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Risk factors associated with invasive orthopaedic interventions in males with haemophilia enrolled in the Universal Data Collection program from 2000 to 2010

P. Tobase[1], **H. Lane**[2], **A.-E.-A Siddiqi**[3], **J. M. Soucie**[3], **R. Ingram-Rich**[4], **S. Ward**[5], **J. C. Gill**[6], and **the Hemophilia Treatment Center Network (HTCN) Study Investigators**

[1]Hemophilia Treatment Center, University of California, San Francisco, CA, USA

[2]Intermountain Hemophilia and Thrombosis Center Primary Children's Medical Center, Salt Lake City, UT, USA

[3]Division of Blood Disorders, Centers for Disease Control and Prevention (CDC), Atlanta, GA, USA

[4]LEND@OHSU, Portland, OR, USA

[5]Department of Physical Therapy, University of Utah College of Health, Salt Lake City, UT, USA

[6]Medical College of Wisconsin and Comprehensive Center for Bleeding Disorders, Blood Center of Wisconsin, Milwaukee, WI, USA

Abstract

Background: Invasive orthopaedic interventions (IOI) are often used to control recurrent haemarthrosis, pain and loss of joint function, in males with haemophilia (Factor VIII and Factor IX deficiency).

Aim: Identify risk factors associated with IOIs in males with haemophilia enrolled in the Universal Data Collection (UDC) surveillance program from 2000 until 2010.

Methods: Data were collected on IOIs performed on patients receiving care in 130 haemophilia treatment centers in the United States annually by health care providers using standardized forms. IOIs included in this study are as follows: 1) synovectomy and 2) arthrodesis or arthroplasty (A/A). Information about potential risk factors was obtained from the preceding UDC visit if available, or from the same visit if not. Patients with no reported IOI at any of their UDC visits were the reference group for the analysis. Multivariate analyses were conducted to identify independent risk factors for synovectomies and arthrodesis/arthroplasty.

Correspondence Patricia Tobase, Hemophilia Treatment Center, University of California, San Francisco, CA, USA., patricia.tobase@ucsf.edu.

AUTHOR CONTRIBUTIONS

PT and JMS wrote the paper. PT, HL, AS, JMS designed the research study. RIR, JCG and RSW contributed to authorship of the paper and assisted in designing the research study. JMS performed the statistical analysis.

DISCLOSURES

All other authors have no conflicts of interest that might be perceived as posing a conflict or bias.

Results: Risk factors significantly associated with the two IOI categories were age, student status, haemophilia severity, number of joint bleeds within the last 6 months, HIV or hepatitis C (HCV) status. Multivariate analyses showed patients on continuous prophylaxis were 50% less likely to have had a synovectomy and were 40% less likely to have an A/A.

Conclusions: This study shows modifiable risk factors, including management of bleeding episodes with a continuous prophylactic treatment schedule are associated with a decreased likelihood of IOIs in males with haemophilia.

Keywords

arthropathy; haemophilia; orthopaedic; risk factors

1 | INTRODUCTION

Haemophilia is an X-linked recessive bleeding disorder that has a clinical manifestation of haemarthrosis that may lead to early onset of arthropathy. Invasive orthopaedic interventions (IOI) such as synovectomy, arthroplasty or arthrodesis are often needed to control bleeding, pain and loss of joint function.[1]

A review of the literature regarding risk factors associated with bleeding disorders for IOIs in the United States is limited to reporting by individual medical centers or surgeons.[1–9] The Universal Data Collection (UDC) program,[10] in collaboration with federally supported haemophilia treatment centers (HTCs) across the United States of America, included data from people with bleeding disorders who have undergone an invasive orthopaedic intervention. This project builds on previous work within the UDC which looked at outcomes in IOI in the ankle[11] and the rates of invasive orthopaedic interventions.[12]

The purpose of our study was to identify risk factors associated with IOIs performed in males with haemophilia enrolled in the UDC surveillance program from 2000 until 2010. The hypotheses that the authors held for the project were as follows: (i). males with haemophilia with a higher body mass index (BMI) enrolled in the UDC had a greater likelihood of undergoing an IOI and (ii) males with haemophilia on continuous prophylaxis were less likely to undergo an IOI.

2 | MATERIALS AND METHODS

The data for the study were collected as part of the Universal Data Collection (UDC) program, a public health surveillance system established in a network of comprehensive care clinics for bleeding disorders throughout the United States.[10] Briefly, people with congenital bleeding disorders were invited to enroll in the UDC program during their annual comprehensive clinic visit. Treatment center staff using standard data collection tools collected demographic and clinical data. Patients or parents of minor children gave informed consent and the program had oversight from the Investigational Review Boards of all participating treatment centers and CDC.

