Original Article

Risk factors for postoperative complications of orthopedic surgery in patients with hemophilia: Second report

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ABSTRACT

This study was conducted to investigate the incidence in patients with hemophilia of postoperative complications and risk factors for these complications. Overall, 12 (6.5%) patients developed a postoperative infection. There were 6 (3.4%) postoperative surgical site infections. The presence of an inhibitor was the only risk factor for surgical site infection. Risk factors for delayed wound healing were older age, higher preoperative serum albumin level and procedures other than joint replacement or arthroscopy. HIV infection status was not a risk factor for postoperative complications.

1. Introduction

Intra-articular hemorrhage is one of the major symptoms in patients with hemophilia (PWH). Recurrent bleeding in joints leads to degradation of cartilage and destruction of the joint structure, a condition called hemophilic arthropathy^{1,2}. Pain and limited motion of involved joints impair activities of daily living and quality of life. Because the effects of conservative treatment such as bracing or rehabilitation are limited, orthopedic surgery is generally recommended for severely destroyed joints³. The development of factor concentrates has made it possible to perform orthopedic surgery safely for PWH. However, operations for hemophilic arthropathy are still challenging because of joint fibrosis, extremely limited range of motion and poor bone quality.

Several studies have reported that prolonged operative time, bleeding and blood-borne viral infections are associated with a higher incidence of complications in PWH, such as surgical site infection and delayed wound healing^{4,5}. Currently, there are few reports on complication rates and risk factors for complications following orthopedic surgery in PWH. Moreover, there is controversy about the influence of human immunodeficiency virus (HIV) infection status on the risk for surgical site infection. Several studies have suggested that patients who carry HIV have a higher postoperative infection rate than those without HIV^{6–8}, but others have reported infection rates associated with HIV positivity similar to those in the general population^{9–12}.

Previously, we investigated the risks associated with elective orthopedic surgery for PWH and found that HIV positivity was not a risk

factor for perioperative complications. The only risk factor for infection we identified in that study was the presence of inhibitor of the factor concentrate¹³. However, that study included a relatively small number of patients, and only univariate analysis was performed. The aim of the present study was to investigate the incidence of postoperative complications and preoperative risk factors for those complications based on a larger number of cases and using multivariate analysis. Additionally, we investigated whether HIV status influences the rate of postoperative complications in PWH. Clarifying such risk factors will aid in the decision for or against surgery and appropriately inform patients of the risks if an operation is contemplated.

2. Materials and methods

2.1. Patients

From 2006 to 2015, we performed 184 major orthopedic surgeries for 100 patients with hemophilia and other coagulation disorders in the Institute of Medical Science Research Hospital. We retrospectively reviewed the clinical characteristics and outcome of these patients to identify risk factors associated with postoperative complications. Data collected from the medical records included age; diagnosis; type of operation; viral infection status (i.e. HIV, hepatitis B [HBV] and hepatitis C [HCV]); Child classification; blood test results before surgery and postoperative complications, including surgical site infection, delayed wound healing and death within 6 months postoperatively.

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2.2. Procedures and perioperative hemostasis

All operations were performed by the same surgical team. For patients without inhibitors, factor VIII or IX replacement therapy was administered with boluses and continuous infusion according to the department protocol. Preoperatively, patients were given a bolus dose of clotting factor aiming for a factor level of 100%, followed by a continuous infusion of factor concentrate to maintain the level at 100% for a several days, depending on the type of surgery. For patients with an inhibitor, a bypassing agent was used, either recombinant activated factor VII (rFVIIa, NovoSeven) or activated recombinant factor concentrate (FEIBA, Baxter). All operations were performed under general anesthesia. No antithrombotic prophylaxis was used.

The diagnosis of surgical site infection was based on the definition in the 1999 guidelines for the prevention of surgical site infection¹⁴. Delayed wound healing was defined as a case in which sutures were left in place for longer than 2 weeks or where the wound required resuturing.

