HHS Public Access

Author manuscript

Haemophilia. Author manuscript; available in PMC 2016 January 01.

Published in final edited form as:

Haemophilia. 2015 January ; 21(1): e39–e43. doi:10.1111/hae.12569.

Hepatitis B vaccination is effective by subcutaneous route in children with bleeding disorders: a universal data collection database analysis

S. L. Carpenter[*], **J. M. Soucie**[†], **R. J. Presley**[†], **M. V. Ragni**[‡], **B. M. Wicklund**[*], **M. Silvey**[*], **H. Davidson**[§], and **The Hemophilia Treatment Center Network Investigators**[¶]

[*]Department of Pediatrics, Children's Mercy Hospital, Kansas City, MO, USA

[†]Division of Blood Disorders, National Center for Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, USA

[‡]Department of Medicine, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

[§]Department of Pediatrics, Phoenix Children's Hospital, Phoenix, AZ, USA

[¶]Hemophilia Treatment Centers

Summary

Subcutaneous (SQ) vs. intramuscular (IM) vaccination may cause fewer injection site complications in children with bleeding disorders, but little is known about comparative immunogenicity. To compare immunogenicity of hepatitis B virus (HBV) vaccination administered SQ or IM to individuals <2 years old with bleeding disorders, we performed a retrospective analysis of HBV surface antibody titres among patients enrolled in the universal data collection database who had received three doses of HBV vaccine solely by one route (SQ or IM). Data reviewed were from an initial visit before 24 months of age, until time of hepatitis antibody titre testing. The SQ and IM study groups did not differ in demographics, haemophilia type or severity or bleeding history. The mean age at the time of HBV surface antibody (anti-HBs) testing was 56.9 ± 20.3 months. Eighty-five of 92 subjects (92.4%) who received vaccine SQ developed a positive antibody titre (>12 IU/L), compared to 101/114 (88.6%) who received IM ($P = 0.30$). There was no statistically significant difference in distribution of titre values. The average age of the subjects at time of testing was 53 ± 20 months in the SQ group vs. 60 ± 20 months in the IM group ($P = 0.02$). The average time between the last dose of vaccine and anti-HBs testing was 47.6 ± 18.5 months among SQ vaccinated subjects vs. 51.6 ± 20.5 months in the IM group ($P = 0.2$). Immunogenicity to hepatitis B vaccination by the SQ and IM routes is similar.

Correspondence: Shannon L. Carpenter, MD, MS, Children's Mercy Hospital, 2401 Gillham Rd., Kansas City, MO 64108, USA. Tel.: 816-234-3508; fax: 816-802-1270; slcarpenter@cmh.edu.

Author contribution

S. Carpenter designed and performed the research, and wrote the paper. J.M. Soucie and R. Presley contributed to the design of the research, collected and analysed the data and wrote, edited and approved the paper. M. Ragni, B. Wicklund, M. Silvey and H. Davidson contributed to the design of the research, edited and approved the paper. Hemophilia Treatment Center Network Investigators collected the data.

Disclosures

The authors stated that they had no interests which might be perceived as posing a conflict or bias.

Keywords

bleeding disorders; haemophilia; hepatitis B; immunizations; intramuscular; subcutaneous; UDC

Introduction

Individuals with haemophilia and other bleeding disorders require immunizations recommended by the Advisory Committee on Immunization Practices (ACIP) to prevent communicable diseases, such as hepatitis B virus (HBV) infection, as good preventive practice, and because of potential transmission by factor infusions and blood product transfusions [1–3]. HBV vaccines in the US are FDA-licensed for intramuscular (IM) administration to achieve optimal protective antibody titres. Hepatitis B vaccines are routinely administered IM to infants as a 3-dose series at birth, 2, and 6 months post-delivery. Hepatitis B vaccine can be administered as a single vaccine or as one portion of a combination vaccination [2,4].

