# Risk Factors Affecting Postoperative Hemorrhage After Tooth Extraction in Patients Receiving Oral Antithrombotic Therapy

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**Purpose:** We investigated risk factors affecting the onset of postoperative hemorrhage after tooth extraction in patients receiving oral antithrombotic therapy.

**Patients and Methods:** A total of 443 tooth extractions were performed in 382 patients. All extractions were performed while continuing conventional antithrombotic therapy, and local hemostatic measures were performed.

**Results:** Among the 17 patients with postoperative hemorrhage, 9 received warfarin monotherapy, 6 received warfarin and antiplatelet combination therapy, and 2 received antiplatelet monotherapy. Postoperative hemorrhage occurred within 6 days in 16 patients (94.1%), with a median of 3 days. The international normalized ratio at the time of extraction was less than 3.0 for all 15 patients receiving warfarin therapy but was prolonged, at 3.0 or greater, in 7 of 12 patients in whom this value was measured at the time of postoperative hemorrhage. As for local hemostatic measures at the time of postoperative hemorrhage, thorough local hemostatic measures were required in 12 (80.0%) of the 15 patients receiving warfarin therapy. Conversely, in the 2 patients receiving antiplatelet therapy, hemostasis was achieved by use of compression alone. Concerning factors affecting postoperative hemorrhage, significant differences were seen in relation to surgical tooth extraction ($P = .008$) and acute inflammation findings ($P = .007$).

**Conclusions:** In patients receiving antithrombotic therapy, surgical tooth extraction and acute inflammatory findings were associated with a significantly increased incidence of postoperative hemorrhage. In more than 90% of cases, postoperative hemorrhage occurred within 6 days of extraction. Thorough local hemostatic measures are therefore required in patients receiving warfarin therapy.



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During tooth extraction in patients receiving oral antithrombotic therapy, continuous administration of a maintenance dose of warfarin and/or antiplatelet therapy is recommended.[1-10] This is because a prothrombin time–international normalized ratio (INR) ranging from 3.0 or less to 4.0 is associated with no marked differences in incidence of postoperative hemorrhage between tooth extraction with or without maintenance dose of warfarin.[1-13] Wahl[14] also reported that when warfarin was discontinued for tooth extraction, the incidence of severe thrombosis was 0.95%, and most patients showing this event died. When endoscopy was performed after warfarin use was reduced or discontinued, the incidence of severe thrombosis was 1.2%, and again, most of these patients died or became disabled.[15] With discontinuation of aspirin, the incidence of cerebral infarction increased 3.4-fold as compared with continuing this therapy.[16] On the

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basis of reports regarding the risks of thromboembolism associated with discontinuing antithrombotic therapy, tooth extraction is now performed by continuing to administer the maintenance dose of antithrombotic drugs.

According to reports in which tooth extraction was performed while maintaining antithrombotic therapy, a certain frequency of postoperative hemorrhage occurred, and the incidence of postoperative hemorrhage in patients receiving warfarin therapy has been reported at 2% to 26%.[2,4-8,11-13] In terms of cause, increased INR values and acute inflammation in connection with the extracted teeth may be involved,[12,17] but no reports have discussed the causes and potential countermeasures.

The present study therefore examined tooth extraction in patients receiving oral antithrombotic therapy while continuing to be administered a maintenance dose of antithrombotic drugs, and the onset of postoperative hemorrhage and hemostatic countermeasures were retrospectively investigated to identify factors affecting the onset of postoperative hemorrhage.

## Patients and Methods

### SUBJECTS

The study protocols were approved by the institutional review board and ethics committee of the National Cerebral and Cardiovascular Center. In this study the medical charts of patients were retrospectively reviewed to investigate the items discussed later.

