CD4 Count is Associated with Postoperative Infection in Patients with Orthopaedic Trauma who are HIV Positive

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Abstract

Background Since the advent of effective antiretroviral therapy, the number of people with AIDS has increased and a certain percentage of these patients will require emergent orthopaedic surgery. Little is known regarding orthopaedic infections and the association of CD4 counts with postoperative infection in patients with HIV infection who experience orthopaedic trauma.

Questions/purposes We questioned whether the postoperative infection rate is higher after orthopaedic trauma surgery for patients who are HIV positive than for patients who are HIV negative undergoing similar surgery and aimed to identify preoperative variables that may be important in predicting postoperative infection in patients who are HIV positive.

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Each author certifies that his or her institution approved the human protocol for this investigation, all investigations were conducted in conformity with ethical principles of research, and that informed consent for participation in the study was obtained.

This study was performed at Grady Memorial Hospital, Atlanta, GA, USA.

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Methods We determined the postoperative infection rate in 64 patients who were HIV positive and who underwent orthopaedic surgery requiring instrumentation or an implant from January 2001 to May 2007. We compared this rate with historical control data from 2003 to 2007 for all orthopaedic procedures at Grady Memorial Hospital. We examined numerous preoperative variables for association with postoperative infection, including CD4 count, length of inpatient stay, polytrauma, and malnutrition.

Results Of the 64 patients, 15 had postoperative infections develop with an infection rate of 23%, compared with the 3.9% rate for the historical control subjects. Analysis of the 64 patients who were HIV positive revealed CD4 counts less than 300 were associated with development of postoperative infection. Hospital stay, polytrauma, and low serum albumin also were found to be associated with postoperative infection.

Conclusions It is evident that patients who are HIV positive with low CD4 counts undergoing emergent orthopaedic intervention are a patient population at risk for infection. Further study is necessary to evaluate preoperative and perioperative interventions that may decrease infections in this population.

Level of Evidence Level III, prognostic study. See Guidelines for Authors for a complete description of levels of evidence.

Introduction

It has been 30 years since recognition of the association of HIV-1 virus and AIDS. Almost 25 million people in the world have died from AIDS, and an estimated 30 million people are currently infected with the HIV virus throughout the world [12]. The majority of the new HIV infections

(63%) in the world occur in Sub-Saharan Africa [1]. In North America, the percentage of patients who are HIV positive is relatively low (< 1%). In certain population groups in the United States, such as patients with trauma in large urban cities, the incidence is much higher [13]. The incidence of HIV infection in patients with penetrating trauma in Baltimore is 13%, and it has been estimated that 29% of the patients admitted to San Francisco General Hospital are HIV positive [3].

The incidence of new HIV infections in the United States has been relatively constant, averaging approximately 40,000 per year [12]. Despite the static infection rate in the United States, the number of patients who are HIV positive continues to increase in the United States, secondary to the declining death rate of patients who are HIV positive. Since the advent of highly active antiretroviral therapy (HAART) in the mid-1990s, the deaths from AIDS have decreased from 70,000 per year in 1993 to 43,000 per year in 2003 [1]. With the declining death rate of patients who are HIV positive, emergent and elective orthopaedic surgery in patients who are HIV positive will increase in the United States. A study was conducted on musculoskeletal infections and wound healing in patients in the elective setting who are HIV positive [10]. However, there is a paucity of literature regarding orthopaedic infections in the trauma setting and no studies analyzing low preoperative CD4 counts associated with postoperative infection in the orthopaedic trauma setting.

We therefore determined (1) whether the postoperative infection rate is higher for patients who are HIV positive undergoing orthopaedic trauma surgery than for patients who are HIV negative undergoing similar surgery, and (2) whether factors in addition to the degree of immune suppression, including length of hospital stay, severity of injury, and malnutrition, are important in predicting postoperative infection in patients who are HIV positive.

