Prospective randomized single-blind study of post-operative bleeding after minor oral surgery in patients with cirrhosis

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ABSTRACT

Background/Aims: *The management of patients with cirrhosis requiring dental extractions is complicated due to an increased risk of post-operative bleeding. Topical hemostatic agents are usually required to control bleeding in these cases, as an adjunct to systemic measures of hemostasis. The aims of this randomized, prospective, single-blind clinical study are twofold. The primary aim is to compare the hemostatic efficacy of chitosan and surgicel in patients with cirrhosis after a tooth extraction, and the secondary aim is to assess the value of the current setting as a clinical model of post-operative bleeding following minor oral surgery.*

Material and Methods: *Fifty patients with cirrhosis scheduled for a tooth extraction under local anesthesia were prospectively included in the study in a randomized fashion. Patients were blinded to the treatment group they were in. The cirrhosis classification, bleeding time, trauma score, and corrected bleeding time (during post-operative reviews) were recorded. Statistical evaluations were done.*

Results: *Study groups had an equal number of teeth extractions (40 teeth each). There were no statistically significant differences between the groups with respect to patient demographics, cirrhosis classification, trauma score, and bleeding time. No side effects were noted.*

Conclusion: *Both Celox and Surgicel are effective for controlling bleeding and are safe after a tooth extraction in patients with cirrhosis.*

Keywords: *Chitosan, liver cirrhosis, surgicel, tooth extraction*

INTRODUCTION

Cirrhosis is a chronic progressive disease characterized by the loss of normal liver parenchyma, an increase in connective tissue, nodular regeneration, and degeneration of vascular structures. Cirrhosis can also lead to an increased bleeding time and coagulation time, as it interferes with platelet distribution resulting in hypersplenism and folate and coagulation factor deficiency (1). Therefore, the management of patients with cirrhosis requiring dental extractions can be complicated due to an increased risk of post-operative bleeding, and topical hemostatic agents are usually required as an adjunct to systemic measures of hemostasis (2).

Surgicel® (Ethicon subsidiary of Johnson & Johnson) is a well-known and effective topical hemostatic agent, widely used in the surgical field. The material is absorbable and does not interfere with healing. It is easy to handle, inexpensive, and does not carry the risk of transmission of viral infections that blood coagulation protein-based products do (3).

Celox™ (MedTrade Products Ltd.) is a relatively new, non-toxic, resorbable, and a potent topical hemostatic agent that is proved to be invaluable, especially in warfare (4,5). It is a copolymer of chitosan that is purified from natural sources of chitin, such as shrimp and other crustacean shells, for a wide variety of bio-medical applications, including promotion of wound healing, bone tissue engineering, and hemostasis (6-8).

Both Celox™ and Surgicel® have shown to be effective in controlling bleeding after minor oral surgery (2). However, we are not aware of any randomized, prospective, and blinded studies comparing their effectiveness after dental extractions in patients with a risk of post-operative bleeding. In addition, there is a need for a safe clinical model of post-operative bleeding following minor oral surgery. Such a model would allow comparison of various medical or sur-

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gical treatments that are expected to reduce the risk of post-operative bleeding. Our primary aim was to compare the hemostatic efficacy of Celox™ and Surgicel® after dental extractions in patients with cirrhosis; second, we aimed to assess the value of this setting as a clinical model of post-operative bleeding following minor oral surgery.

MATERIALS AND METHODS

The study was approved by the Ethics Committee of Ege University School of Medicine. Fifty patients with cirrhosis scheduled for elective tooth extraction(s) under local anesthesia were prospectively included in the study. Participants were randomly assigned to receive either Celox™ or Surgicel® in their extraction sockets. Randomization was achieved using a web-based computer program (www.randomiser.org). Patients were blinded to the treatment groups. The study was carried out in the Department of Oral Surgery (School of Dentistry), in consultation with the Department of Gastroenterology (School of Medicine) in Ege University.

Table 1. Trauma score is determined according to the difficulty of extraction [9]

Trauma Score	Definition
1	Single-rooted tooth extraction
2	Two-rooted tooth extraction
3	Three-rooted tooth extraction
4	Surgical tooth extraction

Table 2. Child-Pugh (CHILD) classification for cirrhosis (Grade A=5-6 Grade B=7-9 Grade C=10-15)

	Parameter	Numerical Score
Encephalopathy	None	1
	Grade I-II	2
	Grade III-IV	3
Ascites	Absent	1
	Slight	2
	Moderate/Severe	3
Bilirubin (mg/dL)	<2	1
	2-3	2
	>3	3
Albumin (mg/L)	≥3.5	1
	2.8-3.4	2
	<2.8	3
Prothrombin time (sec)	1-3	1
	4-6	2
	>6.0	3

Inclusion criteria were the following:

- Patients aged from 18 to 65 years with cirrhosis, who required dental extraction(s)
- Diagnosis of cirrhosis based on clinical, radiological, and laboratory findings
- A maximum trauma degree of four, for an individual patient in one clinical session (9) (Table1)

Exclusion criteria were the following:

- Patients with a history of bleeding disorders and drug allergies
- Patients who used nonsteroidal anti-inflammatory and antiplatelet drugs a week before extraction
- Peripheral platelet count below 50,000/mm^3

Informed consent was obtained from all patients. Patients requiring multiple extractions from different quadrants were scheduled for several appointments with a minimum of 1 week between them. The Child-Pugh (CHILD) classification and the Model for End-Stage Liver Disease (MELD) scores were recorded (Table 2) (10,11). Blood tests, including full blood count (FBC), international normalized ratio (INR), prothrombin time (PT), and activated partial thromboplastin time were requested maximum 24 hours before extractions (12-15). Patients whose INR levels were higher than 1.4 were applied fresh frozen plasma pre-operatively. Amoxicillin applied orally, three times daily (PO, tds) was commenced starting the day before the treatment for 5 days.

