IM = 96.4%). However, we did not find any statistically significant difference between the two groups. We found no statistically significant difference in anti-HBs titer between the two groups, after the first and the third doses.

Finally we found a significantly higher number of high responders (with an anti-HBs antibody titer > 1000 IU/L) in the ID (40%) than in the IM (7.1%) group, and this difference was evident after the first booster dose of...
vaccination (Figure 1). No side effects were recorded in performing both ID and IM injections.

**DISCUSSION**

Literature data describe that 4%-10% of healthy, immune competent individuals fail to elicit protective levels of antibodies to recombinant HBs antigen after completing the standard hepatitis B vaccination schedule[12,13]. Even though the pathogenic mechanism leading to a failed response to hepatitis B vaccine is still unknown, there are several hypotheses trying to explain this link. Recently, Zingone et al[14] reported a possible association with gluten intake at the time of vaccination that may influence the vaccine-induced immune response. Nevertheless, the most likely hypothesis is related to a specific pattern of MHC[13] and HLA-Ⅱ antigens linked to the disease. As a matter of fact, homozygosis for HLA-B8, DR3 and DQ2 alleles was found to have a significantly higher incidence in hepatitis B vaccine non responders[15,16].

This HLA-DQ2 haplotype is present in 90%-95%[14,15] of celiac patients and it seems to explain the relationship between the disease and the non-responsiveness to hepatitis B vaccine. Thus, in celiac non responders a re-vaccination should be recommended because of the worldwide spread of the disease.

Nowadays, there is no consensus on the management of celiac patients with anti-HBs antibody levels <10 IU/L after the IM vaccine. In healthy people a common practice is to administer a higher dose of HBV recombinant vaccine (HBRV) or a second course of three doses of IM recombinant vaccine (IMRV)[16], but it does not seem to be successful. In fact it has been reported that more than 50% of non responders are not able to acquire a protective anti-HBs titer with at least two additional IMRV booster doses in the primary course[17,18].

In human immunodeficiency virus patients, repeated vaccination is commonly considered as a first satisfactory strategy[19]. Some investigators have even increased the dose of hepatitis B vaccine with varying success[20,21] or have used a double dose of a combined hepatitis A and B vaccine[22].

The United States Center for Disease Control and Prevention recommends the administration of an additional series of three doses of IM vaccine in chronic hemodialysis patients[23]. For those non-responders after two series (six doses of vaccine in total), there is no data to support the use of additional doses to induce an immune response.

Another approach is to administer HBRV vaccine by the ID route. In fact a recent meta-analysis by Fabrizi et al[24] concluded that the ID route is associated with higher anti-HBs antibody levels, although this is not sustained over time. Recently in a pilot study we found an effective response after ID administration of HBRV in celiac patients too[25].

At present this is the first study comparing the ID and IM routes in these patients. In our study we found a high percentage of response after the first dose of vaccination in both groups (ID 76.7% vs IM 78.6%) and a higher response after the third booster dose (ID 90% vs IM 96.4%). Moreover, the percentage of responders in both groups after the three doses of vaccine was similar to those found in vaccinated healthy people[26].

Our data confirms that both routes are effective to perform a booster strategy in celiac patients with low anti-HBs antibodies, as 90% of ID patients and 96.4% of IM subjects showed a protective anti-HBs titer after the third booster dose. However the ID route seems to produce a significantly higher percentage (40%) of high responders (anti-HBs > 1000 IU/L) than the IM route (7.1%).

In our opinion, this result may have an important clinical significance, because a protective anti-HBs titer...
may persist to 64% after 10 years in normal children if there is a high value of anti-HBs antibody titer at the end of the initial schedule[21].

However, whether the ID route is a better strategy than IM hepatitis B vaccine still remains an open question. In fact several studies in high-risk groups[22-28] showed that low dose ID injections resulted in long term sero-protection in a large number of subjects non responsive to IM vaccination. However, a recent meta-analysis of 757 adults by Sangaré et al[29] demonstrated that ID hepatitis B vaccination was less effective to achieve sero-protection than IM vaccination.

Recently a randomized study on ID vs IM hepatitis B vaccination in human immunodeficiency virus-infected children, without severe immunosuppression, confirmed this issue[30]. In particular, in the study by Medeiros et al[31] on hemodialysis patients, the percentage of responders was very low (13.3%) in the ID route.

Our data seem to suggest that the use of the ID route for the booster dose of hepatitis B vaccine in celiac patients is a better option to obtain a higher titer of antibodies against HBV. Moreover the ID route allows a better cost/efficacy ratio, because of the cost reduction exceeding 50% (2 μg per dose) compared with a standard IM vaccine regimen (10 μg per dose)[32]. In conclusion, it is important to highlight that the ID route could represent an efficacious and cost-saving option for difficult-to-vaccinate and high-risk patients, as reported in other studies[33-35] and also for the observed 4%-10% of healthy people who normally fail to respond to the standard HBV vaccination regimen[36].

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