Patients and Methods

After approval from our institutional review board, the medical records of all patients treated at the Emory Center for AIDS Research from January 1, 2000, to May 1, 2007, were cross-referenced with orthopaedic diagnostic codes. From this cohort of 204 patients, we reviewed medical records to determine which patients underwent open orthopaedic surgeries during this interval. Inclusion criteria included individuals who were HIV positive undergoing an open orthopaedic procedure requiring instrumentation or an implant. Patients who underwent soft tissue orthopaedic procedures and/or closed reductions were eliminated. The criteria for postoperative infection were in accordance with recommendations from CDC guidelines on organ/space

surgical site infections and were as follows: infection occurring within 30 days after the operative procedure or within 1 year if an implant was placed and appearing to be related to the index procedure [4]. The infection must have involved a part of the body, excluding the skin incision or area superficial to the fascia. One of the following also was present: purulent drainage from a deep drain, organisms isolated from an aseptically obtained culture of fluid or tissue beneath fascia, and an abscess or other evidence of infection involving the organ/space that is found on direct examination by the attending physician.

The selection criteria produced 64 patients who were HIV positive, of whom 15 had postoperative infections and 49 were uninfected. The group of 49 patients who were uninfected represented the HIV-positive comparative control group. We also compared the postoperative infection rate of the 64 patients who were HIV positive with that of an historical control group of all orthopaedic patients requiring instrumentation at Grady Memorial Hospital from 2003 to 2007.

The bacteriology on the HIV-positive infected group was recorded. Of the 15 infections, 12 bacterial isolates were obtained and *Staphylococcus aureus* was the predominant but not exclusive organism (Table 1). In the three cases in which bacterial isolates were not obtained, determination of postoperative infection was based on direct observation by the attending surgeon of an abscess involving the bone or beneath the deep fascia.

Demographic data and the following parameters were recorded for the infected group and the uninfected group:

Table 1. Bacteriology of the infected group

Patient	Organism
1	MRSA
2	Not available
3	MSSA
4	Not available
5	Streptococcus Group G
6	Cryptococcus neoformans
7	MRSA
8	MRSA
9	Citrobacter koseri
10	MRSA
11	MSSA
12	Not available
13	MRSA
14	MSSA
15	Serratia marcescens

MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*.

open versus closed fracture, type of surgery performed, presence of HAART, hepatitis seropositivity, hypertension, excessive alcohol use, smoking, intravenous drug abuse, homelessness, multiple fractures, multiple surgeries, days in hospital, most recent CD4 count, most recent viral load, leukocyte count, erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, and serum albumin. All of the patients in the study were followed for at least 30 days.

These variables then were analyzed for the infected and noninfected groups to determine which variables were associated with postoperative infection. We analyzed the discrete variables with Fisher exact t-test (Table 2) and the continuous variables with the Mann-Whitney U test (Table 3). For all analyses, it was assumed that alpha was 0.05 and a p value less than 0.05 was considered significant. For the continuous variables with p values less than 0.1 and greater than 0.05, the data were discretized with varying cutoffs and analyzed with the Fisher exact t-test. For the CD4 count, threshold values of 100, 200, 300, and 400 were analyzed independently. For serum albumin, cutoffs of 2.4, 2.6, 2.8, 3.0, 3.2, 3.4, and 3.6 were used.

Results

The infection rate of the patients who were HIV positive was 23% (15 of 64), compared with the 3.9% overall infection rate of the historical controls.

Comparing the patients who were HIV positive with and without infections, low CD4 counts, low serum albumin, inpatient stay, and multiple surgeries were found to be risk factors for development of infection. Of the 64 patients who were HIV positive, 34 had recent CD4 counts (within 6 months). Only three patients with a CD4 count greater than 300 had a postoperative infection develop (Fig. 1). A CD4 count less than 300 was associated with infection developing ($p = 0.02$) (Table 4). The patients with CD4 counts less than 400 did not have a significant difference in the incidence of an infection developing. Of the 15 patients with infections, seven underwent multiple surgeries (patients with polytrauma), excluding surgical treatment for postoperative infections. Of the 49 patients without infection who were HIV positive, eight received multiple surgeries. Multiple surgeries also were associated with development of infection ($p = 0.045$) (Table 2). Of the 49 patients who were HIV positive without postoperative infection, the mean hospital stay was 5 days (range, 2–12 days). In the HIV-positive infected group, the average hospital stay was 18 days (range, 5–39 days). The number of days spent in the hospital correlated with polytrauma and also was associated with infection ($p < 0.003$) (Table 3).

