

Risk factors for post-tooth extraction complications in HIV-infected patients:

A retrospective study

Yumiko Nakagawa^{1, 2*}, Yasuyuki Shimada³, Yohei Kawasaki⁴, Haruhito Honda², Takahiro Aoki², Yusuke Takanabe³, Ritsuo Takagi⁵, Yutaka Maruoka³, Shinichi Oka²

¹ Department of Oral health Sciences, Otemae Junior College, Hyogo, Japan

² AIDS Clinical Center, National Center for Global Health and Medicine, Tokyo, Japan

³ Department of Oral and Maxillofacial Surgery, National Center for Global Health and Medicine, Tokyo, Japan

⁴ Faculty of Nursing, Japanese Red Cross College of Nursing, Tokyo, Japan.

⁵ Division of Oral and Maxillofacial Surgery, Faculty of Dentistry & Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan

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Corresponding author:

* Yumiko Nakagawa

Department of Oral health Sciences, Otemae Junior College

6-42 Ochayashocho, Nishinomiya, Hyogo 662-8552, Japan

Tel.: +81-798-34-6331, Fax: +81-798-32-5040

E-mail: yunakaga@otemae.ac.jp

SUMMARY: To assess the rate and risk factors of postoperative complications following tooth extraction in HIV-infected patients by CD4 count. The study subjects were 231 HIV-infected patients who underwent tooth extraction at our institution between January 2007 and December 2011. Results of blood test, underlying diseases, surgical site, extraction method, and postoperative complications were obtained from the medical records. The risk factors potentially involved in postoperative complications were analyzed by multivariate logistic regression. Patients were divided into two groups, 61 (26%) patients with CD4 count of <200 μL , and 170 (74%) patients with ≥ 200 μL . Of the 231 patients, 12 (5.2%) developed postoperative complications (alveolar osteitis, $n=10$; surgical site infection, $n=2$). The rate of complications was not different between the CD4 <200 μL group (1.6%), and the CD4 ≥ 200 μL group (6.5%) (adjusted odds ratio (aOR): 9.328, 95% confidence interval (CI): (0.470, 185.229), $p=0.1431$). Surgical extraction method with bone excavation, but not CD4 count, were identified as risk factors for post-extraction complications (aOR: 22.037, 95% CI: (1.519, 319.617), $p=0.0234$). A low CD4 count is not a risk factor for post-extraction complications in HIV-infected patients. We advise that tooth extraction should be performed based on dental/oral condition, rather than delayed until improvement of CD4 count.

INTRODUCTION

Human immunodeficiency virus (HIV) infection is a progressive and transmissible disease in which the HIV infects CD4-positive T lymphocytes (CD4 cells), leading to gradual destruction of the immune system (1). Because CD4 count reflects the residual immune response capacity of the host, it helps understand the pathological level at a particular point of HIV infection (2). A CD4 count of less than 200 / μ L in patients with HIV infection is a risk factor for the development of various opportunistic diseases (3-5). In addition, if the CD4 count is less than 200 / μ L, it is classified as AIDS because of immunodeficiency in the US guidelines (6).

Although surgical procedures, such as tooth extraction in immunocompromised patients (e.g., those with HIV infection), are potentially associated with postoperative infections and incomplete wound healing (7), there are no safety guidelines for dental treatment in such patients. Ikeda et al. (8) concluded that as long as the CD4 count is above 200 / μ L, there are almost no dental treatments that would pose a risk to patients. While there are reports of postoperative complications in the case of abdominal surgery (9-11) with a CD4 count below 200 / μ L, there are few (12) reports produced outside of Japan concerning the safety of dental treatment as it relates to CD4 count, and in Japan, the only available material is the Ikeda manual. While being the sole report available for clinical reference as a specialist opinion, the aforementioned manual is not backed by clinical data. Nonetheless, considering the current situation in which there are no clinical reports with regard to this important subject matter, this manual represents the commonly accepted theory in Japan.

