Oral surgery in liver transplant candidates: a retrospective study on delayed bleeding and other complications

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Objective. Untreated dental infections pose a threat for immunocompromised liver transplant (LT) recipients. Therefore, pretransplant dental evaluations are recommended. However, risk of bleeding should be considered among patients with end-stage liver disease, and prophylactic blood transfusions may be used to prevent bleeding. We performed a retrospective study of the incidence of and risk factors for oral surgery–related bleeding in candidates for LT and hypothesized that complications may occur despite preoperative and perioperative hemostatic actions.

Study Design. One hundred thirty-four patients who had tooth extractions performed by oral and maxillofacial surgeons before LT were studied. The primary endpoint was bleeding between 24 hours and 2 weeks after extraction. Bleeding risk was analyzed by preoperative platelet (PLT) count and international normalized ratio (INR). Invasiveness of procedures, severity of liver disease, PLT, INR, prophylactic transfusions of PLT, fresh frozen plasma, and tranexamic acid (TA) were included in univariate and multivariate logistic regression analyses to further assess risk.

Results. Twelve patients exhibited minor bleeding; four despite PLT $>100 \times 10^9$/L and INR <1.5. Increased bleeding associated with INR and prophylactic transfusions by univariate analysis; by multivariate analyses, prophylactic TA (odds ratio [OR] = 8.0; 95% confidence interval [CI] 1.7-37.0), and PLT (OR = 8.3; 95% CI 1.1-62.7) remained significant.

Conclusions. Most extractions were safe, but prophylactic transfusions did not ensure adequate hemostasis. Local hemostatic measures and close follow-up are warranted. (Oral Surg Oral Med Oral Pathol Oral Radiol 2016;121:490-495)

Pretransplant dental treatment is a prerequisite in many liver transplantation (LT) programs. This requirement aims to prevent posttransplant infectious complications, such as bacteremia and sepsis, which could be fatal in immunocompromised patients.[1,2] In particular, patients with chronic liver disease (CLD) have shown poor oral health with a high prevalence of dental infections in pre-LT dental evaluations.[3] Often, teeth with obvious severe infections are extracted after administering antibiotic prophylaxis. Although there is no scientific evidence in the literature to support antibiotic prophylaxis for this patient group, our clinic has adopted this protocol to prevent serious postoperative infectious complications in these high-risk patients. Patients with CLD also run a high risk of bleeding after oral surgery because of CLD-associated coagulopathy.[4] Reported incidences of bleeding after oral surgery in patients with CLD vary from 0% to 56%.[4-8] However, previous studies were limited by small cohorts (9-90 patients), and those patients often had well-compensated CLD.[6] Earlier studies that specifically studied LT candidates, that is, patients with advanced or end-stage liver disease, included only 23 to 36 patients.[4,5,7,8]

Platelets (PLT), fresh frozen plasma (FFP), and tranexamic acid (TA) are typically administered before oral surgery in an attempt to prevent bleeding despite the lack of firm evidence to support this strategy. It has been suggested that the risk of bleeding might be predicted by an elevated international normalized ratio (INR) or thrombocytopenia; therefore, prophylactic transfusions of FFP and PLT have been justified to prevent bleeding complications. Because of the high fibrinolytic activity in the oral cavity, systemic antifibrinolytics, such as TA, are sometimes used in addition to the local antifibrinolytics. However, the systemic

Statement of Clinical Relevance

International normalized ratio and platelet count do not reliably predict bleeding after tooth extractions in liver transplant candidates because of rebalanced hemostasis. Hence, routine prophylactic replacement therapy may be ineffective. Alternatively, local hemostatic measures and close postoperative follow-up by a skilled clinician are recommended.

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approach remains controversial because of the risk of thrombotic events. Nevertheless, the effect of these blood products lasts for only a few hours; consequently, they may not have an impact on delayed bleeding that can occur several days later.

The primary aim of the current retrospective study was to investigate the incidence and risk factors of bleeding complications following tooth extractions in candidates for LT. We also investigated the effects of preprocedural transfusions to prevent post−oral surgery bleeding. A secondary aim was to investigate other complications related to oral surgery. We hypothesized that complications might occur, despite preoperative and perioperative hemostatic actions.