The following study variables from the UDC program analysed in this study: age at time of IOI, race/ethnicity, type of insurance coverage, BMI, educational level at time of IOI,

employment status at time of IOI, type and severity of haemophilia, subject's birthplace, type of IOI, number of IOI per subject, factor replacement schedule, number of joint bleeds, reported physical activity level, Hepatitis B and Hepatitis C status, HIV status, and inhibitor status.

Demographic and clinical data collected on males with haemophilia who were 2 years and older and had a UDC visit during the period January 1, 2000 through December 31, 2010 were used for the study. Self-reported information was used to categorize race/ethnicity as white, black, Hispanic (either white or black race) or other. Collected data on place of birth was categorized as USA or other. Four levels of education were used to describe highest educational achievement and those who were currently in school were considered students. Subjects who were employed either part-or full-time were considered employed for the analyses. Health insurance included five categories: commercial, Medicaid, Medicare, other government and uninsured. Those with more than one insurance type were assigned to the primary insurer according to a pre-determined algorithm.[13]

Measured height and weight during the clinic visit were used to calculate body mass index, which was then categorized as underweight/normal, overweight or obese according to standard growth tables for those under 20 years of age, and established reference ranges for subjects ≥20 years. Haemophilia severity was categorized as severe for those with a factor activity level <1, moderate for activity levels 1%-5% and mild for levels >5%-49%.[14] The UDC program defines continuous prophylaxis therapy as a patient receiving treatment product on a regular schedule to prevent any and all bleeding with the expectation to continue indefinitely. Continuous prophylaxis status for this study was defined as positive when an individual was recorded in the UDC program as being on continuous prophylaxis for both the year prior to and the year of the orthopaedic intervention. On demand or intermittent prophylaxis were coded as negative for prophylaxis in our study. Data on number of joint bleeds occurring in any joint in the last 6 months of their UDC visit prior to the IOI were collected from bleeding diaries if available or from patient or parent report otherwise and were categorized as none, 1, 2 to 3, or ≥4 for the analyses. Subjects rated their overall physical activity level based on a 5-level scale from unrestricted school/work and recreational activities to requiring assistance for school/work, self-care and inability to participate in recreation due to pain, loss of motion or weakness. Those who indicated that they were either totally unrestricted or limited only with regard to recreational activity were rated as having a high physical activity level and all others were rated as low physical activity level.

All UDC participants submitted a blood specimen for centralized testing. The results of testing for serologic evidence of current infection with HBV (+HBsAg) and HCV (+anti-HCV) and human -immunodeficiency virus (+HIV1) were used to assess each participant's status with regard to these infections. HTC staff provided the results of any local testing for an inhibitor since the last UDC visit. Only subjects with a reported inhibitor titre of >1 BU or whose current treatment regimen was listed as immune tolerance were considered to have a current inhibitor.

At each UDC visit, HTC staff provided the type and location of any IOIs undergone by the participant since the previous visit. For patients who had an IOI at any time during the study period, data on the procedure were obtained from the first UDC visit at which a procedure was reported and data on risk factors were obtained from the preceding UDC visit if there was one or from the same visit if it was the patient's first UDC visit. Patients enrolled in the UDC who did not report an IOI during any of their UDC visits were used as the reference group for the analyses. Data on risk factors for the reference group were obtained from the last UDC visit that occurred during the study period.

IOIs included in this study were synovectomy (including arthroscopic,- radioisotopic or open synovectomy procedures), -arthrodesis and arthroplasty. We divided the IOIs into two categories: (i) synovectomy and (ii) arthrodesis/arthroplasty (A/A). The "other" IOI category represented a nonspecific group of orthopaedic interventions was excluded in this analyses.

2.1 | Analysis

Bivariate associations between each of the studied risk factors and IOIs were examined separately for each category of procedure and assessed for statistical significance using chi-square statistics. For the multivariate analyses, all risk factor variables were included in a logistic regression initial model and a backwards stepwise elimination strategy was used to remove variables with P values >.05 from the model one at a time. However, the three main effect variables (haemophilia type, severity and BMI) along with age were included in all models regardless of their statistical significance so that the independent effect of these factors on the studied outcomes could be assessed. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC) and factors with P values ≤.05 were considered statistically significant.