Given this situation, in order to determine if risks exist with dental treatment in the case of a CD4 count below 200 / μ L, we divided the HIV-infected patients who underwent tooth extraction at our Department of Oral and Maxillofacial Surgery into two groups—CD4<200 / μ L and CD4 \geq 200 / μ L—and compared their clinical data. We then

analyzed risk factors for postoperative complications with HIV, and also studied the relationship between CD4 count and postoperative complications rate.

MATERIALS AND METHODS

Study design and population

We conducted a retrospective cohort study using medical records from our institution. During the study period between January 2007 and December 2011, 239 HIV-infected patients underwent a total of 565 tooth extractions at the Department of Oral and Maxillofacial Surgery at the National Center for Global Health and Medicine. Patients were selected as follows to assess the association between CD4 count and postoperative complications. The inclusion criteria were 1) CD4 count was assessed just before the tooth extraction, 2) age >18 years, 3) attendance to the AIDS Clinical Center for regular medical checkups. Based on these criteria, we excluded one 8-year-old child and 7 patients who did not fulfill the study inclusion criteria, and 231 patients were included in the study.

The primary end-point in this study was the appearance of complications after tooth extraction. Since some patients underwent more than one tooth extraction during the study period, it was important to set criteria for the selection of the tooth extraction to be included in this study. It is already known that surgical stress associated with tooth extraction is higher in cases with bone excavation, especially for mandibular impacted third molar (13). In addition, the risk of complications (e.g., postoperative infection and alveolar osteitis) is relatively higher in molars than incisors (14). Thus, to select a tooth extraction site with the worst surgical stress, we used the following selection criteria: 1) completely bone impacted wisdom tooth; 2) surgical tooth extraction involving bone excavation/root separation; 3) priority to posterior teeth; and 4) priority to mandibular teeth. To study the effects of risk factors associated with postoperative complications, we obtained data on various clinical

parameters (see below) measured during a maximum period of 3 months before the date of tooth extraction. This period was selected since any analysis of postoperative complications is affected by background factors, such as physical factors (oral hygiene state (15, 16), diabetes mellitus (17)) and clinical status (e.g., CD4 count). Furthermore, at our clinical facility, such patients undergo assessment of CD4 count every 1 to 3 months. To study the incidence of postoperative complications, we recorded all such complications occurring the first 2 weeks after tooth extraction.

This research was reviewed and approved by the Human Ethics Review Committee of the National Center for Global Health and Medicine (NCGM-G-001476-00). The study protocol involved routine clinical service. Therefore, a signed consent form was not obtained from each patient for publication of clinical data. In accordance with the ethics guidelines of our institution, we notified AIDS Clinical Center and the Department of Oral and Maxillofacial Surgery outpatients about this research, in writing, to the effect that their consent with regard to the objective of this research is deemed to have been obtained in the case that they have not stated their opposition within a fixed period of time.

Variables and measures

Data of clinical characteristics, including age at the time of tooth extraction, sex, history of antiretroviral therapy (ART), HIV-RNA level, underlying disease(s), white blood cell count, neutrophil count, platelet count, and CD4 count, causative disease, site, reason and operative method for tooth extraction, and postoperative complications, were retrieved from the medical records.

Statistical analysis

For statistical analysis, patients were divided into two groups based on the latest CD4 count

before tooth extraction, using a cutoff count of 200 / μ L; the CD4<200 / μ L and the CD4 \geq 200 / μ L groups. The Fisher's exact test was used for comparison of rates while differences between continuous variables were assessed by t-test. All data were summarized as mean \pm standard deviation. A two-sided t-test with *P* value less than 0.05 was considered to denote the presence of statistical significance.

As described above, the primary endpoint was the rate of postoperative complications after tooth extraction in HIV-infected patients. For this purpose, we compared the rate of postoperative complications between the CD4<200 / μ L and CD4 \geq 200 / μ L groups. The 95% confidence interval (CI) for each complication in each group was calculated, and the difference compared by the Fisher's exact test (18). Furthermore, we calculated the adjusted odds ratio and 95% CI and used multiple logistic regression analysis to compare the risk factors of such complications. We applied the following parameters as covariate in multiple logistic regression; platelet count, medical history of ART, HIV-RNA, caries, pericoronitis, surgical extraction with gum incision or bone excavation and diabetes mellitus.

