Comparison of the Effects of Warfarin and Heparin on Bleeding Caused by Dental Extraction: A Clinical Study

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Purpose: Replacement of warfarin with heparin for dental extractions in patients on long-term warfarin therapy is associated with wasted time, consumed labor, and increased treatment expenses. The aim of this study was to evaluate the safety of dental extraction without altering the warfarin regimen in patients with an international normalized ratio from 1 to 4.

Patients and Methods: Forty patients who underwent tooth extraction were divided into 4 groups: continuation of warfarin without interruption (group 1), warfarin bridged with low-molecular-weight heparin (group 2), warfarin bridged with unfractionated heparin (group 3), and a control group of healthy individuals (group 4). Total amount of bleeding (milligrams) was measured for 20 minutes after tooth extraction. International normalized ratio values on the operative day and number of extra gauze swabs used for bleeding control in the first 48 hours were recorded for each patient. Results were statistically analyzed by analysis of variance, Fisher least-significant difference post hoc test, Pearson correlation, χ^2 test, and Student *t* test.

Results: Mean amounts of bleeding were 2,486 ± 1,408; 999 ± 425; 1,288 ± 982; and 1,736 ± 876 mg for groups 1, 2, 3, and 4, respectively. There was no severe postoperative bleeding in any patient and the number of used extra gauze swabs did not differ significantly among groups.

Conclusion: With the aid of local hemostatic agents, dental extraction in patients receiving warfarin who have an international normalized ratio from 1 to 4 could be carried out without a significant risk of bleeding and without altering the anticoagulant regimen.

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Lifelong anticoagulation therapy is indicated for several types of cardiologic conditions against the risk of thromboembolism, including atrial fibrillation, artificial heart valves, risk of deep vein thrombosis, rheumatic heart valve disease, and pulmonary embolism.[1] Warfarin is usually the drug of choice for long-term anticoagulation therapy. It deters clot formation by inhibiting vitamin K-dependent synthesis of clotting factors.[2] The perioperative management of patients on warfarin treatment and undergoing an oral surgical procedure is a common and challenging clinical problem. Although dental extractions are considered relatively minor surgical procedures and associated with little blood loss, warfarin therapy may still increase the risk of excessive bleeding during or after extraction.[3]

The decision on how to manage the patients on warfarin therapy before dental extraction is determined according to a patient's current international normalized ratio (INR) and a physician's recommendations. Commonly used protocols are tooth extraction without interruption of warfarin therapy, interruption of warfarin therapy, and interruption of warfarin and bridging anticoagulation with low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH).[3] Interruption of warfarin therapy ex-

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poses patients to an increased risk for thromboembolic events, which can result in major disability or death. Thus, bridging with LMWH/UFH is required for patients at high risk of a thromboembolic event. However, this protocol is associated with increased expense, consumed time, and labor. Several prospective controlled studies have compared the outcomes of different protocols for dental extractions.[4-12] These studies determined bleeding complications by subjective measurement methods, which are based on patients' feedback or clinicians' observations. To our knowledge, no clinical study has used quantitative data to evaluate the outcomes of dental extraction in patients on a warfarin regimen.

Heparin is an indirect anticoagulant, showing its anticoagulant action by activating antithrombin, which is an endogenous inhibitor of various clotting factors.[13] Heparin is a highly sulfated mucopolysaccharide, with a heterogeneous molecular weight of 5,000 to 30,000 Da in its UFH form.[14] LMWH is derived from UFH by chemical or enzymatic depolymerization. LMWH has a similar mechanism of anticoagulant action, with more predictable pharmacokinetic and pharmacodynamic properties, a longer half-life, and a lower risk of nonhemorrhagic side effects compared with UFH.[13]

The aim of this study was to compare the bleeding patterns of dental extraction with or without altering the warfarin regimen in patients with a prosthetic heart valve and an INR from 1 to 4.

Patients and Methods

This clinical, prospective, and controlled study was conducted in 40 adult patients requiring dental extractions who were admitted to the Faculty of Dentistry, Department of Oral and Maxillofacial Surgery and the Faculty of Medicine, Department of Cardiology, Çukurova University from 2004 through 2006. Three study groups and 1 control group were established: patients on warfarin treatment without interruption of warfarin therapy perioperatively (group 1), patients on warfarin treatment and warfarin bridged with LMWH perioperatively (group 2), patients on warfarin treatment and warfarin bridged with UFH perioperatively (group 3), and healthy individuals receiving no medication (group 4). The study was approved by the medical ethical committee of Çukurova University.