Subjects comprised 382 patients in whom tooth extraction was performed while maintaining conventional antithrombotic therapy between April 2002 and March 2009 at the Department of Dentistry of the National Cerebral and Cardiovascular Center (Osaka, Japan). Patients with hematologic diseases or liver dysfunction were excluded. Investigated items were patient characteristics (age and gender), antithrombotic therapy regimen (warfarin monotherapy, warfarin and antiplatelet combination therapy, and antiplatelet monotherapy), degree of anticoagulant effects in patients receiving warfarin therapy (INR value on the day of tooth extraction), total and mean number of extracted teeth, acute inflammatory findings in connection with extracted teeth, type of tooth extraction (simple or surgical tooth extraction), and number of cases of postoperative hemorrhage.

Furthermore, in patients in whom postoperative hemorrhage developed, the age distribution, time of onset of postoperative hemorrhage, INR values at the time of tooth extraction and postoperative hemorrhage, and local hemostatic measures were examined. As for age distribution, the number of postoperative hemorrhages in relation to the total number of tooth extractions was calculated for each age group by decade (≤19 years, 20-29 years, 30-39 years, 40-49 years, 50-59 years, 60-69 years, 70-79 years, and ≥80 years). Only 1 patient was aged less than 10 years, and only 1 patient was aged greater than 90 years. By comparing groups with and without postoperative hemorrhage, factors affecting the onset of postoperative hemorrhage were compared.

In all patients platelet counts were $10 \times 10^4/mm^3$ or greater. Acute inflammatory findings were defined as pus discharge, swelling and redness of soft tissue around the tooth to be extracted, or strong percussion pain in the tooth to be extracted, and patients with at least 1 of these findings were considered as having acute inflammation. In such patients, tooth extraction was performed after administering antibiotics for 1 week.

In patients at risk for infective endocarditis, antibiotics were administered according to the guidelines for preventing infective endocarditis published by the Japanese Circulation Society.[18] As analgesics, either loxoprofen sodium or acetaminophen was administered as needed.

### TOOTH EXTRACTION AND LOCAL HEMOSTATIC MANAGEMENT

Tooth extraction was performed while continuing to administer maintenance doses of warfarin and/or antiplatelet drugs. The same oral surgeon performed all tooth extractions. Local anesthesia was induced by use of 3% Prilocaine (containing 0.054 IU of felypressin; Dentsply Sankin, Tokyo, Japan). Tooth extraction was performed in a minimally invasive manner by use of elevators and forceps, and inflamed granulation tissue was completely curetted. As for local hemostatic measures after tooth extraction, extraction wounds after extracting erupted teeth were packed with oxidized cellulose (Surgicel; Ethicon, Somerville, NJ) and then horizontal mattress sutures with No. 4-0 silk were placed. Extraction wounds after extracting impacted teeth were packed with oxidized cellulose and closed with No. 4-0 silk sutures. When hemostasis was difficult even with these procedures, bleeding points in soft tissue were cauterized by electrocautery when necessary. Each subject was asked to bite down on gauze for 30 minutes for compression, and hemostasis was confirmed. No splint was used during tooth extraction. However, when postoperative hemorrhage was observed, the wounds were protected by a surgical acrylic splint with periodontal packing as needed. Sutures were removed after 1 week. Tranexamic acid was not used for mouthwash, because use of this agent has not been approved in Japan. Likewise, fibrin glue was not used because this agent is not indicated for use with tooth extraction in Japan.

### ASSESSMENT OF POSTOPERATIVE HEMORRHAGE

Postoperative hemorrhage was defined as oozing that could be stopped through compression by biting down on gauze or oozing or marked hemorrhage that could not be stopped by biting down on gauze and required hemostatic measures by an oral surgeon (compression, hematoma removal, oxidized cellulose insertion, resuturing and electrocautery, and/or splint placement).

The state of postoperative hemostasis was confirmed by telephoning the patients on the night of tooth extraction and the next morning to inquire about the state of hemostasis. Patients were asked to visit the Department of Dentistry both 3 days and 1 week after tooth extraction to confirm the state of wounds. The cell phone number of the surgeon was given to patients so that they could contact the surgeon if any problems arose. Hemorrhage was monitored from 30 minutes up to 1 week after tooth extraction.

### STATISTICAL ANALYSIS

Statistical analyses were performed with SPSS software, version 15.0 (SPSS Japan, Tokyo, Japan).