We aggregated the background information of the cases with or without postoperative complication and compared them. With regard to discrete value, we calculated number of experiment and ratio and executed the Fisher's exact test in order to investigate whether the difference of ratio appear between the groups. We calculated descriptive statistics such as number of experiments, average, standard deviation, minimum, median and maximum in terms of continuous variables. Further, we conducted 2-sample t-test in order to investigate if any difference existed between population mean of each group. We indicated the number of postoperative complication case and the ratio by every 200 / μ L of CD4 count. The rate of complications in our HIV-infected patients was compared with that reported in previous studies. All statistical procedures were performed using SAS version 9.4 for Windows (SAS Institute Inc.; Cary, NC).

RESULTS

Differences between CD4<200 / μ L and CD4 \geq 200 / μ L groups

The study patients comprised CD4 count was <200 / μ L in 61 (26%) patients and \geq 200 / μ L in the remaining 170 (74%) patients. The following background factors were significantly different between the two groups: use of anti-HIV agent, diabetes mellitus as underlying disease, caries, pericoronitis and surgical extraction with gum incision or bone excavation. In addition, platelet count and HIV viral load were significantly different between the two groups (Table 1).

Effects of background factors on postoperative complications

Of the 12 patients who developed postoperative complications (alveolar osteitis, n=10; surgical site infection, n=2), one was part of the 61 CD4<200 / μ L group (1.6%), while the other 11 were from the 170 CD4 \geq 200 / μ L group (6.5%). There was no significant difference in the rate of postoperative complications between CD4<200 / μ L group and CD4 \geq 200 / μ L group. (95% CI: (-9.7128, 0.0503), $p=0.1910$) (Table 2). The results of multiple logistic regression showed no differences in CD4 count between the two groups (aOR: 9.328, 95% CI: (0.470, 185.229), $p=0.1431$). One factor independently and influenced the primary outcome; surgical extraction with gum incision or bone excavation (aOR: 22.037, 95% CI: (1.519, 319.617), $p=0.0234$) (table 3).

Comparison the groups by if postoperative complications appears or not

We discovered the factor which influenced incident of postoperative complications was age ($p=0.0342$), pericoronitis as a reason ($p=0.0062$), and the surgical extraction with gum incision or bone excavation as a method ($p=0.0007$). The number of patients with

underlying disease, was 18 with congenital coagulopathies, 15 with diabetes mellitus, and 1 with antithrombotic. In patients with inherited bleeding disorders, when they underwent tooth extraction, blood products were administered before and after extraction to control bleeding (19). As a result, although one (CD4 count: 668 / μ L) out of the 18 patients had surgical site infection, there were no postoperative bleeding. Regarding 15 patients who had diabetes mellitus, prolonged bleeding was observed only in one patient (CD4 count: 790 / μ L). Neither hereditary hemorrhagic disease nor diabetes was identified as a significant risk factor for postoperative complications in this study (Table 4).

Comparison of postoperative complications rate by CD4 count

In this research, the number of postoperative complications case was one out of 61 cases in the groups CD4<200 / μ L, which incident rate was 1.6%, and it was 11 cases out of 170 cases in the group CD4 \geq 200 / μ L, which incident rate was 6.5%. Although the incidence rate of the CD4 \geq 200 / μ L was higher by about 5%, no statistically significant difference appeared (95% CI: (-9.7128, 0.0503), p-value=0.1910) (table 2). It was 5.2% for entire 231 cases. Moreover, we verified the distribution of incident rate of postoperative complications every 200 / μ L, and the highest rate; 8.8% which was 3 out of 34 cases, was observed more than 600 / μ L (fig. 1).

DISCUSSION

In this study, we investigated risk factors of post-tooth extraction complications in HIV-infected patients in related to CD4 count. Previous reports concluded that there was no risk of postoperative infection or delayed healing in most dental treatments in their patients if their CD4 count were over 200 / μ L (7, 8). However, according to our survey, they were not associated with any CD4 count. Therefore, CD4 count alone was not an indicator for

complication of post-tooth extraction.