3 | RESULTS

A total of 14,861 males with haemophilia were eligible for the study. Almost one-half (49.3%) of the subjects were <20 years old, two-thirds (68.0%) were white, about one-half (48.5%) were currently in school and one-third (31.3%) were employed (Table 1). Approximately, half (53.3%) had commercial insurance and only 5% were uninsured. Risk factor data were taken from the same visit for 37% of subjects who reported their IOI on their first UDC visit.

Three-quarters (77.6%) of the subjects had haemophilia A, nearly half (48.6%) had severe disease and one-fourth (25.9%) were pre-scribed continuous prophylaxis (Table 1). Almost half (48.3%) of all participants were either overweight or obese and one-quarter (26.5%) reported having had at least one joint bleed in the 6-month period preceding the UDC visit. Nonetheless, 85% of the subjects reported a high level of physical activity. The prevalence of infectious disease ranged from 2% with active HBV to 35.9% with HCV. Ten per cent of subjects were infected with HIV and 743 (5%) had a current inhibitor.

During the study period, 366 (2.5%) subjects had a synovectomy, and 332 (2.2%) had an arthrodesis or arthroplasty. The bivariate associations between the risk factors and the two categories of procedures are also presented in Table 1. Synovectomies were performed in a

higher proportion of patients with haemophilia A, severe disease and young age but in a lower proportion of those who were over weight or obese. Other characteristics associated with higher proportions of synovectomies included white or black race, student status, increased frequency of joint bleeds, low reported physical activity level, positive inhibitor status and infection with HIV or HBV or HCV.

In contrast to synovectomies, arthrodesis/arthroplasty was more frequently performed among older subjects and those who were overweight (Table 1). As with all IOIs, higher proportions of subjects with severe haemophilia had these procedures but there was no difference in the frequency between haemophilia A or B. All of the other studied risk factors were associated with these procedures except for place of birth and inhibitor status.

The results of the multivariate analyses are presented in Tables 2 and 3. After adjustment for the other risk factors, patients with haemophilia B were less likely to have a synovectomy (Table 2). Patients with moderate or severe disease were much more likely to have had a synovectomy than those with mild disease as were those <20 years old, those who were students or employed, those who were HBV or HCV infected. Patients with two or more joint bleeds in any joint were much more likely to have had synovectomy than those with less joint bleeding. On the other hand, those on continuous prophylaxis were 50% less likely to have had a synovectomy (Table 2).

Older patients, those with moderate or severe haemophilia A or B and those who were overweight were significantly more likely to have arthrodesis/athroplasty after adjusting for the other studied risk factors (Table 3). The likelihood of having these procedures also increased for those patients with a college degree, ≥2 joint bleeds, a low physical activity level or HCV infected. Subjects who were students or who used continuous prophylaxis were similarly 40% less likely have one of these procedures.

4 | DISCUSSION

Our study is the largest cohort to date reporting on the IOIs in males with haemophilia. Our analysis of this cohort of 14, 861 males with haemophilia found that reporting two or more joint bleeds in any joint within the last 6 months and a positive HCV status were associated with greater likelihood of having an IOI. Managing the number of joint bleeding episodes using a continuous prophylactic treatment schedule is associated with less IOIs.

Our data show that having two or more joint bleeds in any joint in the past 6 months has been associated with increased likelihood of synovectomy, arthrodesis and arthroplasty. Prophylactic treatment in males with haemophilia has been shown to decrease joint bleeding episodes.[15–17] Our findings support the idea that prophylactic treatment to prevent joint bleeding episodes will lead to a lower likelihood of IOI, as we found that males with haemophilia on continuous prophylaxis were 40% less likely to have undergone a joint arthroplasty or arthrodesis. Furthermore, males with haemophilia who were on continuous prophylactic treatment were 50% less like to undergo a synovectomy for their joint bleeding and pain.

Synovectomy is an invasive orthopaedic intervention typically performed to decrease the frequency of haemarthrosis and to help with management of pain or range of motion.[18–20] Our data support the belief based on the authors' clinical observations prior to this study, that synovectomies are typically performed at an earlier age, less than 20 years, to aggressively manage haemarthrosis and synovitis.

Arthrodesis and arthroplasty are invasive orthopaedic procedures typically reserved to manage end-stage joint disease symptoms such as pain and limitation of function.[1,2,6] Thus, it would be expected to have an older (>20 years) population undergo these types of procedures. Because severe arthropathy can cause pain and limitation in participation in physical activities, the association with a low physical activity level is expected. A previous study using UDC data demonstrated that overweight and obesity are associated with an increased rate of joint mobility loss.[21] While there was no association of overweight/obesity with synovectomy, the present study adds support to the evidence that maintenance of a healthy body weight can lower the risk of joint damage requiring arthrodesis or arthroplasty.