MATERIALS AND METHODS

This retrospective study was conducted in agreement with the Declaration of Helsinki and was received exemption from institutional review board approval. The primary endpoint of the study was oral bleeding related to oral surgery that appeared within 2 weeks from surgery. Replacement therapy was considered effective when good hemostasis was achieved during the procedure and the patient did not show any delayed bleeding.

During 2000−2006, a total of 306 adult LTs were performed in Finland. Of these patients, 263 had dental evaluations before LT at the Department of Oral and Maxillofacial Diseases, Helsinki University Hospital, Helsinki, Finland. As part of routine practice before LT the Transplantation and Liver Surgery Clinic referred patients to an oral and maxillofacial (OMF) surgeon in our department for dental treatments.

We retrieved data from patient medical records, tomographic radiographs, and the hospital laboratory database. Medical records were reviewed when any oral surgery−related bleeding complication required hospital care. These events were considered bleeding complications in the present study. We defined "bleeding" as continuous or delayed bleeding, observed at least 24 hours following tooth extractions, which required a return visit to an OMF surgeon for treatment. The bleeding was recorded by either a medical doctor or nurse at the hospital ward. The amount of blood loss was not recorded.

Data collected from the patient records included type of liver disease, number of teeth, number of extracted teeth, number of difficult extractions (impacted wisdom teeth, representing invasive procedures), oral surgery related complications, and preoperative PLT and INR values, as well as intravenous (IV) preprocedural replacement therapies: PLT (8−16 IU), FFP (2−4 IU), and TA (1−3 g oral or IV administration). These replacement therapies were given prophylactically, based on the anesthesiologist's individual clinical assessment of bleeding risk, when the PLT count was low and the INR was high.

The Model for End-stage Liver Disease (MELD) was used to categorize patients in this study. MELD scores reflect the severity of liver disease, and they are used to predict the risk of death. The scores were calculated with the Mayo Clinic online calculator. The calculation included blood creatinine, bilirubin, and INR values recorded at the time the patient was listed for LT. The MELD equation assumed an upper limit of 350 μM for plasma creatinine.

Statistical analysis

Data were analyzed with PASW statistical software, version 17.0 (SPSS Inc., Chicago, IL). The χ^2 test was used to evaluate categorical variables, and the Mann−Whitney test was used for continuous variables. The effect of various factors on bleeding risk was assessed by univariate and multivariate logistic regression analyses. A two-sided $P < .05$ was considered significant.

RESULTS

Patient demographic characteristics are given in Table I. The final study population comprised 134 patients who required tooth extractions before LT. Most patients returned to the in-patient clinic for at least one night following tooth extractions. In some cases, patients stayed overnight at the Department of Oral and Maxillofacial Diseases. In either case, postoperative follow-up was readily available. TA was routinely used locally. It was applied in liquid form to saturate gauzes, which were then placed tightly over alveolar sockets after tooth extractions. Other local hemostatic measures were provided to all patients, including careful, tight suturing of the wounds and close follow-up in the recovery room.

One patient had acute liver failure, and all others had CLD. Of the patients, 12 exhibited bleeding complications more than 24 hours postoperatively, which required treatment from an OMF surgeon. In the present study, all bleeding complications were minor and fairly simple to treat. In most cases, bleeding occurred 1 to 2 days postoperatively, but one case exhibited excessive bleeding 8 days postoperatively. That patient had remained in the ward; thus, treatment was easily available. In cases of delayed bleeding, an OMF surgeon was called, and the alveolar socket was either resutured or local hemostatic agents were administered (e.g., with local TA surges/rinse or with gelatin sponges), and tight gauze pads were placed on bleeding alveolar sockets.