The study investigated the association between postoperative complications and CD4 count, so postoperative complications focused on alveolar osteitis and surgical site infection. Diabetes is an underlying disease associated with alveolar osteitis and surgical site infection, but none of the diabetic patients in this study had such cases. Also, none of the 15 diabetic patients had HbA1c exceeded 9.0 mg / dL (20). Although diabetes mellitus was not identified as the significant risk factor of the postoperative complications in this study (Table 4), if control of diabetes mellitus was worse than our patient population, risk of the postoperative complications should be considered.

In order to compare the incidence rate of postoperative complications with prior researches, each rate was displayed in table 5. The rates of post-extraction complications in HIV-infected patients ranged from 3.1 to 22.4% in previous studies (12, 21-24). In three of these studies, the complications rates were not significantly different between patients with or without HIV infection (21, 22, 24). Dodson et al (23) reported postoperative complications rate in HIV-infected patients of 20.9% was significantly higher than that in non-HIV patients of 2.9% (Relative Risk (RR): 7.0, 95%CI: (2.0, 25.0), $p=0.001$). However, the same group reported no significant difference between the two in another review study (24). One can infer from the results of Dodson's Prospective study that dental treatment of HIV-infected patients was not conducted proactively at that era, with resultant high surgical stress and the associated high rate of complications. Considering that the former one was retrospective while the later one was prospective, it was probably due to better methodology applied, including least invasiveness, during the tooth extraction procedure. One can infer from the results of the prospective study that dental treatment of HIV-infected patients was not conducted proactively at that era, with resultant high surgical stress and the associated high rate of complications. In addition to the better surgical procedure, since our study was

conducted between 2007 and 2011, the general condition of the patient was likely more stable under ART compared with earlier studies (25), suggesting another reason for the differences between the studies. Postoperative complications rate in previous studies cannot be compared with those in the present study because of differences in study populations and analytical methods. However, in previous studies, postoperative complications rate among HIV-infected patients who received highly invasive surgical tooth extraction ranged from 11.8 to 14.3% (12, 21), and no significant differences in postoperative complications rate were reported between whole populations and patients with CD4 count less than 200 / μ L. Also, the rate is almost the same as 12.2% in this study.

We compared postoperative complications rate after surgical extraction of the mandibular third molar between the present subjects and non-HIV-infected patients in previous studies. Blondeau and Daniel (26) reported a postoperative complications rate of 6.9% (38/550) among 550 patients who underwent surgical extraction for impacted mandibular third molars; the postoperative complications included alveolar osteitis (20 patients; 3.6%), infection (12 patients; 2.2%), and paresthesia (6 patients; 1.1%). The complications rate after surgical extraction in the present study was 12.2%, and all complications were alveolar osteitis. The overall rate of postoperative complications in the present study is higher compared to that in the previous study, which might be because of the higher rate of alveolar osteitis in the former. This difference might be because of immunodeficiency as a result of decrease in CD4 count in HIV-infected patients. However, no significant differences were observed among postoperative complications rate stratified by CD4 count (Fig. 1). Sabbah et al. also reported CD4 count had no impact on failure rate (CD4>500 / μ L: 3.8%, 300–500 / μ L: 8.5%, 200–300 / μ L: 7%, <200 / μ L: 10%) for implants that were as invasive as tooth extraction (27). Which is comparable to that observed in the present study, despite differences in the rates of individual complications.

Although it is difficult to discuss dental and medical surgeries in the same terms, Whitney et al. reported CD4 count to be the best indicator of frequency and mortality of perioperative complications (9). Surgical extraction of the mandibular third molar is the most invasive method among the more frequently practiced tooth extraction procedures in dental practice. Nevertheless, our findings demonstrated no significant relationship between CD4 count and complications rate after this procedure. Taken together, the present and previous results suggest that the frequency of postoperative complications after highly invasive surgeries, such as those evaluated by Whitney et al., is relatively high when the CD4 count is low. Additionally, in case of less invasive surgeries such as tooth extraction, in which surgery is limited to the oral cavity, it is unnecessary to postpone tooth extraction even if the CD4 count is low.

There were some limitations in this study. First, we chose only one tooth for one patient. Therefore, we could not examine the risk of multiple tooth extractions performed in a single session on the same day. In addition, we did not investigate the effect of smoking and oral hygiene state. Furthermore, drugs prescribed for underlying diseases other than HIV infection were not included in the risk factor analysis in this study.