Table 2. Postoperative infection versus categorical variables

Variable	Frequency (%)		p value infected group*
	Noninfected group (n = 49)	Infected group (n = 15)	
Sex			0.99
Male	69%	73%	
Female	31%	27%	
Open fracture			0.99
No	63%	67%	
Yes	37%	33%	
Any HIV medications			0.30
No	69%	86%	
Yes	31%	14%	
HAART			0.71
No	75%	86%	
Yes	25%	14%	
Hepatitis			0.99
No	81%	86%	
Yes	19%	14%	
Hypertension			0.99
No	81%	79%	
Yes	19%	21%	
Alcohol			0.77
No	56%	50%	
Yes	44%	50%	
Smoking			0.99
No	54%	50%	
Yes	46%	50%	
Drugs			0.36
No	60%	43%	
Yes	40%	57%	
Homelessness			0.69
No	85%	80%	
Yes	15%	20%	
Multiple fractures			0.16
No	81%	60%	
Yes	19%	40%	
Multiple surgeries			0.045
No	83%	53%	
Yes	17%	47%	

* Fisher's exact test; HAART = highly active antiretroviral therapy.

Discussion

As the incidence of HIV continues to increase, orthopaedic surgeons continue to face difficult challenges. In the HIV-positive population, concern exists that impaired immune defense to common and uncommon surgical pathogens may lead to delayed wound healing and osteoarticular infection. We therefore determined (1) whether the

Table 3. Postoperative infection versus continuous variables

Variable	Noninfected group (n = 49)		Infected group (n = 15)		p value infected group*
	Median	IQR	Median	IQR	
Age (years)	43	33.5–49.5	43	38–52	0.55
Days in hospital	5	2–12	18	5–39	0.003
Viral load (IU/mL)	7.24	4.26–11.72	3.91	6.66–11.02	0.53
Leukocyte count ($\times 10^9$ cells/L)	6.7	5.01–8.52	6.70	3.56–11.27	0.86
Erythrocyte count ($\times 10^{12}$ cells/L)	3.69	3.03–4.28	3.91	3.48–4.47	0.82
Hemoglobin (g/dL)	11.8	10.33–13.73	11.55	11.05–12.35	0.53
Hematocrit (%)	35.6	30.5–41.0	37.2	33.45–38.55	0.74
Mean corpuscular volume (fL)	94	88–107	89.5	85.75–98.50	0.27
Mean corpuscular hemoglobin concentration (g/dL)	33.5	32.3–34.2	33.55	31.65–35.48	0.43
Erythrocyte distribution width (%)	13.1	12.3–14.0	15.05	13.05–15.76	0.116
Serum albumin (g/dL)	3.6	2.78–4.10	3.15	2.50–3.75	0.082

* Mann-Whitney U test; IQR = interquartile range.

Fig. 1A–B CD4 counts for the patients who were HIV positive who were (A) not infected and (B) infected are shown.

postoperative infection rate is greater in patients who are HIV positive undergoing orthopaedic trauma surgery than in patients who are HIV negative undergoing similar surgery, and (2) whether factors in addition to the degree of immune suppression, including length of hospital stay, severity of injury, and malnutrition, are important in predicting postoperative infection in patients who are HIV positive.