Data are expressed as mean ± standard deviation for age and mean number of extracted teeth and as median (interquartile range) for timing of hemorrhage and INR values (at tooth extraction and at postoperative hemorrhage) in patients with postoperative hemorrhage.

On statistical analyses, age and mean number of extracted teeth were examined by use of unpaired $t$ tests, and $\chi^2$ tests were used to compare the incidence of postoperative hemorrhage among age groups. A Mann-Whitney $U$ test was used to compare gender, antithrombotic therapy regimen, type of tooth extraction, and acute inflammatory findings. A Wilcoxon rank sum test was used to compare INR value at the time of tooth extraction and that at the time of hemorrhage in patients with postoperative hemorrhage. For all analyses, the level of significance was set at $P <$ .05. For local hemostatic measures, the number of patients with postoperative hemorrhage that was stopped with compression alone was too small to analyze statistically.

## Results

### PATIENT CHARACTERISTICS

The 382 patients included 238 men and 144 women. The mean age was 61.5 ± 17.7 years (range, 6-91 years). In 433 tooth extractions, a total of 794 teeth were extracted (mean, 1.8 ± 1.3 teeth/extraction). Warfarin monotherapy was administered to 188 patients (219 tooth extractions), warfarin and antiplatelet combination therapy to 66 patients (73 tooth extractions), and antiplatelet monotherapy to 128 patients (141 tooth extractions) (Table 1).

Regarding the type of tooth extraction, 341 simple tooth extractions and 92 surgical tooth extractions were performed. Acute inflammatory findings were present in 91 extractions and absent in 342 extractions. Postoperative hemorrhage occurred in 17 extractions (3.9%) (Table 1).

### ANALYSIS OF PATIENTS WITH POSTOPERATIVE HEMORRHAGE

Among the 17 patients with postoperative hemorrhage, 9 received warfarin monotherapy, 6 received warfarin and antiplatelet combination therapy, and 2 received antiplatelet monotherapy. Ages ranged from 19 to 85 years (mean, 54.9 ± 21.8 years). No significant differences existed in the incidence of postoperative hemorrhage among age groups ($\chi^2$ = 7.86, $P$ = .25) (Fig 1).

Timing of the onset of postoperative hemorrhage ranged from 1 to 10 days after tooth extraction, and hemorrhage occurred within 6 days in 16 patients (16 of 17 patients [94.1%]). Median onset was 3 days (interquartile range, 2-4.5 days) (Fig 2). In a patient in

**Table 1. PATIENT CHARACTERISTICS**

| | Antithrombotic Therapy | | | |
|---|---|---|---|---|
| | Warfarin | Warfarin + Antiplatelet Drug | Antiplatelet Drug | Total |
| No. of patients | 188 | 66 | 128 | 382 |
| Age (yr) | 60.7 ± 17.5 | 61.5 ± 17.5 | 62.4 ± 18.2 | 61.5 ± 17.7 |
| No. of extraction (occasions) | 219 | 73 | 141 | 433 |
| No. of teeth extracted | 404 | 129 | 261 | 794 |
| No. of teeth surgically extracted | 50 | 18 | 24 | 92 |
| Mean No. of teeth extracted (/occasion) | 1.9 ± 1.2 | 1.7 ± 1.1 | 1.9 ± 1.5 | 1.8 ± 1.3 |
| No. of postoperative hemorrhages (incidence) | 9 (4.1%) | 6 (8.2%) | 2 (1.4%) | 17 (3.9%) |