In conclusion, the present study indicated that surgical extraction (highly invasive extraction including bone excavation), but not CD4 count, is a significant risk factor for postoperative complications after tooth extraction in HIV-infected patients. In addition, no significant differences were observed among postoperative complications rate stratified by CD4 count. Based on these results, we recommend that tooth extraction should be conducted in HIV-infected patients based on dental assessment, rather than on CD4 count. The tooth should not be postponed until the CD4 count increases to more 200 / μ L. We recommend that the timing of tooth extraction (with regard to avoiding postoperative complications) should not be linked to CD4 count.

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Conflict of interest None to declare regarding to this study.

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Figure legends

Figure 1. Postoperative complications rate of every CD4 count 200 / μ L

It showed the distribution of incident rate of postoperative complications every 200 / μ L. The highest rate was 8.8% more than 600 / μ L, just because CD4 count is low, it did not mean a higher postoperative complications rate.

Cochran-Armitage Trend test: p-value=0.3050

alveolar osteitis: n=10, surgical site infection: n=2

Table 1. Differences in background factors between HIV-infected patients with CD4 count of <200 / μ L and those with CD4 \geq 200 / μ L

	CD4 count, <200 / μ L		CD4 count, \geq 200 / μ L		Total	p-value
	(n=61)		(n=170)			
	n	%	n	%		
Sex (M/F)	57/4	93.4/6.6	163/7	95.9/4.1	220/11	0.4868
Age, median (range)	42 (22-72)		39 (19-72)			0.1426
ART (yes/no)	42/19	68.9/31.1	141/29	82.9/17.1	183/48	0.0269 *
Laboratory data						
WBC count (/ μ L), median (range)	4430.0 (1120-13280)		5130.0 (2130-80720)			0.1132
Neutrophil count (/ μ L), median (range)	2500.0 (66-12882)		2830.0 (621-9686)			0.9787
Platelet count (/ μ L), median (range)	16.5 (3.7-51.6)		20.5 (3.3-39.3)			0.0040 *
HIV-RNA (copy/mL) (<50/ \geq 50)	19/42	31.1/68.9	108/62	63.5/36.5	127/104	<.0001 *
Clinical history						
Congenital coagulopathies (yes/no)	4/57	6.6/93.4	14/156	8.2/91.8	18/213	0.7871
Diabetes mellitus (yes/no)	8/53	13.1/86.9	7/163	4.1/95.9	15/216	0.0287 *
Antithrombotic (yes/no)	0/61	0/100	1/169	0.6/99.4	1/230	1.0000
Dental history						
Reasons for extraction						
Caries (yes/no)	35/26	57.4/42.6	70/100	41.2/58.8	105/126	0.0359 *
Periodontitis (yes/no)	12/49	19.7/80.3	17/153	10.0/90.0	29/202	0.0697
Periapical periodontitis (yes/no)	4/57	6.6/93.4	22/148	12.9/87.1	26/205	0.2388
Pericoronitis (yes/no)	8/53	13.1/86.9	59/111	34.7/65.3	67/164	0.0016 *
Type of procedure						
Surgical tooth extraction (yes/no)	14/47	23.0/77.0	68/102	40.0/60.0	82/149	0.0193 *

ART, antiretroviral therapy.

Congenital coagulopathies, Including Hemophilia A, Hemophilia B, von Willebrand disease.

Diabetes mellitus, No poor glycemic control patients with HbA1c over 9.0 mg/dL.

Table 2. Comparison of postoperative complications rate by CD4 count

	Number of patients	Median (Range)	Complications	non-Complications	Risk Difference (95% CI)	Fisher <i>p</i> -value
Any CD4 count (/μL)	231	330 (3-1079)	12	219	NA	
CD4 count, <200 /μL	61	121 (3-197)	1 (1.6%)	60 (98.4%)	-4.8312	0.1910
CD4 count, ≥200 /μL	170	400 (202-1079)	11 (6.5%)	159 (93.5%)	(-9.7128, 0.0503)	

postoperative complications (alveolar osteitis, n=10; surgical site infection, n=2).