In this study, HCV was associated with all invasive procedures (arthrodesis/arthroplasty and synovectomy) and HBV was associated with synovectomies. Low bone mineral density has been reported in individuals with chronic HCV without cirrhosis.[22] A meta-analysis examining bone mineral density in haemophilia patients found that low bone mineral density was worse in HCV-positive patients[23] and recent research has shown a relationship between low bone mineral density and fracture risk in people with HIV, HBV and HCV infection.[24] It is not clear that contributing factors such as physical activity level, vitamin D levels and drug treatment have effects on bone health.[24,25] The relationship between chronic inflammation such as HCV and HBV, and bone health are not well understood at this time. Low bone mineral density and chronic inflammation may have a role in the joint health in people with bleeding disorders. Infections such as HBV and HCV may be markers of worse joint disease. Additionally, patients who re-ceived factor replacement prior to the 1990s may have been exposed to contaminated plasma-derived clotting factors containing both viral infections; and in this same cohort, in their childhood, "on-demand" factor replacement was standard of care, vs prophylaxis. Prophylaxis has since been shown to reduce risk of early joint.[26]

4.1 | Limitations

Data were collected from individuals who were enrolled in the UDC program only; therefore, it is not representative of all individuals with haemophilia in the United States. Our study consists of retrospective reporting, which has inherent limitations of inaccurate reporting (eg joint fusion may be categorized under "other" vs "arthrodesis"). Additionally, our study reports on an 11-year time period in which data about previous factor replacement history, or exposure to contaminated plasma-derived clotting factors were not collected.

5 | CONCLUSION

Our study shows that modifiable risk factors, including management of joint bleeding episodes with a continuous prophylactic treatment schedule is associated with a decreased likelihood of invasive orthopaedic interventions in males with haemophilia.

Recommendations for future areas of study include the impact of chronic inflammation on rates of IOI in people with haemophilia.

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TABLE 1

Demographic and clinical characteristics of 14 861 males with haemophilia and relations with invasive orthopaedic procedures (IOIs)

	Total		Synovectomy			Arthrodesis/Arthroplasty		
Characteristic	**N**	**%**	**N**	**%**	***p*-value**	**N**	**%**	***p*-value**
Age (years)								
2–19	7321	49.3	215	2.9	<.001	16	0.2	<.001
20–39	4684	31.5	120	2.6		151	3.2	
40–59	2168	14.6	27	1.2		138	6.4	
60+	688	4.6	4	0.6		27	3.9	
Haemophilia Type								
A	11 538	77.6	317	2.8	<.001	265	2.3	.3
B	3323	22.4	49	1.5		67	2.0	
Haemophilia Severity								
Mild	4036	27.2	9	0.2	<.001	23	0.6	<.001
Moderate	3590	24.2	62	1.7		66	1.8	
Severe	7217	48.6	295	4.1		243	3.4	
BMI								
Low/Normal	7280	49.0	206	2.8	.01	134	1.8	<.001
Overweight	3856	26.0	79	2.0		127	3.3	
Obese	3310	22.3	67	2.0		61	1.8	
Race/Ethnicity								
White	10 102	68.0	251	2.5	<.001	250	2.5	<.001
Black	1761	11.8	60	3.4		45	2.6	
Hispanic	1972	13.3	33	1.7		25	1.3	
Other	1026	6.9	22	2.1		12	1.2	
Place of Birth								
USA	13 771	92.7	335	2.4	.4	303	2.2	.3
Other	1090	7.3	31	2.8		29	2.7	
Education Level								
Pre- or primary	11 204	75.4	278	2.5	.6	150	1.3	<.001
Technical	626	4.2	21	3.4		28	4.5	
College degree	2353	15.8	52	2.2		129	5.5	
Other	677	4.6	15	2.2		25	3.7	
Student								
No	7653	51.5	137	1.8	<.001	301	3.9	<.001
Yes	7208	48.5	229	3.2		31	0.4	
Employed								
No	10 205	68.7	254	2.5	.8	161	1.6	<.001
Yes	4656	31.3	112	2.4		171	3.7	
Insurance								
Commercial	7918	53.3	200	2.5	.2	161	2.0	<.001