The average number of teeth extracted was five (range 1-20); four patients required full mouth

Table I. Basic characteristics of the study population

	All patients; n (%)	*Patients with bleeding; n (%)*	*Patients without bleeding; n (%)*	*P*
Patients	134	12	122	
Age	50 (11)	45 (12)	51 (11)	.088
Gender, male	54 (40)	6 (50)	48 (39)	.47
Etiology of liver disease				**.017**
Chronic liver disease				
PBC	20 (15)	3 (25)	17 (14)	
PSC	33 (25)	1 (8)	32 (26)	
Alcohol	27 (20)	4 (33)	23 (19)	
Cryptogenic cirrhosis	9 (7)	0 (0)	9 (7)	
Other cirrhosis*	23 (17)	3 (25)	20 (16)	
Tumor	14 (10)	0 (0)	14 (12)	
Other†	7 (5)	0 (0)	7 (6)	
Acute liver failure	1 (1)	1 (8)	0 (0)	
Platelet level (10^9/L), mean ± SD	134 (88)	114 (74)	136 (90)	.48
<100	66 (49)	6 (50)	60 (49)	.96
<50	13 (10)	3 (25)	10 (8)	.06
INR, mean (SD)	1.5 (0.6)	2.0 (1.2)	1.4 (0.5)	.08
>1.5	47 (35)	6 (50)	41 (34)	.26
>2.0	17 (13)	4 (33)	13 (11)	**.024**
MELD, mean (SD)	14.4 (8.2)	18.8 (9.8)	14.0 (7.9)	.12
Number of teeth, mean (SD)	25 (6)	26 (3)	25 (6)	.94
Number of extractions, mean (SD)	5 (4)	5 (3)	5 (4)	.79
≥6	46 (34)	4 (33)	42 (34)	
Number of difficult extractions	26 (19)	2 (17)	24 (20)	
Preprocedural hemostatic agents				
PLT	22 (16)	6 (50)	16 (13)	**.001**
FFP	28 (21)	6 (50)	22 (18)	**.009**
Tranexamic acid	23 (17)	7 (58)	16 (13)	**<.001**

PBC, Primary biliary cirrhosis; *PSC*, primary sclerosing cholangitis; *SD*, standard deviation; *INR*, international normalized ratio; *MELD*, Model for End-stage Liver Disease; *PLT*, platelets; *FFP*, fresh frozen plasma.
Bold values represent statistical significance.
*Other cirrhosis patients include those with autoimmune cirrhosis or viral hepatitis.
†Other patients include patients with biliary atresia or metabolic liver disease.

extractions. The number of teeth extracted or the difficulty of extractions did not correlate with bleeding episodes; three patients had bleeding even after simple extractions of one or two teeth. However, another three patients experienced bleeding after sinus perforations as a result of extraction of molars in the upper jaw.

Compared with patients with no bleeding, patients with bleeding tended to have higher mean MELD scores (19 vs 14), higher INRs (2.0 vs 1.4), and lower PLT counts (114 vs 136 × 10^9/L). Although these differences were not significant, a significantly higher proportion of patients with bleeding had INR >2.0, compared with those without bleeding (Table I). The etiology of liver disease significantly affected bleeding risk. Among the patients with primary biliary cirrhosis, alcohol cirrhosis, and other cirrhosis (those with autoimmune cirrhosis or viral hepatitis), a substantially higher proportion exhibited bleeding compared with groups with other etiologies, such as primary sclerosing cholangitis patients (11 vs 1, respectively).

Table II. Bleeding incidences according to different INR or platelet levels

	INR <1.5; n (%)	*INR >1.5; n (%)*	*P*
Platelet level (10^9/L)			
>100	4/54 (7)	2/14 (14)	.45
<100	2/33 (6)	4/33 (12)	.39
P	.81	.84	
>50	6/44 (14)	3/37 (8)	.99
<50	0/4 (0)	3/7 (43)	.067
P	.37	**.01**	

INR, International normalized ratio.
Bold values represent statistical significance.

Among all patients, prophylactic transfusions were administered as follows: 16% received PLT (mean 8 IU), 21% received FFP (mean 4 IU), and 17% received TA (mean 1 g × 3). In addition, one patient received prophylactic 1250 IU Fibrogrammin IV (purified concentrate of blood coagulation factor XIII; CSL Behring, UK) and 2 g fibrinogen (glycoprotein, factor I, which is converted into fibrin). Preprocedural transfusions were performed significantly more often in patients with bleeding than in patients without bleeding (Table I). In general, prophylactic FFP and PLT transfusions were administered when INR exceeded the threshold of 2.0 and PLT counts fell under 100 × 10^9/L. However, marked individual variations in these thresholds existed; therefore, these thresholds were relaxed on the basis of other contributing factors, including the type of operation, patient blood volume status, the degree of portal hypertension, a history of bleeding tendency, and the perceived bleeding risk.