2.3. Statistical analysis

The association of individual risk factors with postoperative complications was determined using univariate and multivariate analysis. Univariate analysis was performed using Fisher's exact test for categorical variables and Student's t-test for continuous variables. Patient variables included in the analysis were age, diagnosis, viral infection status, type of surgery, presence of inhibitor, Child classification, preoperative laboratory values and pre-operative infection. Multivariate analysis was performed using logistic regression including the presence of HIV (fixed) and covariates selected by the backward elimination method. Covariates for multivariate analysis included age, type of hemophilia, type of surgery, preoperative laboratory values (white blood cell count, hemoglobin, platelet count, alanine aminotransferase, alkaline phosphatase, total protein, albumin, presence of an inhibitor, HBV surface antigen and HCV RNA) and preoperative infection. Some measurements were not included due to multicollinearity, missing values or lack of importance. Backward elimination was applied with the criterion to exclude with $P > 0.05$ until at least three variables remained, considering adjustment for confounding with the small number of the events. In addition, patients who were HCV-negative and those who underwent an arthroscopic procedure were excluded from multivariate analysis because none had a new infection or delayed wound healing. Statistical significance was set at a p value of < 0.05 . All statistical analyses were performed using SPSS (IBM).

3. Results

From June 2006 to July 2015, 184 procedures were performed in 100 patients in our institution. The patients' characteristics are shown in Table 1. The average age was 41.0 ± 13.5 years at the time of the surgery. The type of hemophilia included hemophilia A in 142 (77%), Hemophilia B in 40 (21.7%), factor VII deficiency in 1 (0.5%) and von Willebrand disease in 1 (0.5%). The operations included 108 arthroplasties (20 total hip arthroplasties, 3 revisions of hip arthroplasty, 82 total knee arthroplasties, 2 total elbow arthroplasties, and 1 total ankle arthroplasty), 34 arthroscopic procedures and 42 other operations (e.g. removal of pseudo tumor, limb amputation). HBV, HCV and HIV infections were present in 4.3%, 84.8% and 26.1% of patients, respectively. The mean preoperative CD4 count in patients with HIV were 411.2 ± 212.4 (range, 43–979) cells/ mm^3 . The mean length of hospital stay was 47.2 ± 28.5 days. Four patients died within 6 months postoperatively. Causes of death included chronic liver disease (2), acute myelogenous leukemia (1) and suicide (1). Overall, 12 patients (6.5%) developed a postoperative infection. Excluding 10 operations in patients who already had pre-existing infections, 6 (3.4%) new postoperative surgical site infections occurred. Delayed wound

Table 1

Baseline characteristics of patients enrolled in this study.

		Surgical cases
Gender	male	182
	female	2
Age	years (range)	41.0 (13–72)
Diagnosis	Haemophilia A (%)	142 (77.2)
	Haemophilia B (%)	40 (21.7)
	FVII deficiency (%)	1 (0.5)
	von Willebrand disease	1 (0.5)
Surgery	THA or re-THA	23
	TKA or re-TKA	82
	TEA	2
	TAA	1
	AS	34
	others	42
Inhibitor	negative (%)	162 (88.0)
	positive (%)	22 (12.0)
Viral infection	HCV negative/HIV negative (%)	27 (14.7)
	HCV positive/HIV negative (%)	109 (59.2)
	HCV negative/HIV positive (%)	1 (0.5)
	HCV positive/HIV positive (%)	47 (25.5)
Pre-existing infection	negative (%)	174 (94.6)
	positive (%)	10 (5.4)

THA: total hip arthroplasty, TKA: total knee arthroplasty, TEA: total elbow arthroplasty, TAA: total ankle arthroplasty, AS: arthroscopic surgery.

healing occurred in 4 (2.2%) cases. On univariate analysis, only the presence of an inhibitor was a significant risk factor for a new infection ($p = 0.024$). No infections occurred in patients who were not HCV-positive or among those who underwent arthroscopic surgery. The risk of delayed wound healing was significantly higher in patients who underwent procedures other than arthroscopy or arthroplasty ($p = 0.002$), patients with pre-existing infection ($p = 0.003$), those with a high preoperative total protein level ($p = 0.001$) and advanced age ($p < 0.001$). Death within 6 months was significantly associated with Child classification B or C, low preoperative white cell count, low preoperative hemoglobin, low preoperative platelet count, high preoperative aspartate aminotransferase, high preoperative alkaline phosphatase and low preoperative albumin level (Table 2).