	Total		Synovectomy			Arthrodesis/Arthroplasty		
Characteristic	**N**	**%**	**N**	**%**	***p*-value**	**N**	**%**	***p*-value**
Medicaid	3656	24.6	104	2.8		48	1.3	
Medicare	1353	9.1	28	2.1		85	6.3	
Other government	988	6.6	17	1.7		28	2.8	
Uninsured	816	5.5	15	1.8		9	1.1	
Treatment Type								
Continuous prophylaxis	3846	25.9	89	2.3	.5	36	0.9	<.001
Other	11 015	74.1	277	2.5		296	2.7	
Joint Bleeds in last 6 mo								
None	10 915	73.4	111	1.0	<.001	116	1.1	<.001
One	1046	7.0	18	1.7		13	1.2	
2–3	951	6.4	44	4.6		33	3.5	
4+	1945	13.1	193	9.9		170	8.7	
Physical activity level								
High	12 675	85.3	291	2.3	.01	168	1.3	<.001
Low	2182	14.7	75	3.4		164	7.5	
HIV positive								
No	13 350	89.8	314	2.4	.01	204	1.5	<.001
Yes	1511	10.2	52	3.4		128	8.5	
HBV positive								
No	14 570	98.0	348	2.4	<.001	315	2.2	<.001
Yes	291	2.0	18	6.2		17	5.8	
HCV positive								
No	9522	64.1	185	1.9	<.001	29	0.3	<.001
Yes	5339	35.9	181	3.4		303	5.7	
Inhibitor								
No	14 118	95.0	330	2.3	<.001	314	2.2	.7
Yes	743	5.0	36	4.8		18	2.4	

All totals do not sum to 100% due to missing data.

p-value from chi-square goodness-of-fit test.

TABLE 2

Multivariate associations between demographic and clinical characteristics and synovectomies in 14 861 males with haemophilia

Characteristic	OR	95% CI	*P* value*
Age (years)			
2–19	ref		
20–39	0.3	0.2–0.5	<.001
40–59	0.2	0.1–0.3	<.001
60+	0.1	0.02–0.5	<.01
Haemophilia Type			
A	ref		
B	0.7	0.5–0.9	.05
Haemophilia Severity			
Mild	ref		
Moderate	5.6	2.7–11.9	<.001
Severe	11.5	5.6–23.7	<.001
Body Mass Index (BMI)			
Low/Normal	ref		
Overweight	0.9	0.7–1.3	.9
Obese	0.8	0.6–1.1	.2
Employed			
No	ref		
Yes	1.4	1.0–1.9	.02
Student			
No	ref		
Yes	1.9	1.4–2.6	<.001
Treatment Type			
Other	ref		
Continuous prophylaxis	0.5	0.4–0.7	<.001
Joint bleeds in last 6 mo			
None	ref		
One	1.3	0.8–2.2	.3
2–3	2.8	1.9–4.1	<.001
4+	6.1	4.7–8.0	<.001
HBV positive			
No	ref		
Yes	1.8	1.0–3.2	.04
HCV positive			
No	ref		
Yes	2.1	1.5–2.9	<.001

* *p*-value from overall Wald Chi-square test, ref = reference group

TABLE 3

Multivariate associations between demographic and clinical characteristics and arthrodesis/arthroplasty in 14 861 males with haemophilia

Characteristic	OR	95% CI	*P* value*
Age (years)			
2–19	ref		
20–39	2.3	1.2–4.3	.01
40–59	3.6	1.8–7.3	<.001
60+	3.8	1.7–8.4	.001
Haemophilia Type			
A	ref		
B	1	0.7–1.3	1.0
Haemophilia Severity			
Mild	ref		
Moderate	2.3	1.4–3.7	.001
Severe	2.9	1.8–4.6	<.001
Body Mass Index (BMI)			
Low/Normal	ref		
Overweight	1.3	1.0–1.7	.03
Obese	0.9	0.7–1.3	.8
Education Level			
Pre- or primary	ref		
Technical	1.3	0.8–2.0	.3
College degree	1.7	1.3–2.3	<.001
Other	1.2	0.8–1.9	.5
Student			
No	ref		
Yes	0.6	0.4–0.9	.02
Treatment Type			
Other	ref		
Continuous prophylaxis	0.6	0.4–0.8	<.01
Joint bleeds in last 6 mo			
None	ref		
One	1.1	0.6–2.1	.8
2–3	2.9	1.9–4.3	<.001
4+	4.4	3.3–5.7	<.001
Physical activity level			
High	ref		
Low	1.7	1.3–2.2	<.001
HCV positive			
No	ref		

Characteristic	OR	95% CI	*P* value*
Yes	3.7	2.3–5.9	<.001

*
p-value from overall Wald Chi-square test, ref = reference group