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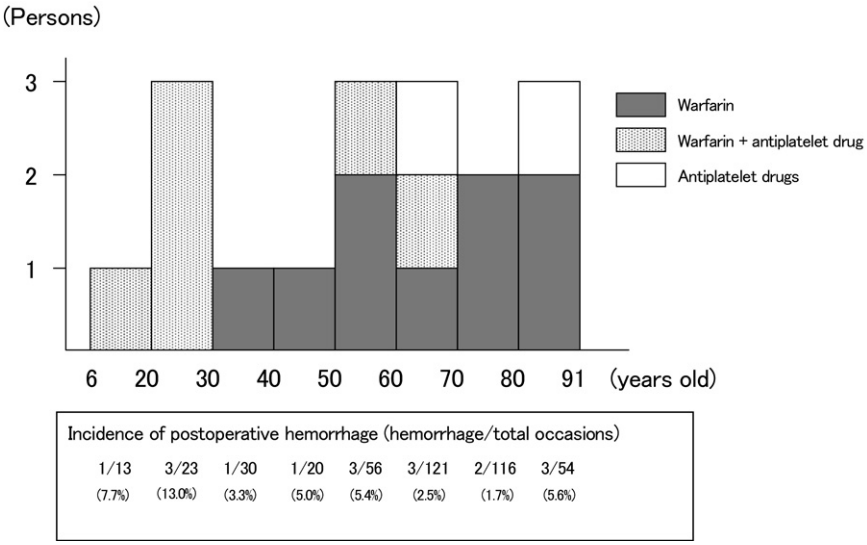


**FIGURE 1.** Distribution of patient age. The ages of the 17 patients with postoperative hemorrhage ranged from 19 to 85 years (mean, 54.9 ± 21.8 years). No significant differences existed in incidence of postoperative hemorrhage among age groups ($\chi^2 = 7.86$, $P = .25$).

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whom hemorrhage developed 5 days after tooth extraction, INR values were markedly prolonged postoperatively, and blood oozed from the extraction wound. Hemorrhage was stopped by local hemostatic measures and by correcting INR values with vitamin K administration. In a patient in whom hemorrhage developed 10 days after tooth extraction, the upper right first molar extraction caused oroantral fistula in the oral cavity, which was closed by use of a buccal flap. On day 10 of an INR value greater than 3.0, right nasal hemorrhage was seen but hemorrhage stopped by correction of INR values through warfarin dose reduction.

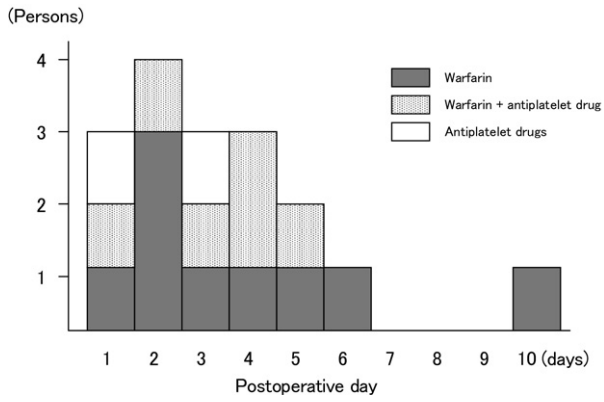


**FIGURE 2.** Distribution of postoperative onset of hemorrhage. The timing of onset of postoperative hemorrhage ranged from 1 to 10 days after tooth extraction. Median onset was 3 days (interquartile range, 2-4.5 days).

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Among the 15 patients receiving warfarin therapy, INR at the time of tooth extraction ranged from 1.50 to 2.96. Among the 12 patients in whom INR was measured at the time of postoperative hemorrhage, INR ranged from 1.50 to 4.42 in 11 patients, with INR being unable to be measured because of marked prolongation in 1 patient (7 [58.3%] of the 12 patients showed INR ≥3.0). The median INR value was 2.24 at the time of tooth extraction (interquartile range, 2.00-2.40) and 3.30 at postoperative hemorrhage (interquartile range, 2.14-3.53). Although no significant difference was seen ($P = .060$), INR at the time of hemorrhage tended to be greater when compared with that at the time of extraction (Fig 3).

