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LETTER TO THE EDITOR

Intramuscular vaccination of haemophiliacs: Is it really a risk for bleeding?

Dear Editor,

In patients with haemophilia, it is consensual that all routine vaccinations should be given at the appropriate time following national guidelines.[1,2] However, whether these should be administered using the intramuscular or subcutaneous route is still under debate as there is a challenging risk-benefit balance in this specific population. In France, the consensus is to perform all vaccinations by the subcutaneous route for all haemophiliacs. The risk associated with intramuscular injection is the development of intramuscular bleeding leading to factor exposure and potential inhibitor risk,[1,2] whereas subcutaneous injection increases the risk of local side effects (oedema, erythema, itching and granuloma formation) in particular for adjuvant-containing vaccines.[3-5] In addition, there is ongoing debate regarding vaccine immunogenicity and tolerability with this alternate route of administration; for example, immunogenicity appears to be decreased in case of subcutaneous injection as reflected by significantly lower seroconversion rates and more rapid decay of antibody response.[3-5] This may be in relation to the poor vascularity of this localization that may result in slow mobilization and processing of antigen presentation.[3-6]

Recent data may modify this risk-benefit balance. Last year, the European Pediatric Network for Haemophilia Management (PedNet) group found no association between vaccinations given shortly before or after FVIII exposure (48 hours before and 24 hours after) and inhibitor development in previously untreated patients (before 75 EDs); in this study, it is of note that among 375 children with severe haemophilia, the route of administration was intramuscular for 18.9% of patients, subcutaneously for 74.0%, and unknown for 6.9%.[7] The occurrence of inhibitor remains the primary concern of physicians when haemophilia is diagnosed, in particular, if severe or moderate. The choice of the subcutaneous route may thus limit haemorrhagic complications and early use of antihaemophilic treatment. However, we know that some countries (such as France) are currently facing vaccine hesitancy or vaccine refusal leading to a resurgence of pertussis and measles,[8] but also to insufficient herd immunity to protect haemophilic patients with potentially lower seroconversion rates after subcutaneous vaccination.

We, therefore, decided to evaluate the development of intramuscular haematoma requiring factor infusion in case of intramuscular vaccination in severe and moderate (<2%) haemophilic patients. The population of the present study was composed of patients included in the national haemophiliac cohort (FranceCoag) by the haemophilia care centres of Bordeaux, Lille, Lyon and Marseille; FranceCoag is a national prospective cohort of patients with inherited coagulation factor deficiencies.[9] We included all haemophilic patients, with factor VIII or IX <2%, born between January 2000 and January 2019. The exclusion criteria were a diagnosis of haemophilia made before 2 months of age (age of first vaccine administration in France) and/or the absence of intramuscular vaccination at the time of diagnosis. We thereby obtained a homogenous population of severe or moderate haemophiliacs who had received at least one intramuscular vaccination (according to the French recommendations) before the diagnosis of haemophilia. No specific precautions (such as prolonged compression) were used for these children. Data were collected by practitioners in each centre in January 2019. Collected data were age at diagnosis, type of haemophilia, FVIII or FIX level, number of intramuscular vaccinations, type of vaccine, date of injections, presence of haematoma after injection, need for medical consultation and need for haemostatic treatment following injection. Data from patients were retrospectively collected. In this context, and according to our institutional guidelines, we obtained an authorization for data collection from the national data protection commission (*Commission Nationale Informatique et Libertés*, CNIL – number CNIL DEC19-031).

Among the 242 identified patients, we excluded 120 because they were diagnosed before 2 months of age, and 9 because they did not receive any vaccine. Among the 113 patients included, median age at diagnosis was 9 months (range: 2-74 months). Fifteen had haemophilia B (13%) and 98 had haemophilia A (87%). Sixteen had moderate haemophilia (14%) and 97 had severe haemophilia (86%). Patients received a total of 549 intramuscular vaccinations; corresponding to median of five injections per patient (range: 1-15). Among the 549 intramuscular vaccinations, we observed the absence of reported haematoma in 538 cases (98%), while haematoma was reported in 11 times in 11 different patients (2%). Among the 11 patients developing haematoma, 10 had haemophilia A and one had haemophilia B; of the 11, nine had severe haemophilia and two had moderate haemophilia. Seven haematomas required no action, three haematomas were followed by a medical consultation, and one required antihaemophilic treatment leading to diagnosis of haemophilia.

In the present study population, children had undiagnosed haemophilia (factor <2%) and received intramuscular vaccinations as recommended by the French health authorities, and without any precaution regarding haemostasis. Despite this, <1% of intramuscular injection cases (among 549 injections) led to medical consultation

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(0.5%) or concentrate factor treatment for haematomas (0.2%). Furthermore, the data published by the PedNet group (alluded to earlier) showed that antihaemophilic treatment can be used in close proximity to vaccine injection without increasing inhibitor occurrence. However, it needs to be pointed out that most vaccinations given to the PedNet cohort were given intramuscularly. Hence, we should not assume that the lack of an association between inhibitor development and vaccinations (mainly given subcutaneously) will apply to vaccinations given intramuscularly. One of limitation of this retrospective study is that as haemophilia was undiagnosed, some small haematomas may have gone unreported as parents might not have thought it was important to contact their child's physician. We could not study the tolerance and immunization rate in this cohort for patients who received subcutaneous vaccination, but, as mentioned above, the subcutaneous route is less well tolerated (rash, oedema, itching…) and the immunogenicity of this route is questioned (worse processing of antigen presentation). On the basis of these data, the intramuscular route for vaccine administration in haemophiliac patients seems possible. In order to minimize the haemorrhagic risk, perhaps this choice could be accompanied by practical recommendations such as administration early in the day (allowing all day parental observation), using the smallest gauge needle possible, in an easily compressible area (such as the arm or thigh) in collaboration with general practitioner or paediatrician, with prolonged compression (at least 10 minutes) without rubbing, and monitoring by parental observation. However, this recommendation is obviously not applicable for other types of intramuscular injections. Indeed, the volume of vaccine injections are extremely small (0.5 mL) that allows the use of smallest needles (23-25 G), whereas, for example, the volume of 1 g of ceftriaxone (an antibiotic often used in the paediatric population) is 3.5 mL and that 1 mg of vitamin K1 (used for prevention of haemorrhagic disease in neonates) is 1 mL.

In conclusion, the results presented herein suggest that vaccines could be administered safely by intramuscular injection in haemophiliac patients. Nevertheless, further studies are still needed to examine inhibitor development in case of intramuscular vaccination, which has never been specifically studied, including in the PedNet experience.

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

AUTHOR CONTRIBUTIONS

AH and SM wrote the paper. All the authors designed the research study, performed the research and analysed the data.

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