Children with bleeding disorders, especially with severe disease, are at risk for muscle haematomas with IM injections. Clotting factor concentrates can be administered to minimize this risk; however, factor is very expensive and requires intravenous administration which can be technically difficult in babies and small children. Thus, there has been interest in subcutaneous (SQ) vaccination, but few data exist concerning its safety. Moreover, there has been concern that the SQ route may not provide the same level of immunogenicity [5,6]. There are few published studies comparing SQ and IM routes for HBV vaccination within the bleeding disorder population. Zanetti, et al. found that 98% of people with haemophilia immunized SQ developed antibodies to HBV [7]. Based on these data, the World Federation of Hemophilia (WFH) has recommended that children with haemophilia receive SQ vaccinations [8]. However, in the U.S., the ACIP recommends that individuals with bleeding disorders be vaccinated IM unless the patient's physician feels that it is unsafe. In addition, the guidelines specifically state that if the vaccine is given in any way other than IM, the dose must be repeated within 1 month [2]. This recommendation is supported by the guidelines of the National Hemophilia Foundation's Medical and Scientific Advisory Committee (MASAC) [1]. Therefore, there continues to be disagreement regarding the most efficacious and safe way to administer the HBV vaccine in the bleeding disorders population.

The Centers for Disease Control and Prevention (CDC) has supported a public health surveillance system established in a network of haemophilia Treatment Centres (HTC) throughout the U.S. called the universal data collection (UDC) project [9]. In this study, we used data collected in the UDC project to compare the rate of seroconversion to HBV vaccine in children who had received HBV vaccination SQ to those who had received it IM.

Methods

To test the hypothesis that there is no difference in the proportion of patients with haemophilia A or B, von Willebrand Disease, or other bleeding disorders that develop protective levels of hepatitis B surface antibodies (anti-HBs) among patients vaccinated for

hepatitis B either by the SQ or IM route, we conducted a retrospective study. Data for the study were collected during the period July 2003 to September 2011 by medical care providers. The project was conducted with approval from the Institutional Review Boards of CDC and all participating institutions. Participants (or parents of minor children) gave informed consent.

Patients receiving care in HTCs were eligible to participate in UDC at any age. Among those enrolled before their second birthday, data were collected using special forms relevant to young children including information on vaccinations. A registration form collected data on month and year of birth, sex and parent- reported race and ethnicity. For this analysis, race and ethnicity were categorized as non-Hispanic white, non-Hispanic black, Hispanic (either black or white) or other. Data entered into the UDC by the treating HTC were used to determine the type of bleeding disorder and severity. For children with haemophilia, severity was based on the factor activity at baseline with values <1%, 1–5% and >5% of normal categorized as severe, moderate and mild disease respectively. Clinic records were used to determine whether the child had ever had a bleeding episode prior to enrolment in UDC.

Children could participate in UDC as often as every 6 months until they reached age 2 years, after which participation was limited to once per year. Prior to age 2 years, data were collected on hepatitis B vaccination including the route of administration (SQ or IM) and the dates for up to three doses. In addition, data were collected on the number of bleeding episodes according to body site including intramuscular haematoma. No blood draws were required for children under 2 years of age in UDC.

For UDC participants older than 2 years of age, a blood sample was collected, isolated and frozen and sent overnight on cold packs to the CDC serum bank according to a standard protocol. Specimens were then tested for serologic evidence of infection or exposure to hepatitis B by the CDC coagulation laboratory using the Vitros ECi Immunoassay Analyzer (Ortho-Clinical Diagnostics, Raritan, NJ, USA) to perform a chemiluminescent immunometric assay that involves the reaction of anti-HBs in the sample with HBsAg coated onto wells. According to manufacturer specifications for this assay, a result ≥12.0 mIU/mL anti-HBs was considered positive and the individual is presumed to be immune to HBV infection [10]. All testing was performed according to instructions provided by the manufacturer and all results were within manufacturer-supplied quality control guidelines. All blood specimens were also tested for hepatitis B core antibody and, when positive, for surface antigen.

For the present study, we searched the UDC database for participants with at least one visit both before and after 2 years of age and a CDC-reported serologic test result for hepatitis B surface antibodies. A positive anti-HBs test in the absence of a positive core antibody test was presumed to be indicative of an effective vaccine response to hepatitis B vaccination.