At the first visit, a full medical history was taken, and radiographic and clinical examinations were performed. Patients were informed about the study, and an informed consent form was signed by the patients who agreed to participate. Patients were scheduled for tooth extraction. A preoperative INR was measured for all patients except the control group on the day of operation. If a patient's INR was >4.0 on the day of operation, extraction was postponed until the INR level was <4.0 according to medical personnel. Extractions were performed in the clinics of Faculty of Dentistry, Department of Oral and Maxillofacial Surgery. Patients in groups 1 through 3 who were at risk of endocarditis underwent oral antibiotic prophylaxis in accordance with American Heart Association guidelines.[15] Patients in group 1 were hospitalized for 1 day and patients in groups 2 and 3 were hospitalized for 3 or 4 days for perioperative medical management.

EXTRACTION PROCEDURE

Dental extractions were performed under local anesthesia using 3% prilocaine without adrenalin (Citanest, Eczacıbaşı Ilaç San Lim Şti, Istanbul, Turkey). Before extraction, the oral cavity was protected from salivary secretions by placing sponge gauze pads on the orifices of the bilateral parotid, submandibular, and sublingual gland ducts and by continuous suctioning with surgical aspirators. All extractions were performed by the same surgeon using laxators and forceps. Extractions that were complicated during the operation and required a flap elevation were excluded from the study. At completion of the extraction, tamponades were used to staunch bleeding from the extraction sockets, and these were subsequently changed for gauze swabs for 20 minutes. Each gauze swab was pressed gently over the extraction socket and changed for a new swab once it absorbed a sufficient amount of blood. The weights of gauze swabs used before and after tamponade were measured using a fine electronic weight measurement device (Shimadzu, Kyoto, Japan; Fig 1). Weight differences before and after tamponade gauzes were interpreted as the amount of bleeding (AOB; milligrams). After 20 minutes of tamponade, each extraction socked was packed with oxycellulose dressing (Surgicel; Ethicon, Neuchatel, Switzerland) and sutured with 3.0 silk sutures (Doğsan, Istanbul, Turkey). A new gauze swab was placed over the surgical area, and the patient was instructed to bite on it for 1 hour. Patients were given additional gauze swabs to be used if bleeding continued and advised to present to the emergency department for severe bleeding. They were asked to count the number of extra gauze swabs used for bleeding control during the first 48 hours. Paracetamol 500 mg was prescribed for pain control. No postoperative antibiotics or mouthwashes were prescribed. All patients were clinically examined and questioned about the number of gauze pads used for bleeding control, and the sutures were removed 48 hours after extraction. Patients were recalled at 7 days postoperatively for evaluation of wound healing.

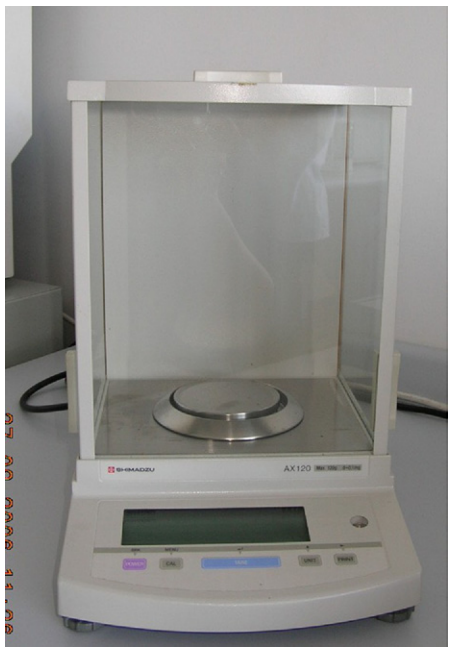

FIGURE 1. Photograph of the fine electronic weight measurement device used in the present study.

Karslı et al. Warfarin and Heparin in Dental Extraction. J Oral Maxillofac Surg 2011.