When stratified by INR and PLT levels, the highest bleeding incidences occurred among patients with simultaneous INR >1.5 and PLT counts <50 × 10^9/L (Table II). Nonetheless, four patients exhibited bleeding, despite PLT counts >100 × 10^9/L and INRs <1.5. Regardless of the pre−oral surgery PLT level prophylactic PLT transfusions were associated with an increased risk of bleeding (Table III). A similar association was found between INR and prophylactic FFP transfusions, although this association was significant only among patients with INRs >1.5 (Table III).

In univariate logistic regression analyses, INR and prophylactic transfusion of hemostatic agents were associated with higher bleeding risk (Table IV). In the

Table III. Effect of preprocedural transfusion of platelets or FFP on bleeding incidences according to preprocedural platelet (10^9/L) or INR level

	Bleeding incidence; n (%)	*P*
PLT <100		**.004**
PLT transfusion	5/21 (24)	
No PLT transfusion	1/45 (2)	
PLT >100		**.001**
PLT transfusion	1/1 (100)	
No PLT transfusion	5/66 (8)	
INR >1.5		**.048**
FFP transfusion	5/22 (23)	
No FFP transfusion	1/25 (4)	
INR <1.5		.34
FFP transfusion	1/6 (17)	
No FFP transfusion	5/79 (6)	

FFP, Fresh frozen plasma; *INR*, international normalized ratio; *PLT*, platelets (shown in 10^9/L).
Bold values represent statistical significance.

multivariate analyses, prophylactic TA use (and PLT transfusion) remained significant (Table IV).

Other complications after oral surgery were rare. Four patients had high fever postoperatively, and they were treated with IV antibiotic therapy. Milder complications included one case with slight swelling in the facial region. In another instance, the medical status of a patient with cirrhosis worsened considerably after extraction of seven teeth, and the patient needed hospital treatment.

DISCUSSION

We aimed to investigate the incidence of bleeding complications from oral surgery among candidates for LT. We also wanted to investigate how preprocedural replacement therapy affected bleeding and whether the laboratory values typically used to indicate bleeding risk could predict bleeding risk in this group of patients.

This study is one of the largest, to date, on bleeding after oral surgery in patients with end-stage liver disease. We found that the majority of tooth extractions (91%) were performed safely, without bleeding complications. The highest bleeding incidences were observed among patients with concurrent, severe thrombocytopenia (PLT $<50 \times 10^9$/L) and impaired coagulation factor synthesis (INR >1.5). Preprocedural blood-product replacement therapy with PLT, FFP, or TA failed to ensure hemostasis. These results implied that prophylactic replacement therapies were ineffective. However, it remained unclear whether this ineffectiveness was secondary to the types of agents, the doses, or the timing employed.

The bleeding frequency of 9% found in our study was within the range of 3% to 17%, as reported in previous studies that included only LT candidates.[4,5,7,8] Earlier studies, however, were markedly different from our study in terms of the severity or type of liver disease and the size of the patient population (the previous studies included less than 40 patients). For example, in a recent study by Perdigao et al.,[5] only one bleeding event occurred among 23 patients, and local hemostatic measures (TA and absorbable sponges) were sufficient to correct that postoperative bleeding complication, without the need for blood transfusions.

Recent studies have challenged the long-held belief that patients with liver disease are at increased risk of bleeding because of impaired coagulation factor synthesis and mild to moderate thrombocytopenia and that this bleeding risk can be reduced with prophylactic FFP or PLT transfusions delivered before invasive procedures.[9,10] Growing evidence has shown that even in end-stage liver disease, concomitant with deficiencies in natural anticoagulants the body can produce elevated levels of factor VIII and von Willebrand factor to rebalance the hemostatic state and thus preserve the capacity to generate thrombin and fibrin.[9-12] INR and platelet counts do not reflect this rebalanced hemostasis, and therefore, they are poor predictors of bleeding in liver disease.[9,10] Moreover, it has been shown that prophylactic blood product transfusions are often ineffective[13,14] and may even be harmful[15-17] because the associated fluid overload may increase bleeding risk by aggravating portal hypertension.[18,19] Consequently, recent recommendations regarding invasive procedures in patients with end-stage liver disease have emphasized the need to monitor patients closely when bleeding occurs, and they strongly discourage the routine use of prophylactic transfusions.[10,20,21] Our present findings are in full agreement with those recommendations. Perdigao et al.[5] found a low postoperative bleeding incidence without prophylactic blood transfusions among patients with advanced cirrhosis, and a study by Stanca et al.[7] showed that intranasal desmopressin was as effective as a blood transfusion for achieving hemostasis. Moreover, the effects of blood product replacement therapy are transient; thus, this strategy may not prevent delayed bleeding.