As for local hemostatic measures at the time of postoperative hemorrhage, among the 15 patients receiving warfarin therapy, hematoma removal, compression, oxidized cellulose insertion, and resuturing were performed on 12 patients (12 of 15 [80.0%]) and electrocautery and/or splint placement was also used in 6 patients (6 of 15 [40.0%]). Hemostasis was achieved by compression alone in only 1 patient (1 of 15 [6.7%]). In 7 patients in whom INR was prolonged at the time of postoperative hemorrhage, values were corrected by reducing or discontinuing the warfarin dose, and vitamin K was administered to 1 patient. In the 2 patients receiving antiplatelet therapy, hemostasis was obtained by compression alone (Fig 4). Among the patients in whom postoperative hemorrhage developed, no severe hemorrhage requiring transfusion was seen.

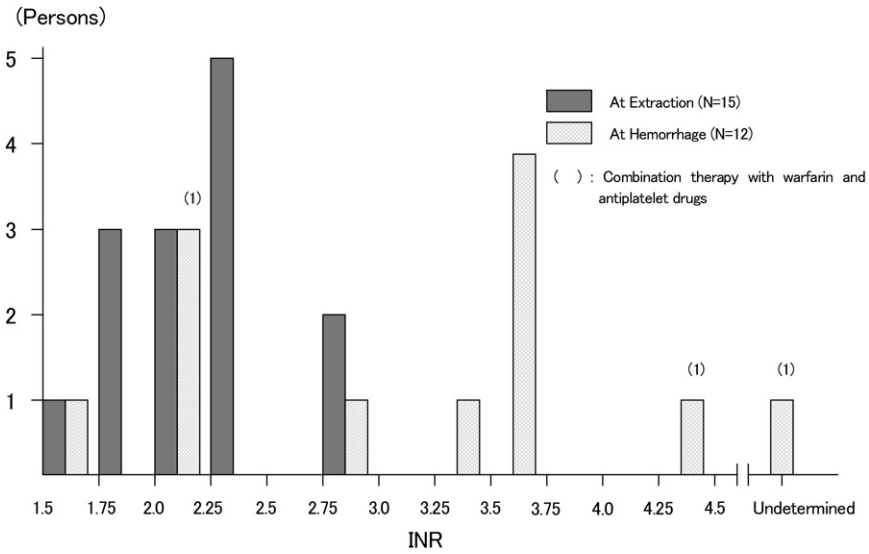


**FIGURE 3.** Distribution of INR values. The median INR value was 2.24 at the time of tooth extraction (interquartile range, 2.00-2.40) and 3.30 at postoperative hemorrhage (interquartile range, 2.14-3.53). Although no significant difference was seen ($P = .060$), INR at the time of hemorrhage tended to be greater when compared with that at the time of extraction.

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## ANALYSIS OF FACTORS AFFECTING POSTOPERATIVE HEMORRHAGE

Of the 433 tooth extractions, 416 extractions that did not result in postoperative hemorrhage and 17 extractions that resulted in hemorrhage were compared (Table 2). No significant differences existed between the 2 groups in the following factors: age; gender; antithrombotic therapy regimen (warfarin monotherapy, warfarin