MEDICAL MANAGEMENT OF GROUPS 2 AND 3

Patients in groups 2 and 3 stopped warfarin use 3 days preoperatively. They were hospitalized 3 days before the extraction for preoperative medical management. Patients in the 2 groups started to receive heparin administration once the INR was <2.0. Activated partial thromboplastin time was maintained at 2 to 3 times higher than the normal range for patients in group 2 by administering subcutaneous LMWH and at 2.5 to 3.5 times higher than the normal range in group 3 by administering intravenous UFH. Dental extractions were performed 24 hours after the last heparin administration for patients receiving heparin by subcutaneous route and 6 hours after the last dose for patients receiving heparin by the intravenous route. Heparin treatment was continued after hemostasis was provided. Forty-eight hours after extraction, heparin was stopped and the patients continued receiving warfarin. The cost of the medical treatment also was determined for each group.

STATISTICAL ANALYSIS

Data retrieved from each group were compared using analysis of variance, the Fisher least-significant difference post hoc test, *t* test, Pearson correlation test, and χ^2 test. Analyses were performed using SPSS 10.5 (SPSS, Inc, Chicago, IL).

Results

Fifty-two tooth extractions were performed in 40 patients (21 male, 19 female). The mean age for all patients was 43.5 years (range, 26 to 72 years). Of 40 patients, 27 were on long-term warfarin therapy because of an artificial heart valve and 13 were healthy individuals. All patients on warfarin were under routine follow-up by the cardiology department and warfarin dose was regulated monthly according to current INR value and any history of spontaneous bleeding. Only 1 tooth was extracted from each patient in 1 session. To equalize the number of extracted teeth for each group, some patients on warfarin who required multiple dental extractions presented in a different study group for the other extraction. Thus, 13 extractions were performed for each group. Complicated surgical extractions were needed for 1 extraction in group 2 and for 2 extractions in group 3. Therefore, these extractions were excluded from the study. A summary of patient demographics and distribution of extracted teeth for each group are presented in Table 1.

All patients tolerated the procedures well without any severe intraoperative or postoperative bleeding. All patients who received antibiotic prophylaxis against the risk of bacterial endocarditis tolerated the medications well and none had signs or symptoms of cardiac complications. None of the patients presented to the emergency department or called the surgeon for any emergency situations. None of the patients had a hypersensitivity reaction against the medications used before, during, or after the procedure. None of the extraction sockets developed dry socket, hematoma, or postoperative infection.

Mean AOBs were 2,486 ± 1,408; 999 ± 425; 1,288 ± 982; and 1,736 ± 876 mg for groups 1, 2, 3, and 4, respectively (Fig 2). Mean INR values were 2.6 ± 0.7, 1.6 ± 0.4, and 1.6 ± 0.4 for groups 1, 2, and 3, respectively. AOB and INR values showed significant differences among groups according to 1-way analysis of variance ($P = .002$ for AOB; $P = .001$ for INR values; Table 2).

The Fisher least-significant difference post hoc test was used for dual comparisons among the particular groups. Differences in AOB values were significant between groups 1 and 2 ($P = .001$) and between groups 1 and 3 ($P = .008$) and insignificant between groups 2 and 3 ($P = .509$). Similarly, differences in INR values were significant between groups 1 and 2 ($P = .001$) and between groups 1 and 3 ($P = .001$) and insignificant between groups 2 and 3 ($P = .794$).

For comparison of AOB values between groups 1 and 4, the *t* test was used. There was an increase in AOB values in group 1 compared with group 4. How-

Table 1. DEMOGRAPHICS OF THE PATIENTS AND DISTRIBUTION OF EXTRACTED TEETH FOR EACH GROUP

Patient Number	Age (yrs)/ Gender	Group 1 (Tooth Extracted)	Group 2 (Tooth Extracted)	Group 3 (Tooth Extracted)	Group 4 (Tooth Extracted)
1	45/M	18		3	
2	51/M	18	19		
3	45/M	11			
4	32/F	9		29	
5	62/M	18			
6	55/M	27	18		
7	69/F	22		4	
8	48/F	17			
9	33/F	5			
10	43/F	30		16	
11	40/M	31			
12	34/M	12			
13	44/F	11	18		
14	32/F		6		
15	41/M		19	2	
16	45/F		15		
17	26/F		28		
18	31/M		10	12	
19	50/F		11	18	
20	42/M		20		
21	52/F		28	6	
22	72/M		14	4	
23	67/F			26	
24	45/M			2	
25	28/M			14	
26	51/M			30	
27	42/F			10	
28	32/M				7
29	29/M				18
30	50/F				26
31	33/M				31
32	41/F				12
33	43/F				3
34	61/M				14
35	37/M				19
36	51/F				14
37	40/M				30
38	31/F				31
39	35/F				16
40	42/M				5

NOTE. Teeth were coded according to the Universal Tooth Numbering System; 25 teeth were extracted from the mandible and 27 from the maxilla. Group 1: warfarin continued; group 2: warfarin bridged with low-molecular-weight heparin; group 3: warfarin bridged with unfractionated heparin; group 4: healthy individuals.