This study has several limitations associated with retrospective analysis, including possible selection bias. Selection bias is possible because all of the patients in the

Table 4. Postoperative infection versus CD4 categorical variables

CD4 count	Noninfected group	Infected group	p value*
CD4 $\leq$ 200			0.03
No	62%	23%	
Yes	38%	77%	
CD4 $\leq$ 300			0.02
No	57%	15%	
Yes	43%	85%	
CD4 $\leq$ 400			0.10
No	43%	15%	
Yes	57%	85%	

* Fisher exact test.

study were retrieved from the Emory Center for AIDS Research database, which was cross-referenced with orthopaedic codes to identify the patients to be retrospectively studied. Therefore, all of the patients in the study knew they were HIV seropositive and were patients at the Emory Center for AIDS research at the time of their trauma event. This cohort of patients who were HIV positive may not be representative of all patients who are HIV positive because many are unaware of their diagnosis and are not monitored or treated. Also, the CD4 counts were not all obtained directly before surgery and were retrieved retrospectively. Furthermore, an historical control was used for the 3.9% overall infection rate for all orthopaedic surgeries at Grady Memorial Hospital from 2003 to 2007, and the HIV serostatus of patients in the historical control was not known for all individuals. Also, if patients did not have signs of infection develop by postoperative Day 30, they were considered infection free. It is possible that patients

who were HIV positive in the noninfected group may have had infection develop inside a 1-year interval and would have increased the number of patients in the infected group. In addition, multivariate analysis was not performed owing to the small sample size and large number of variables. When multivariate analysis is used in this scenario, the estimates of the regression line are unstable and would not be reproducible.

Buehrer et al. [3] reported on early postoperative surgical infections in patients with hemophilia and HIV undergoing elective procedures and found no differences between wound infections in patients who were HIV positive and HIV negative. Hoekman et al. [8] found early postoperative infection rates of 5%, 0%, and 23% after open reduction internal fixation in 171 patients who were HIV negative, 26 patients who were asymptomatic and HIV positive, and 17 who were symptomatic and HIV positive, respectively. The increased rate of infection in patients who were symptomatic and HIV positive was attributed to lack of prophylactic antibiotics and the degree of immune suppression. CD4 counts were not available for these patients who were symptomatic and HIV positive.

Retrospective studies of patients who are HIV positive undergoing orthopaedic trauma surgery have had varying results, with some showing an increased postoperative infection rate in patients who are HIV positive compared with those who are HIV negative [7, 8, 14]. Harrison [6] reported comparable postoperative infection rates in HIV-positive and HIV-negative cohorts. There have been attempts to retrospectively determine preoperative risk factors for postoperative infections in patients who are HIV positive, including the percentage of CD4 cells [15], low CD4 counts [9], and the presence of AIDS. Avidan et al. [2] investigated preexisting opportunistic infections for independent risk factors of postoperative infection. In addition to immune suppression, malnutrition was implicated in a large retrospective study of 56,000 patients with postoperative infections [4]. Using regression models, a low serum albumin was the best predictor of mortality and morbidity in patients with postoperative infections [5].

Our study showed that in the emergent setting patients who are HIV positive have increased early postoperative infections. Patients with CD4 counts less than 300 who received plate osteosynthesis, intramedullary nails, or external fixation, had an increased risk of having postoperative infections develop. In correlation with previous studies, malnutrition (low serum albumin) also was associated with postoperative infection. The postoperative infection rate in our study was 23% compared with an historical control of 3.9%. This increased infection rate in patients who are HIV positive with CD4 counts less than 300 may distinguish this cohort from patients who are HIV positive with CD4 counts greater than 300. There was a

greater incidence of multiple surgeries in the HIV-positive infected group (46%) than in the HIV-positive noninfected group (17%). In the future, the HIV-positive infected group may be considered for special perioperative optimization. Medical interventions have been suggested for preoperative optimization of patients who are HIV positive, including extending perioperative antibiotics, initiating HAART therapy, cessation of bone marrow-suppressing therapies (didanosine and zalcitabine), correction of anemia, and reversal of coagulopathies, but these have not been prospectively examined [11].

Patients who are seropositive for HIV with low CD4 counts are a unique population with increased risk for early postoperative infection in the emergent orthopaedic trauma setting. We believe preoperative counseling regarding postoperative infection rates should be included in the informed consent for surgery, and absolute rather than relative operative indications should be applied when considering surgery in this population. Further study is needed to prospectively evaluate whether preoperative interventions may contribute to lower postoperative infection rates in this unique patient population.

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