We hypothesized that there would be no difference between the routes of administration in the proportion of patients who develop a protective level of anti-HBs immune response, and we anticipated that analysis of the main study outcome would result in a failure to reject this null hypothesis. There are two reasons that this outcome could occur: either there is truly no

difference in immunogenicity between the two routes of administration, or there is a lack of adequate power to detect a meaningful difference in rates of immunogenicity even if such a difference exists.

To calculate the sample size necessary to detect a clinically meaningful difference in immunity if it in fact was present, we determined by consensus of the authors that if one of the routes of administration resulted in 15% fewer subjects achieving an antibody response, this would represent a clinically meaningful difference in efficacy of the vaccination. The average rates of HBV seroprotection after three doses are 85–90% [11]. Based on previous studies of immunity after hepatitis B vaccination in haemophilia patients, we expected that at least 95% of subjects would seroconvert to a minimum of a protective anti-HBs titre of 12 mIU/mL after vaccination [7,12–16]. Therefore, we considered that a seroconversion rate of <80% would be a less than acceptable level. Thus, based on the normal distribution, we determined a sample size of nearly 100 subjects in each group would provide 80% power to detect a 15% difference in seroprotection rates, specifically 95% in one group and 80% in the other group.

Statistical analysis

All UDC participants with data collected both prior to and after age 2 years, and who had received exactly three doses of Hepatitis B vaccine, were categorized as receiving vaccination either entirely through the SQ or IM or a combination of routes. Only data collected from subjects receiving three vaccination doses recorded as solely by one route (either SQ or IM) were used in the analyses. We compared the distributions of demographic and clinical characteristics between subjects who had been vaccinated exclusively by the SQ or the IM route and between subjects with and without an immune response to immunization using chi-squared tests. The proportions of subjects who reported intramuscular haematomas at UDC visits prior to age 2 years were also compared using chi-squared tests.

Since none of the studied characteristics was known to be associated with either the exposure (vaccination route) or the outcome (immune status), there was no potential for confounding by these characteristics. Therefore, we assessed the strength of the association between route of administration and immune status using Student's *t*-test. We compared antibody levels, age at serologic testing and time intervals between vaccination and testing by vaccination route, using an analysis of variance. All analyses were performed using SAS statistical software (SAS Institute, Cary, NC, USA), and statistical testing with resultant *P*-values ≤0.05 were judged statistically significant.

Results

There were a total of 767 subjects who participated in UDC both before and after age 2 years during the period July 2003–September 2011. Of these, while some information on the route of vaccination was available on 436 (56.8%), complete information on all three doses of vaccine was available on 256 (33.4%). Two-hundred seven had all three doses by only one route. One subject who had a negative surface antibody test but a positive core antibody test was excluded leaving 206 subjects who formed the study population. Of these, 92/206 subjects (44.7%) received all doses by the SQ route and 114/206 subjects (55.3%) received

all doses by the IM route. For the SQ route, 69% had all doses by 7 months and 94% by 12 months. For the IM route, 59% of those subjects had all 3 doses by 7 months and 88.5% by 12 months.

Characteristics of the study population are shown in Table 1, including bivariate associations with route of administration and anti-HBs status. The racial and ethnic distribution of the study subjects was similar to that of all UDC participants and most study subjects were males, reflecting the predominantly male haemophilia population. Nearly 60% of subjects with haemophilia had severe disease and 71% of subjects had a history of a bleeding episode at the time of enrolment in UDC. No subjects were HIV infected or otherwise immunocompromised.

There was no statistically significant association between race/ethnicity, sex, type of bleeding disorder or bleeding history and the route of vaccination administration (Table 1). Subjects with mild haemophilia were less likely to receive vaccine by the SQ route. The proportions attaining a positive antibody level were uniformly high and no associations with patient characteristics reached statistical significance (Table 1).