Abbreviations: F, female; M, male.

Karslı et al. Warfarin and Heparin in Dental Extraction. J Oral Maxillofac Surg 2011.

ever, the difference was not statistically significant ($P = .79$).

The Pearson correlation test showed a positive correlation between patients' INR and AOB values ($P = .01$). There was no significant difference among groups in the use of extra gauze swabs according to the Pearson χ^2 test ($P = .468$; Table 3). The mean costs of medical management of patients were 160 Turkish liras for group 1; 930 for group 2; and 1,910 for group 3. This cost included the fees for medications, hospital stay, and laboratory tests.

Discussion

Warfarin is the most commonly used anticoagulant, and management of patients on warfarin undergoing dental extractions presents a dilemma.[8,11] This study evaluated the bleeding tendency and postoperative outcomes of dental extractions in patients on long-term warfarin therapy who were treated with different perioperative anticoagulation protocols.

Administration of epinephrine containing local anesthetics is not an absolute contraindication for pa-

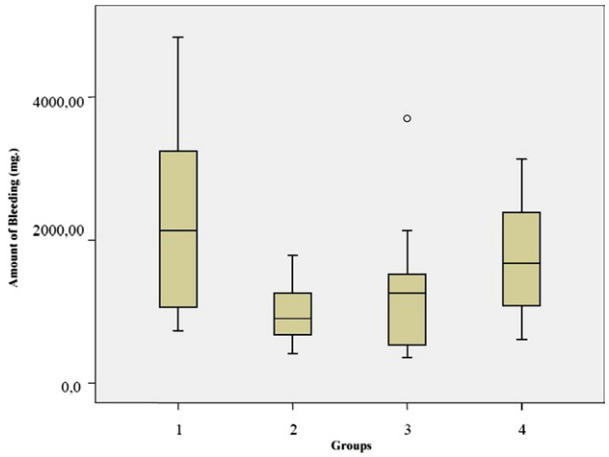

FIGURE 2. Graphic showing the mean amounts of bleeding among groups.

Karslı et al. Warfarin and Heparin in Dental Extraction. J Oral Maxillofac Surg 2011.

tients with cardiac disease.[16] Nonetheless, a 3% prilocaine solution without epinephrine was chosen to eliminate the vasoconstrictive effects of epinephrine on extraction sockets, which may deteriorate standardization of the procedure. To achieve standard conditions, extractions requiring flap elevations were not included in the study. Pressure with gauze swabs on the extraction socket is a standard application for providing effective hemostasis, and the amount of blood absorbed by the gauze swab is a good indicator of bleeding.[17] The amount of immediate postoperative bleeding was determined by measuring the weights of the gauze swabs before and after use within a certain period (20 minutes). Early postoperative bleeding was determined based on the count of extra gauze swabs within 48 hours after extraction. The method used for determination of immediate postoperative bleeding might be considered difficult to perform because of possible salivary contamination. A dry environment was created by isolating all salivary gland orifices and continuous meticulous suctioning during the measurement period. Previous studies have evaluated the AOB after dental extraction mostly by subjective evaluation methods, which were based on the clinicians' or patients' observations.[6,8,9,11,18] To our knowledge, no study has provided quantitative data for comparison of the postoperative AOB in patients on warfarin. A fine electronic balance was used for determination of AOB, which interpreted the AOB as milligrams of blood loss.

In the present study, patients on warfarin and with prosthetic heart valves underwent 3 different treatment protocols for dental extractions. Oxidized cellulose was used locally as a hemostatic agent. Other frequently used hemostatic agents include resorbable gelatin sponge, collagen sponge, tranexamic acid, and fibrin glue.[18-20] In all cases, including group 1, which consisted of patients with higher INRs, hemostasis was successfully established locally by packing the extraction sockets with oxidized cellulose and suturing with 3.0 silk sutures.