On multivariate logistic analysis, the only independent risk factor for a new infection was the presence of inhibitor (odds ratio [OR], 23.2; 95% confidence interval [CI], 2.8–193.5; $p = 0.004$; Table 3), while risk factors for delayed wound healing were higher age (OR, 1.2; 95% CI, 1.1–1.3; $p = 0.002$), type of operation classified as 'others' (OR, 28.9; 95% CI, 3.8–222.4; $p = 0.001$) and high preoperative albumin (OR, 16.8; 95% CI, 1.9–151.1; $p = 0.012$). HIV infection was not a risk factor for any complication in this study population. An anti-FVIII inhibitor developed in 2 patients after total knee arthroplasty, 1 of whom had an inhibitor titer of 2 Bethesda units (BU) which disappeared after 9 months from the first detection and 1 who continued to have a titer of 1 BU. There were no thromboembolic events in this series.

4. Discussion

The current study investigated the incidence of complications after orthopedic surgery in PWH and identified risk factors for these complications. We found that the incidence of infections for patients without pre-existing infections was 3.4%. The only significant risk factor for this complication was the presence of an inhibitor. HIV status was not significantly related to infections or delayed wound healing. Previous studies have shown that postoperative infection rates in PWH are much higher than patients without bleeding disorders^{6,7,15}. Kelly et al. reported no early infections but three (11%) late infections after hip arthroplasty in PWH¹⁶. Rodriguez et al. reported that late infection is the main concern following total knee arthroplasty in PWH¹⁷. The relatively low rate of infection in our study may have been due to the short observation period (6 months). A longer follow-up period might

Table 2

The incidence of postoperative complications for demographic and clinical factors by univariate analysis.

		New infection							
Factor		Total	Absent		Present			p value	
HBs infection	negative	166	161	97.0%	5	3.0%	0.249		
	positive	8	7	87.5%	1	12.5%			
HCV infection	negative	28	28	100.0%	0	0.0%	0.591		
	positive	146	140	95.9%	6	4.1%			
HIV infection	negative	129	124	96.1%	5	3.9%	1.000		
	positive	45	44	97.8%	1	2.2%			
Type of procedure	arthroscopy	34	34	100.0%	0	0.0%	0.704		
	arthroplasty	112	107	95.5%	5	4.5%			
	other	28	27	96.4%	1	3.6%			
Inhibitor	negative	153	150	98.0%	3	2.0%	0.024		
	positive	21	18	85.7%	3	14.3%			
Child classification	A	102	96	94.1%	6	5.9%	1.000		
	B or C	10	10	100.0%	0	0.0%			
Diagnosis (haemophilia A/B)	A	117	112	95.7%	5	4.3%	1.000		
	B	27	26	96.3%	1	3.7%			
Pre-existing infection									
	negative								
	positive								
				mean	SD	mean	SD		
White blood cell		174	168	5457.4	1773.3	6	5038.3	1266.8	0.568
Haemoglobin		174	168	14.2	1.8	6	14.1	1.0	0.940
Platelet		174	168	20.0	6.5	6	23.4	6.5	0.208
Aspartate transaminase		174	168	30.7	20.7	6	28.8	15.5	0.825
Alanine transaminase		174	168	32.4	25.4	6	24.7	21.5	0.465
Alkaline phosphatase		174	168	310.8	110.7	6	244.5	70.5	0.148
Total protein		172	166	7.3	0.5	6	7.7	0.5	0.057
Albumin		171	165	4.3	0.5	6	4.5	0.3	0.360
CRP		172	166	0.5	1.3	6	0.2	0.2	0.614
Age		174	168	40.0	13.3	6	44.0	11.7	0.474
Albumin/Globrin ratio		171	165	1.5	0.4	6	1.5	0.3	0.773