Among those vaccinated SQ, 92.4% were anti-HBs positive, whereas 88.6% of those with IM vaccination were antibody positive ($P = 0.3$). The mean age at time of hepatitis B titre was 56.9 ± 20.3 months and ranged from 8 to 97 months. There was no difference in the distribution of titre values between the two groups. The average age of testing was 53 ± 20 months in the SQ group vs. 60 ± 20 months in the IM group ($P = 0.02$). The average time between the last dose of vaccine and testing for hepatitis B antibodies was 47.6 ± 18.5 months among subjects vaccinated SQ vs. 51.6 ± 20.5 months among those receiving IM vaccination ($P = 0.2$).

Among the 92 subjects who had received SQ vaccination, 10 (10.9%) children had a total of 12 intramuscular haematomas recorded in their clinical records. Among the 114 subjects receiving IM vaccination, 23 (20.2%) children had a total of 38 intramuscular haematomas. The difference between the proportions of children experiencing intramuscular haematomas by vaccination route did not reach statistical significance ($P = 0.07$). Given the nature of the data, there was no way to determine if haematoma formation was related to vaccine administration.

Discussion

There is discrepancy among recommendations published by international bleeding disorder expert panels regarding the route of vaccination in patients with bleeding disorders [1–3,17,18]. The Association of Hemophilia Clinic Directors of Canada, the United Kingdom Haemophilia Centre Doctors' Organisation and WFH recommend that SQ HBV vaccination is preferred for patients with bleeding disorders [3,8,17–19]. In contrast, ACIP and MASAC recommendations specifically recommend IM injection of hepatitis B vaccination [1,2]. Despite these inconsistencies, of the 767 children who participated in the surveillance, 222 (29%) had received at least one dose of HBV vaccine SQ and these subjects were distributed throughout 52 (58.4%) of the 89 enrolling HTCs. Therefore, more than one-half of the

federally supported U.S. HTCs providing care to children with bleeding disorders appear to be recommending SQ administration of HBV vaccine. We speculate that the reasons for this recommendation are to avoid IM haematoma formation at the site of injection and to minimize need for factor in patients not on prophylactic therapy [6].

Ragni, *et al*. evaluated seroconversion to hepatitis A vaccine in those receiving the vaccination SQ. They found SQ injection to be as effective as IM in inducing immunity in their population [20]. Zanetti, *et al*. found that hepatitis B vaccination resulted in the development of antibodies to hepatitis B surface antigen in 98% of haemophilia patients immunized SQ [7]. Conversely, Fessard, *et al*. found that antibody response was higher when vaccination was given IM [5]. It is possible that early investigation of immunogenicity of hepatitis B vaccination by varying routes was influenced by concomitant HIV infection and the continued potential for hepatitis infection from factor products [7,11,13,21]. Our results show no significant difference in immunogenicity between SQ and IM routes for the HBV vaccine. However, the overall seroconversion for this population was lower than expected a priori, which was estimated at approximately 95% [7,12–16]. We hypothesize that this may be due to a delay in HBV titre ascertainment, which averaged closer to 50 months after the last dose of immunization in both groups rather than the recommended 1 month.

The proportion of subjects with local haematoma formation appeared higher in those receiving vaccination by the IM route in our study, but this difference did not reach statistical significance. It should be noted that no information was available regarding the cause of the intramuscular haematoma. It is likely that some of the haematomas that occurred were unrelated to vaccination or could be subject to recall bias, as data collection in the UDC database relies on parent history. A previous study of IM HBV vaccination of 51 children with haemophilia resulted in a haematoma rate of 4%, none of which were treated with factor infusion [22]. No serious complications from SQ administration were reported in any previous studies that examined side effects of this method [12–14,16,20,23]. Several studies reported local inflammation at the site of injection in a minority of subjects [5,12,13,16,20]. Because our study used surveillance data rather than that from a research study designed to address this particular issue, we did not have data regarding specific complications arising from vaccination.