The contemporary literature contains strong evidence of safe methods for dental extractions in pa-

Table 2. SUMMARY OF AMOUNT OF BLEEDING IN MILLIGRAMS (INTERNATIONAL NORMALIZED RATIO) FOR EACH GROUP

Patient Number	Group 1 (Warfarin Not Stopped) (n = 13)	Group 2 (Warfarin Replaced With LMWH) (n = 12)	Group 3 (Warfarin Replaced With UFH) (n = 11)	Group 4 (Healthy Individuals) (n = 13)
1	4,513.7 (3.23)	877.5 (1.26)	667.5 (1.6)	2,287.6
2	901.8 (2.02)	1,610.5 (0.98)	1,262.6 (2.51)	2,384.1
3	4,166.8 (3.27)	1,142.3 (1.8)	887.3 (1.0)	1,673.3
4	2,127.7 (2.05)	1,265.4 (1.2)	2,129.0 (1.62)	2,493.4
5	4,838.6 (3.19)	899.7 (1.22)	1,644.0 (1.31)	1,350.6
6	1,015.7 (3.51)	621.2 (1.4)	1,399.5 (1.2)	620.2
7	2,020.3 (1.55)	910.8 (1.64)	3,698.8 (1.89)	3,124.4
8	3,023.5 (3.86)	407.5 (1.6)	399.8 (1.169)	2,293.2
9	1,936.4 (3.14)	1,246.8 (2.1)	394.1 (1.71)	1,082.7
10	2,742.9 (1.89)	496.4 (2.0)	1,337.4 (2.0)	2,804.4
11	3,238.1 (2.03)	734.0 (2.2)	357.2 (2.28)	1,193.7
12	1,056.8 (2.13)	1,784.6 (1.8)		612.5
13	737.3 (2.86)			654.7
Mean±SD	2,486 ± 1,408* (2.6 ± 0.7†)	999 ± 425* (1.6 ± 0.4†)	1,288 ± 982* (1.6 ± 0.4†)	1,736 ± 876*

Abbreviations: LMWH, low-molecular-weight heparin; SD, standard deviation; UFH, unfractionated heparin.
*Significant difference between groups according to 1-way analysis of variance ($P = .002$).
†Significant difference between groups according to 1-way analysis of variance ($P = .001$).

Karslı et al. Warfarin and Heparin in Dental Extraction. J Oral Maxillofac Surg 2011.

Table 3. NUMBER OF PATIENTS WHO DID OR DID NOT USE EXTRA GAUZE SWABS DURING FIRST 48 HOURS FOR BLEEDING CONTROL

	Group 1 (n)	Group 2 (n)	Group 3 (n)	Group 4 (n)
Patients who needed extra gauze swabs	6	3	3	3
Patients who did not need extra gauze swabs	7	9	8	10
Total	13	12	11	13

NOTE. No significant difference among groups in use of extra gauze swabs according to Pearson χ^2 test ($P = .468$).

Karslı et al. Warfarin and Heparin in Dental Extraction. J Oral Maxillofac Surg 2011.

tients with INR levels lower than 4.0, in which hemostasis is provided by local measures. Bajkin et al[11] compared the outcomes of simple dental extractions in 214 patients on warfarin. Half the patients continued warfarin therapy without interruption, whereas the other half underwent bridging therapy with LMWH. The researchers did not find any significant difference in postoperative bleeding between the 2 groups. They claimed that patients on warfarin with an INR lower than 4.0 can undergo simple dental extraction safely without discontinuing the drug. Salam et al[12] evaluated postoperative bleeding in 150 patients on warfarin who continued warfarin treatment on the day of extraction. Patients' INR values were lower than 4.0. The investigators reported no difference in postoperative bleeding between patients whose INRs were lower than 2.5 and patients whose values were above 2.5. A randomized study by Evans et al[6] showed that dental extractions cause clinically tolerable bleeding in patients on warfarin with an INR level below 4.0. Similar results have been reported in other studies.[7-10,18] From the results of these studies, it can be concluded that continuing the regular dose of warfarin does not confer an increased risk of bleeding for dental extractions if a patient's INR is below 4.0 and local hemostatic measures are undertaken. The findings of the present study similarly showed that continuing warfarin in patients with INR levels below 4.0 did not result in significantly increased postoperative bleeding, according to patients' feedback and the number of gauze swabs used.