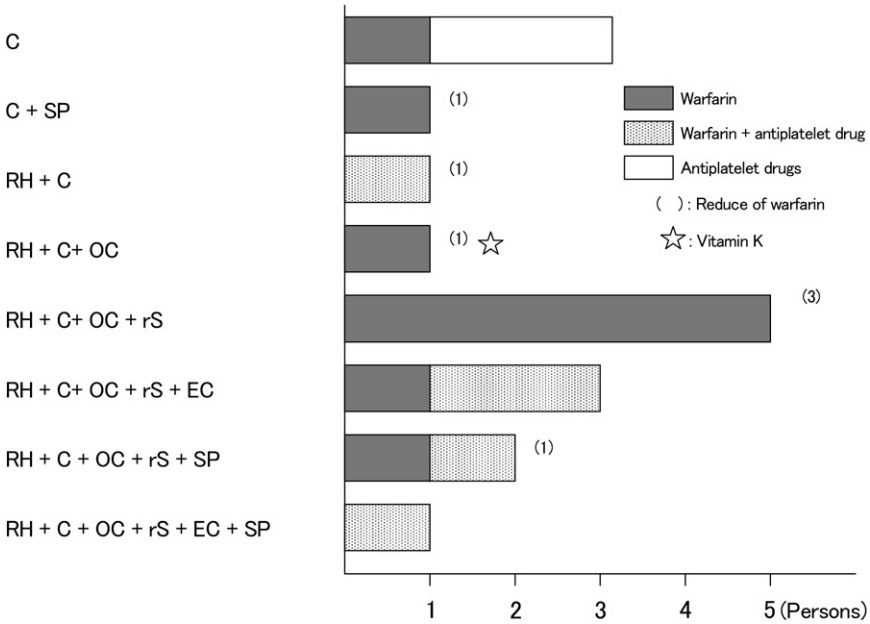


**FIGURE 4.** Local hemostasis for hemorrhage. Among the 15 patients receiving warfarin therapy, hematoma removal, compression, oxidized cellulose insertion, and resuturing were performed on 12 patients and electrocautery and/or splint placement was also used in 6 patients. In 7 patients with prolonged INR at the time of postoperative hemorrhage, values were corrected by warfarin dose adjustment. (C, compression; SP, splint; RH, removal of hematoma; OC, oxidized cellulose; rS, resuture; EC, electrocautery.)

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and antiplatelet combination therapy, and antiplatelet monotherapy); INR value at the time of tooth extraction (only in patients receiving warfarin therapy); and mean number of extracted teeth. The incidence of postoperative hemorrhage was 8.6% (8 of 92 patients) for surgical tooth extraction (vs 2.6% [9 or 341 patients] for simple tooth extraction) and 7.7% (7 of 91 patients) for acute inflammation (vs 2.9% [10 of 342 patients] without acute inflammation). Significant differences existed in relation to type of tooth extraction ($P = .008$) and acute inflammation findings ($P = .007$). The incidence of postoperative hemorrhage was higher in the presence of surgical tooth extraction and acute inflammatory findings.

## Discussion

On the basis of the results of this study on factors associated with onset of postoperative hemorrhage after tooth extraction in patients receiving antithrombotic therapy, the incidence of total postoperative hemorrhage was 3.9%, and it was significantly higher for surgical tooth extraction and acute inflammation. In more than 90% of patients with postoperative hemorrhage, hemorrhage occurred within 6 days (median, 3 days). As far as local hemostatic measures were concerned, many patients receiving warfarin therapy required not only hematoma removal, compression, oxidized cellulose insertion, and resuturing, but also electrocautery and/or splinting.

In patients receiving antithrombotic therapy, postoperative hemorrhage occurred in all age groups from 19 to 85 years, and no marked differences existed in incidence among the age groups. Bailey and Fordyce reported[19] that postoperative hemorrhage occurred within 5 days of tooth extraction, but not after 6 days. In our study most hemorrhages occurred within 6 days of tooth extraction, and hemorrhage occurred at more than 7 days after extraction only in a patient with factors in addition to tooth extraction (hemorrhage from the maxillary sinus). Therefore, when extracting teeth in patients receiving antithrombotic therapy, special attention must be paid to hemorrhagic events within 6 days of tooth extraction.

No significant difference existed between INR values at the time of extraction and those at the time of hemorrhage in patients with postoperative hemorrhage. INR thus could not be confirmed as a risk factor associated with postoperative hemorrhage. However, INR value at the time of postoperative hemorrhage was prolonged, at greater than 3.0, in about 60% of such patients, and statistical analysis also showed a tendency for prolonged INR values greater than 3.0. Al-Mubarak et al[7] reported that INR values greater than 3.0 significantly increased postoperative hemorrhage the day after tooth extraction, supporting the present results. In these patients, warfarin dose adjustment and vitamin K administration were required in addition to local hemostatic procedures. INR values are known to increase after tooth extraction,[20] and antibiotics and nonsteroidal antiinflammatory drugs may be involved.[9,10] Therefore we recommend not only minimizing the dosage of these drugs but also periodically measuring INR values after surgery and adjusting the warfarin dose as needed.