Hyperfibrinolysis may occur in advanced liver disease. This condition is potentially a common cause of delayed bleeding after various procedures.[10] There are no readily available methods for detecting hyperfibrinolysis in routine practice. It is known, however, that the oral cavity has high fibrinolytic activity,[22] which supports the use of antifibrinolytics, such as TA, after tooth extraction, particularly in patients with liver disease. Nevertheless, in our analysis, systemic TA failed to protect from delayed bleeding. However, because the effect of TA lasts only for some hours, it might be speculated that extended TA use over several days could protect from delayed bleeding more effectively.

Table IV. Factors associated with bleeding complications by univariate and multivariate logistic regression analyses

	Univariate		*Multivariate model 1*[*]		*Multivariate model 2*[†]	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*	*OR (95% CI)*	*P*
Number of tooth extractions	0.99 (0.86-1.15)	.92			0.93 (0.78-1.12)	.44
Difficult extraction (e.g., impaction)	0.82 (0.17-3.98)	.80			0.82 (0.12-5.54)	.84
Platelet level	1.00 (0.99-1.01)	.42			1.00 (0.99-1.01)	.58
INR	**3.05 (1.31-7.10)**	**.01**	1.58 (0.43-5.80)	.49	1.30 (0.31-5.47)	.72
MELD score	1.07 (1.00-1.14)	.06	1.01 (0.90-1.13)	.89	1.01 (0.91-1.13)	.83
Preprocedural platelet transfusion	**6.63 (1.90-23.0)**	**.003**	5.45 (1.0-29.8)	.051	**8.32 (1.10-62.7)**	**.04**
Preprocedural FFP transfusion	**4.55 (1.34-15.4)**	**.02**	0.62 (0.09-4.24)	.62	0.66 (0.09-4.97)	.69
Preprocedural tranexamic acid use	**9.28 (2.63-32.8)**	**.001**	**6.65 (1.58-28.0)**	**.01**	**7.99 (1.72-37.0)**	**.008**

OR, Odds ratio; *CI*, confidence interval; *INR*, international normalized ratio; *MELD*, Model for End-stage Liver Disease; *FFP*, fresh frozen plasma. Bold values represent statistical significance.
*Only factors with $P < .1$ on univariate analysis included.
†All univariate factors included.

Our study had several limitations. First, it was retrospective in nature. Also, although bleeding risk assessments in clinical practice have largely been based on INR and PLT counts, we did not account for other potential factors that may have determined a need for preprocedural transfusions. Nevertheless, our results partly confirmed the study hypothesis that complications may occur despite preoperative and perioperative hemostatic measures.

Douglas et al.[23] recommended that for blood product replacement therapy in oral surgery, FFP should be administered to patients with INRs $\geq$3.0. In contrast, the results of the present study suggested that the need for prophylactic FFP transfusions should be carefully evaluated. Our results were consistent with several previous studies showing that INR was indeed a poor predictor of the risk for bleeding in patients with end-stage liver disease.[9,10] Individual evaluations are required to weigh the benefits and drawbacks of transfusing PLT or other blood clotting factors in patients with cirrhosis.

CONCLUSIONS

Our results showed that the risk of bleeding is difficult to predict in patients with cirrhosis but that frequency of delayed bleeding is in general low. We recommend that atraumatic surgical techniques be applied by qualified practitioners along with the use of local hemostatic agents and close postoperative follow-up. Finally, our results suggest that use of prophylactic blood coagulation factors requires individual assessment.

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