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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 joints [3]. 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 concentrate [13]. 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 infection [14]. 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 re-suturing.

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, pre-operative 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 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 pre-operative aspartate aminotransferase, high preoperative alkaline phosphatase and low preoperative albumin level (Table 2).

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.

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 PWH [16]. Rodriguez et al. reported that late infection is the main concern following total knee arthroplasty in PWH [17]. 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