As for local hemostatic measures, hemostasis could not be achieved by compression alone in many patients receiving warfarin therapy. In about 80% of such cases, hematoma removal, compression, oxidized cellulose insertion, and resuturing were needed, and electrocautery and/or splinting were also required in 40% of cases. Conversely, for patients receiving antiplatelet monotherapy, hemostasis was obtained with compression alone. According to past studies, the incidence of postoperative hemorrhage in patients receiving warfarin therapy was 2% to 26%,[2,4-8,11-13] as compared with 0% to 2% in patients receiving antiplatelet drug therapy.[12,21-24] Bleeding tendency is thus more likely for warfarin, and more thorough local hemostatic measures are required.

In Western countries, when teeth are extracted in patients undergoing antithrombotic therapy, tranexamic acid mouthwash (2 minutes per time, 4 times per day) is recommended during the first 2

**Table 2. COMPARISON OF FACTORS FOR POSTOPERATIVE HEMORRHAGE**

| | Postoperative Hemorrhage | | Statistical Analysis |
|---|---|---|---|
| | Absent (n = 416) | Present (n = 17) | |
| Age (yr) | 61.8 ± 17.5 | 54.9 ± 21.8 | $P = .21$ |
| Gender (male/female) | 257/159 | 12/5 | $P = .46$ |
| Antithrombotic therapy (warfarin/warfarin + antiplatelet drug/antiplatelet drug) | 210/67/139 | 9/6/2 | $P = .31$ |
| INR value at tooth extraction | 2.03 (1.65-2.31) | 2.24 (2.00-2.40) | $P = .064$ |
| Mean No. of extracted teeth | 1.81 ± 1.30 | 2.18 ± 1.19 | $P = .26$ |
| Type of tooth extraction (simple/surgical) | 332/84 | 9/8 | $P = .008$ |
| Acute inflammatory findings (-/+) | 332/84 | 10/7 | $P = .007$ |

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postoperative days to control excessive bleeding.[9,10] When this technique was used in our study, the incidence of postoperative hemorrhages could be suppressed by use of simple hemostatic measures.

Surgical tooth extraction and acute inflammation were factors significantly associated with postoperative hemorrhage in patients receiving antithrombotic therapy, but no significant differences were seen in age, gender, antithrombotic therapy regimen, INR value at the time of tooth extraction, or mean number of extracted teeth. Regarding dental treatment in patients receiving antithrombotic therapy, Scully and Wolff[17] observed that, in patients receiving warfarin therapy, inflammation such as gingivitis increased the risk for hemorrhage. Our findings provided supporting statistical data. Whereas the incidence of postoperative hemorrhage is not that high for surgical extraction (8.6%) and acute inflammation (7.7%), associations of these factors with onset need to be kept in mind.

According to a past study, the incidence of severe hemorrhagic events such as intracranial hemorrhage in patients receiving antithrombotic therapy was 1.21% for single antiplatelet drug therapy, 2.00% for dual antiplatelet drug therapy, 2.06% for warfarin monotherapy, and 3.56% for warfarin and antiplatelet combination therapy.[25] When compared with single antiplatelet drug therapy, the onset of hemorrhagic complications was about twice as likely for dual antiplatelet drug therapy or warfarin monotherapy and about 3 times as likely for warfarin and antiplatelet combination therapy.[25] Furthermore, when INR values are 3.0 or greater (or ≥2.6 for the elderly), hemorrhagic events are reportedly increased.[26] Unlike other fields, local hemostatic measures could be thoroughly performed for tooth extraction. As a result, no marked differences were seen in the incidence of postoperative hemorrhage in relation to antithrombotic therapy regimen.

On the basis of these findings, a high degree of invasiveness (surgical tooth extraction) and acute inflammatory findings appear to be associated with significantly increased incidence of postoperative hemorrhage in patients receiving antithrombotic therapy. In most cases, postoperative hemorrhage occurred within 6 days of surgery, and in about 60% of cases, INR values were prolonged at 3.0 or greater. Compared with patients receiving antiplatelet drug therapy, more thorough local hemostatic measures are required for patients receiving warfarin therapy.

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