Table 3. Analysis of factors that influenced primary outcome

Variable	Adjusted odds ratio	95%CI	<i>p</i> -value
Intercept	-	-	0.9736
Anti-retroviral therapy	3.786	0.601, 23.838	0.1562
Platelet count (/μL)	1.222	0.353, 4.231	0.7521
HIV-RNA (copy/mL)	1.000	1.000, 1.000	0.2507
CD4 count (/μL), <200 vs ≥200	9.328	0.470, 185.229	0.1431
Diabetes mellitus	<0.001	<0.001, >999.999	0.9682
Caries	2.163	0.257, 18.208	0.4777
Pericoronitis	1.127	0.088, 14.483	0.9271
Surgical tooth extraction	22.037	1.519, 319.617	0.0234

Table 4. Differences in background factors between HIV-infected patients with postoperative complications appears or not

	Complications (n=12)		non-Complications (n=219)		Total	p-value
	n	%	n	%		
Sex (M/F)	12/0	100/0	208/11	95.0/5.0	220/11	1.0000
Age, median (range)	34.5 (24-54)		39 (19-72)			0.0342 *
ART (yes/no)	10/2	83.3/16.7	173/46	79.0/21.0	183/48	1.0000
Laboratory data						
WBC count (/μL), median (range)	4970.0 (2990-6730)		4980.0 (1120-80720)			0.6433
Neutrophil count (/μL), median (range)	2711.0 (1148-4489)		2709.0 (66-12882)			0.6220
Platelet count (/μL), median (range)	20.6 (16.3-30.5)		20.2 (3.3-51.6)			0.6195
HIV-RNA (copy/mL) (<50/≥50)	8/4	66.7/33.3	119/100	54.3/45.7	127/104	0.5544
CD4 count (/μL) (<200/≥200)	1/11	8.3/91.7	60/159	27.4/72.6	61/170	0.1910
Clinical history						
Congenital coagulopathies (yes/no)	1/11	8.3/91.7	17/202	7.8/92.2	18/213	1.0000
Diabetes mellitus (yes/no)	0/12	0/100	15/204	6.8/93.2	15/216	1.0000
Antithrombotic (yes/no)	0/12	0/100	1/218	0.5/99.5	1/230	1.0000
Dentall history						
Reasons for extraction						
Caries (yes/no)	4/8	33.3/66.7	101/118	46.1/53.9	105/126	0.5539
Periodontitis (yes/no)	1/11	8.3/91.7	28/191	12.8/87.2	29/202	1.0000
Periapical periodontitis (yes/no)	0/12	0/100	26/193	11.9/88.1	26/205	0.3698
Pericoronitis (yes/no)	8/4	66.7/33.3	59/160	26.9/73.1	67/164	0.0062 *
Type of procedure						
Surgical tooth extraction (yes/no)	10/2	83.3/16.7	72/147	32.9/67.1	82/149	0.0007 *

ART, antiretroviral therapy.

Congenital coagulopathies, Including Hemophilia A, Hemophilia B, von Willebrand disease.

Diabetes mellitus, No poor glycemic control patients with HbA1c over 9.0 mg/dL

Table 5. Comparison of postoperative complications rate between the present and previous studies

	Robinson et al (21)	Porter et al (22)	Glick et al (12)	Dodson et al (23)	Dodson (24)	Nakagawa et al (present study)
Year	1992	1993	1994	1994	1997	2020
Country	UK	UK	USA	USA	USA	Japan
HIV patients						
Total complications rate (%)	5/163 (3.1)	4/100 (4.0)	16/326 (4.9)	9/43 (20.9)	17/76(22.4)	12/231 (5.2)
Surgical extraction rate (%)	2/14 (14.3)		4/34 (11.8)			10/82 (12.2)
non-HIV patients						
Total complications rate (%)	3/70 (4.3)	2/68 (2.9)	-	3/101 (3.0)	10/75 (13.3)	-
Surgical extraction rate (%)						

Data are number of extractions (percentage)

Fig 1. Postoperative complications rate of every CD4 count 200 / μ L