One distinction of the present study from the previous studies is that the amount of immediate postextraction bleeding was determined by measuring the AOB. All previous studies determined the course of postoperative bleeding after application of local hemostatic agents. The amount of blood loss during the first 20 minutes after extraction was estimated before packing the extraction socket with oxycellulose. Thus, the direct effects of different anticoagulation treatments on patients' bleeding patterns could be evaluated. The results of the AOB measurements confirm the statement—simple dental extractions are associated with little blood loss—made in the clinical guidelines of American Chest Physicians.[3] The maximum AOB occurred in group 1, which resulted in 2.4 g of blood loss in the first 20 minutes after extraction under gentle gauze swab pressure. This AOB might be considered insignificant compared with other major general surgical procedures. Mean AOB values in patients continuing warfarin therapy were significantly higher than in patients undergoing bridging therapy and nonmedicated patients. After packing the extraction socket with oxycellulose and suturing, an efficient hemostasis was provided for all patients. None of the patients presented to a hospital or called the surgeon because of excessive bleeding. The number of gauze swabs used did not differ significantly among groups.

The present study also compared 2 different heparin preparations used for bridging therapy. For long-term use, LMWH has gradually been replacing UFH because of its advantageous pharmacologic properties and the subcutaneous administration by a patient without monitoring activated partial thromboplastin time.[21] Although the cost of the LMWH preparation is more than UFH, intravenous administration of UFH requires a hospital setting, which increases treatment cost.[21] Recent clinical studies have implied that subcutaneous UFH is as effective and safe as LMWH in the treatment of acute venous thromboembolism.[22] In the present study, the average cost for 3- to 4-day medical management for procedures undertaken with intravenous UFH was about 2 times more expensive than subcutaneous LMWH treatment. To maintain a stable activated partial thromboplastin time, continuous intravenous UFH infusion is required with strict monitoring, which increases the cost of treatment. Despite the lower cost and better tolerance by patients, a similar clinical outcome was achieved with LMWH and UFH in the present study. There was no significant difference in AOB and INR values and the number of used gauze swabs between patients treated with LMWH and UFH. Thus, subcutaneous LMWH appears to be a better treatment choice than intravenous UFH for patients on warfarin undergoing bridging therapy for dental extraction.

The INR values showed a significant correlation with the AOB in the present study. Some clinical studies have evaluated the effects of INR value on

postoperative bleeding complications. Morimoto et al[7] divided patients who were on warfarin therapy and undergoing dental extractions into 4 groups according to their INR levels. Although incidences of postoperative bleedings were higher in patients with higher INRs, the differences were not statistically significant. Sacco et al[18] compared postoperative bleeding events after certain oral surgical procedures, including cyst enucleations in patients with INR values lower and higher than 2.0. Of 511 procedures, there were 15.1% bleeding events in patients with an INR above 2.0 and 9.2% events in patients with an INR below 2.0. The difference was statistically insignificant. The present study suggests that higher INR values result in greater blood loss after dental extraction. However, with efficient local hemostatic measures, the postoperative course will be uneventful in patients with lower INR values.

One conflicting aspect of the present study is the bridging regimen applied in groups 2 and 3. The patients receiving LMWH were hospitalized for 3 days, which may be considered over-management, and they underwent dental extraction 24 hours after the last LMWH dose, which is also a relatively long period. Subcutaneous LMWH administration usually does not require hospitalization of the patient.[3] Patients were hospitalized particularly for this study for close-up and continuous monitoring of their INRs. It is advised to stop subcutaneous LMWH therapy 12 to 24 hours before dental extractions for patients at high risk of thromboembolism.[23] The standard hospital management was used for this study, in which dental extractions are conducted 24 hours after the last dose of subcutaneous LMWH. Another aspect is the establishment of a treatment group consisting of patients receiving intravenous UFH for bridging therapy, which has been mostly abandoned by many clinics. Despite the loss of popularity of this regimen, it remains the most commonly used bridging regimen worldwide.[3] Therefore, this regimen was included in the present study.

According to the present results, efficient hemostasis can be provided with local measures by packing the extraction socket with oxycellulose and 3.0 silk sutures, and warfarin therapy should not be discontinued for simple tooth extractions when an INR value is below 4.0. Continuing warfarin is associated with more blood loss compared with bridging therapy with LMWH or UFH, but this amount of blood loss is clinically insignificant and does not require special attention. If bridging therapy is indicated because of relatively more complicated surgeries such as extraction of an impacted tooth, subcutaneous LMWH should be preferred over intravenous UFH because of its similar efficiency, lower treatment cost, and easier application. The INR value has a significant correlation with the amount of blood loss after extraction and presents a significant parameter for perioperative evaluation of patients on anticoagulation therapy.

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