		Delayed wound healing							
Factor		Total	Absent		Present			p value	
HBs infection	negative	176	166	94.3%	10	5.7%	1.000		
	positive	8	8	100.0%	0	0.0%			
HCV infection	negative	28	28	100.0%	0	0.0%	0.364		
	positive	156	146	93.6%	10	6.4%			
HIV infection	negative	136	128	94.1%	8	5.9%	1.000		
	positive	48	46	95.8%	2	4.2%			
Type of procedure	arthroscopy	34	34	100.0%	0	0.0%	0.002		
	arthroplasty	113	110	97.3%	3	2.7%			
	other	37	30	81.1%	7	18.9%			
Inhibitor	negative	162	152	93.8%	10	6.2%	0.611		
	positive	22	22	100.0%	0	0.0%			
Child classification	A	108	100	92.6%	8	7.4%	1.000		
	B or C	12	11	91.7%	1	8.3%			
Diagnosis (haemophilia A/B)	A	126	118	93.7%	8	6.3%	1.000		
	B	28	26	92.9%	2	7.1%			
Pre-existing infection	negative	124	118	95.2%	6	4.8%	0.003		
	positive	10	6	60.0%	4	40.0%			
				mean	SD	mean	SD		
White blood cell		184	174	5503.7	1808.9	10	5722.0	2012.6	0.713
Haemoglobin		184	174	14.1	1.8	10	13.2	2.9	0.117
Platelet		184	174	20.4	7.0	10	20.9	5.7	0.822
Aspartate transaminase		184	174	30.5	20.9	10	28.5	13.8	0.762
Alanine transaminase		184	174	31.8	25.4	10	20.9	14.0	0.182
Alkaline phosphatase		184	174	309.6	111.2	10	351.8	89.1	0.241
Total protein		182	172	7.3	0.5	10	7.8	0.3	0.001
Albumin		181	171	4.3	0.5	10	4.4	0.5	0.413
CRP		182	172	0.5	1.3	10	1.4	2.7	0.055
Age		184	174	39.9	13.0	10	59.2	9.1	< 0.001
Albumin/Globrin ratio		181	171	1.5	0.4	10	1.3	0.3	0.213

		Death						
Factor		Total	Absent		Present			p value
HBs infection	negative	175	171	97.7%	4	2.3%	1.000	
	positive	8	8	100.0%	0	0.0%		
HCV infection	negative	28	28	100.0%	0	0.0%		

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Table 2 (continued)

Factor		Death				p value	
		Total	Absent		Present		
HIV infection	positive	155	151	97.4%	4	2.6%	1.000
	negative	135	133	98.5%	2	1.5%	
Type of procedure	positive	48	46	95.8%	2	4.2%	0.282
	arthroscopy	34	33	97.1%	1	2.9%	
Inhibitor	arthroplasty	112	110	98.2%	2	1.8%	
	other	37	36	97.3%	1	2.7%	0.813
Child classification	negative	161	157	97.5%	4	2.5%	
	positive	22	22	100.0%	0	0.0%	1.000
Diagnosis (haemophilia A/B)	A	108	108	100.0%	0	0.0%	
	B or C	12	10	83.3%	2	16.7%	0.009
Pre-existing infection	A	125	123	98.4%	2	1.6%	
	B	28	26	92.9%	2	7.1%	0.153
	negative	123	120	97.6%	3	2.4%	
	positive	10	10	100.0%	0	0.0%	1.000
				mean	SD	mean	SD
White blood cell		183	179	5580.11	1783.50	4	2655.00
Haemoglobin		183	179	14.11	1.83	4	11.85
Platelet		183	179	20.60	6.82	4	12.10
Aspartate transaminase		183	179	29.97	20.01	4	52.25
Alanine transaminase		183	179	31.29	25.32	4	28.50
Alkaline phosphatase		183	179	305.55	100.14	4	602.50
Total protein		181	177	7.31	0.49	4	6.88
Albumin		180	176	4.29	0.48	4	3.55
CRP		181	177	0.57	1.46	4	0.41
Age		183	179	40.86	13.64	4	47.50
Albumin/Globulin ratio		180	176	1.49	0.38	4	1.13

yield different results.