There are a number of other limitations to this study. First, the retrospective nature of the data collected in UDC likely introduced recall bias into some of the exposures and outcomes. This may be especially pertinent regarding vaccination, which often takes place at the child's primary care provider rather than the HTC. A second limitation is that to ensure that we could attribute the immune response to either the SQ or IM vaccination route; we excluded subjects who received the vaccine through multiple routes, thus limiting our sample size. Nonetheless, there was adequate sample size to detect a clinically significant difference had it been present. We were also unable to identify the type of hepatitis vaccine administered. In addition, dates of occurrence were not collected for all events which precluded a better assessment of the relationship between certain exposures and outcomes, such as the risk of haematomas or inhibitors in association with vaccination. Specifically, UDC data do not include date of inhibitor detection; therefore, we were unable to establish

when inhibitors developed relative to vaccination. Finally, we did not have data on the frequency of factor product administration prior to IM vaccination solely to avoid a haematoma. To the extent that this practice occurs, the SQ route provides an effective alternative strategy that may decrease the costs and rates of complications associated with vaccination. However, caution should be used when extending these data to other vaccinations, as comparison of the rate of immunogenicity between the SQ and IM routes has only been performed on a selected few immunizations.

Conclusion

Hepatitis B vaccination given SQ appears to be equally efficacious as IM injection in inducing protective immunity in individuals with bleeding disorders. Long-term immunity and complications of immunization administration in the bleeding disorder population will require prospective evaluation.

Acknowledgements

The authors would like to acknowledge the support of the Centers for Disease Control and Prevention for their help in designing and completing this research and for the use of the UDC data. The analysis and writing represented in this publication was supported by the Grant/Cooperative Agreement Prevention of Bleeding Disorder Complications through Regional Hemophilia Treatment Centers. We would also like to thank the patients, staffs and physicians of the Hemophilia Treatment Centers who contribute to the UDC database, whose efforts were critical to the completion of this work.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

References

1. The Medical and Scientific Advisory Committee of the National Hemophilia Foundation. MASAC recommendation #128. 2001 Available at http://www.hemophilia.org.
2. Kroger AT, Sumaya CV, Pickering LK, Atkinson WL. General recommendations on immunization: Recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR. 2001; 60(RR02):1–60.
3. Steele M, Cochrane A, Wakefield C, et al. Hepatitis A and B immunization for individuals with inherited bleeding disorders. Haemophilia. 2009; 15:437–447. [PubMed: 19335752]
4. American Academy of Pediatrics. Section 1: active and passive immunizations. In: Pickering, LK.; Baker, CJ.; Kimberlin, DW.; Long, SS., editors. Red Book: 2009 Report of the Committee on Infectious Diseases. 28th ed.. Elk Grove Village, IL: American Academy of Pediatrics; 2009. p. 9-20.
5. Fessard C, Riche O, Cohen JHM. Intramuscular versus subcutaneous injection for hepatitis B vaccine. Vaccine. 1988; 6:469. [PubMed: 2977459]
6. Orto C, Harrison T. Route of administration for immunizations in haemophiliacs. Haemophilia. 1995; 1:215.
7. Zanetti AR, Mannucci PM, Tanzi E, et al. Hepatitis B vaccination of 113 hemophiliacs: lower antibody response in anti-LAV/HTLV-III- positive patients. Am J Hematol. 1986; 23:339–345. [PubMed: 3098092]
8. Shrivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia. 2013; 19:e1–e47. [PubMed: 22776238]