Both univariate and multivariate analysis revealed that the presence of an inhibitor was the only significant risk factor for infection, which confirmed our previous results of univariate analysis of data from a smaller number of subjects¹³. Solimeno et al. reported that the presence of an inhibitor is the main risk factor for infection, having a high attributable risk. They speculated that prolonged operative time, bleeding and/or delayed wound healing may explain the higher infection rates in patients with inhibitors¹⁸. In the present study, it was difficult to compare operative time in patients with or without inhibitors because we included a variety of surgical procedures which normally require varying lengths of time. The presence of an inhibitor in our patients was not significantly associated with delayed wound healing, suggesting that the higher incidence of infections in patients with an inhibitor may have been related to greater amounts of bleeding or perhaps prolonged operative time. Delayed wound healing was significantly associated on multivariate analysis with advanced age, operations other than arthroplasty or arthroscopy and a high preoperative albumin. It has been well documented that ageing adversely affects wound healing because of reduced inflammatory or proliferative

response and fragility of the ageing skin^{19,20}. The 'other' category of operations included those for surgical site infection (e.g. debridement) and amputation, in which wound complications often occur because of vascular problem and reduced tissue viability. This may be why the 'other' category of procedures was a significant risk factors for delayed wound healing. The adverse effects of malnutrition on wound healing are well known and the serum albumin level is clinically useful parameter for patients' nutritional status. Many studies have demonstrated the adverse effect of low serum albumin on wound healing^{21–23}, which makes our finding of a high albumin level as a risk factor for poor healing surprising. The reason for this discrepancy, whether sample size or unknown confounders, is unclear.

In the present study, both univariate and multivariate analysis showed that HIV infection status was not associated with the incidence of complications. Ragni et al. reported a higher postoperative infection rate in HIV-positive patients with hemophilia whose CD4 counts were 200/mm³ or less than the rates of infection in the general population⁷. Due to recent advances in HIV treatment and care, the immunologic outcome and life expectancy of patients infected with HIV have improved dramatically. In principle, we only perform elective surgery in

Table 3
Multivariate logistic regression analysis.

Risk for new infection		Odds ratio	95% CI	Adjusted p value
Inhibitor		23.2	[2.8–193.5]	0.004
Alkaline phosphatase ^a		0.99	[0.97–1.0]	0.062
Total protein ^a		6.3	[0.8–50.8]	0.084
HIV-positive		0.7	[0.1–6.7]	0.939
Risk for delayed wound healing		Odds ratio	95% CI	Adjusted p value
Age ^a		1.2	[1.1–1.3]	0.002
Type of procedure (others vs. arthroplasties)		28.9	[3.8–222.4]	0.001
Albumin ^a		16.8	[1.9–151.1]	0.012
HIV-positive		1.6	[0.2–13.1]	0.67

^a Odds ratio was determined per 1-unit increase.

patients with CD4 counts > 400 cells/mm³, so our results are not particularly surprising, given that the mean CD4 counts in our series was 411.2 cells/mm³. Optimal antiviral therapy and proper patient selection therefore are likely to reduce the risk of postoperative complications in patients who are HIV-positive.

The current study has several limitations. First, due to the very small number of the events (around 10 or less), it was difficult to assess outcome-related factors, despite statistical methods that included multivariate analysis. Second, the follow-up period after surgery was short at 6 months. Therefore, complications that might have occurred later, such as late infections, were undetected. Third, because the current study included various types of operations, it was difficult to compare complications among patients undergoing the same procedure. In spite of these limitations, the strength of our study is that all procedures were performed by the same surgical team with the same hemostatic protocols at a single institution.

In conclusion, the overall complication rate in our patients was low. The presence of an inhibitor was the only risk factor for surgical site infection, while higher age, higher preoperative serum albumin level and surgeries other than joint replacement or arthroscopy were risk factors for delayed wound healing. HIV infection status was not a risk factor for postoperative complications.

Contributions

J.H. and H.T. designed research, performed research, collected data and wrote the manuscript; M.N. performed statistical analyses of data; T.K. wrote and reviewed the manuscript. The authors stated that they had no interests which might be perceived as posing a conflict or bias.

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Conflict of interest

None.

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