9. Soucie JM, McAlister S, McClellan A, Oakley M, Su Y. The universal data collection surveillance system for rare bleeding disorders. Am J Prev Med. 2010; 38(4 Suppl):S475–S481. [PubMed: 20331946]
10. Ismail N, Fish GE, Smith MB. Laboratory evaluation of a fully automated chemiluminescence immunoassay for rapid detection of HBsAg, antibodies to HBsAg, and antibodies to hepatitis C virus. J Clin Microbiol. 2004; 42:61–617.
11. Coates T, Wilson R, Patrick G, Andre F, Watson V. Hepatitis B vaccines: assessment of the seroprotective efficacy of two recombinant DNA vaccines. Clin Ther. 2001; 23:392–403. [PubMed: 11318074]
12. Janco RL. Immunogenicity of subcutaneous hepatitis B vaccine in hemophiliacs. J Pediatr. 1985; 107:316. [PubMed: 3160838]
13. Hedner U, Hansson BG, Vermylen J, Verstraete M, Colaert J, Desmyter J. Immunizations of haemophiliacs against hepatitis B. Scand J Haematol Suppl. 1984; 40:317–321. [PubMed: 6236549]
14. Santagostino E, Mannucci PM, Gringeri A, et al. Accelerated schedule of hepatitis B vaccination in patients with hemophilia. J Med Virol. 1993; 41:95–98. [PubMed: 8283182]
15. Miller EJ, Lee CA, Karayiannis P, Holmes S, Thomas HC, Kernoff PBA. Immune response of patients with congenital coagulation disorders to hepatitis B vaccine: suboptimal response and human immunodeficiency virus infection. J Medical Virol. 1989; 28:96–100.
16. Gazengel C, Courouce AM, Torchet MF, et al. Use of HBV vaccine in hemophiliacs. Scand J Haematol Suppl. 1984; 40:323–328. [PubMed: 6236550]
17. World Federation of Haemophilia. Guidelines for the management of haemophilia. 2005 Available at http://www.wfh.org.
18. Association of Hemophilia Clinic Directors of Canada. Hemophilia and von Willebrand's disease: 1. Diagnosis, comprehensive care and assessment. 1999 (Edition 2, Update 2: 1999-07-07) Available at http://www.ahcdc.ca/publications-and-guidelines/34.
19. Makris M, Conlon CP, Watson HG. Immunization of patients with bleeding disorders. Haemophilia. 2003; 9:541–546. [PubMed: 14511291]
20. Ragni MV, Lusher JM, Koerper MA, Manco-Johnson M, Krause DS. Safety and immunogenicity of subcutaneous hepatitis A vaccine in children with haemophilia. Haemophilia. 2000; 6:98–103. [PubMed: 10781196]
21. Oon LLE, King A, Higgins JA, Lee CA, Kernoff PBA, Goodall AH. Protective antibodies to hepatitis B virus in haemophiliacs. J Med Virol. 1991; 33:19–25. [PubMed: 1826737]
22. Evans DIK, Shaw A. Safety of intramuscular injection of hepatitis B vaccine in haemophiliacs. Br Med J. 1990; 300:1694–1695. [PubMed: 2143948]
23. Zuckerman JN, Moore S, Smith J, Tyrrell H, Bazter A, Lee CA. A study to assess the immunogenicity, reactogenicity and safety of hepatitis A vaccine administered subcutaneously to patients with congenital coagulation disorders. Haemophilia. 1996; 2:235–239.

Table 1

Associations between demographic and clinical characteristics of 206 children with bleeding disorders and vaccination route and hepatitis B antibody positivity.

	Total		Subcutaneous Route			Antibody positive		
Characteristic	***n***	**%**	***n***	**%**	***P*-value**	***n***	**%**	***P*-value**
Race/Ethnicity								
White	136	66.0	55	40.4	0.3	124	91.2	0.1
Black	19	9.2	7	36.8		18	94.7	
Hispanic	29	14.1	18	62.1		24	82.8	
Other	22	10.7	12	54.5		20	90.9	
Sex								
Male	202	98.1	92	100.0	0.1	183	90.6	0.3
Female	4	1.9	0	0.0		3	75.0	
Bleeding disorder								
Haemophilia A	151	73.3	73	48.3	0.1	136	90.1	1.0
Haemophilia B	40	19.4	17	42.5		36	90.0	
VWD	13	6.3	2	15.4		12	92.3	
Other	2	1.0	0	0.0		2	100	
Haemophilia Severity*								
Mild	30	15.6	7	23.3	0.003	25	83.3	0.2
Moderate	47	25.0	24	50.0		43	89.6	
Severe	114	59.4	59	51.8		105	92.1	
History of a bleed								
Yes	146	70.9	65	44.5	0.9	132	90.4	1.0
No	60	29.1	27	45.0		54	90.0	

*Total proportions are based on the number of subjects with haemophilia.

Haemophilia. Author manuscript; available in PMC 2016 January 01.