Following teeth extraction, sockets were packed with either of the trial hemostatic agents up to soft tissue level, and polyglactin 910 rapide 4.0 sutures were applied. Patients were provided with post-operative instructions in a written form and orally, including returning to the clinic immediately if secondary bleeding was more serious than blood stained saliva or if they were worried. Additionally, patients were interviewed over the phone to determine if there was either minor or significant bleeding that would require treatment (16-18). Follow-up calls were made 4 and 10 hours post-operatively on the operation day and twice daily for 5 days (9am, 10pm). The following questions were asked during the post-operative phone reviews, for temporal characterization of secondary bleeding:

- Did you bleed after leaving the clinic?
- Are you bleeding now?
- If yes,
  - What did you do to stop the bleeding?
  - Did you apply pressure with the extra gauze you were provided with?
- Is your saliva pink colored, or are there red (blood) lines in your saliva?

These questions allowed us to find out how long minimal secondary bleeding lasted or if there was a significant post-operative bleeding that our patients failed to report on their own. This in turn enabled statistical comparisons across the study groups. This period was named as "statistically adjusted secondary bleeding time" (SABT).

The parameters recorded for each patient were the following:

- SABT
- Hemostatic material used and hemostasis time (time needed for hemostasis immediately post-operatively)
- The trauma score according to the difficulty of extraction (Table 1)
- The CHILD classification and MELD scores (Tables 2 and 3)

Table 3. Descriptive statistics of the recorded parameters

Hemostatic Material		CHILD*	MELD*	Trauma Score	Hemostasis Time
Celox	n	39	40	40	40
	Mean	7.85	14.08	2.40	3.38
	Median	7.0	13.50	2.00	3.00
	Minimum	5.0	7.00	1.00	1.00
	Maximum	14.0	29.0	5.00	7.00
	Standard deviation	2.15	5.54	1.11	1.60
	Standard error of mean	0.34	.088	0.18	0.25
Surgicel	n	40	40	40	40
	Mean	7.70	14.68	2.25	2.94
	Median	7.0	13.0	2.0	2.0
	Minimum	5.0	6.00	1.00	1.00
	Maximum	14.0	41.00	4.00	10.00
	Standard deviation	2.20	7.29	1.10	1.93
	Standard error of mean	0.35	1.15	0.18	0.31
Total	n	79	80	80	80
	Mean	7.77	14.37	2.32	3.16
	Median	7.0	13.50	2.0	3.0
	Minimum	5.0	6.00	1.00	1.00
	Maximum	14.0	41.00	5.00	10.00
	Standard deviation	2.16	6.44	1.10	1.77
	Standard error of mean	0.24	0.72	0.12	0.20

*CHILD: Child-Pugh; **MELD: Model for End-Stage Liver Disease

Statistical analysis

The Mann-Whitney U test was used to compare the data among the groups; Spearman's rho correlation was used to measure the association between variables. All data analyses were performed using the Statistical Package for the Social Sciences (SPSS) 12.0 for Windows (SPSS Inc.; Chicago, IL, USA), and p-values of less than 0.05 were considered significant.

RESULTS

A total of 80 teeth were removed from 50 patients under local anesthesia. Forty teeth were removed in each group (Celox™ and Surgicel®). There were equal number of men and women in the study groups. Thirty-five patients whose INR levels were higher than 1.4 were applied fresh frozen plasma pre-operatively. Remaining 15 patients did not require fresh frozen plasma as their INR was less than 1.4. None of the patients required platelet transfusion. Fifteen patients required surgical extractions.

Descriptive statistics of hemostasis time, trauma score, the CHILD and MELD classifications based on Celox™ and Surgicel® are shown in Table 3 (1,10,11). There were no significant differences between the groups in patient demographics, CHILD and MELD classifications, trauma score, and hemostasis time (p>0.05) (Table 3).

There was no bleeding in any of the patients beyond the 5th post-operative day. Only four patients (two from each group) had minimal secondary bleeding on the 5th post-operative day (Table 4). There were no significant differences between the study groups' CHILD classification, MELD scores, trauma scores, and hemostasis time (p>0.05) (Table 5).

The trauma scores were 4, 3, 2, and 1 in 15, 17, 26, and 22 cases, respectively. There is no significant correlation between the SABT and trauma score in the Celox® group (p=0.354); however, there is a significant correlation between the SABT and trauma score in the Surgicel® group (p=0.009) (Spearman's rho correlation analysis).

There is no statistically significant relation between the SABT and CHILD and MELD classifications of liver disease (for CHILD p=0.902; for MELD p=0.944; Spearman's rho correlation analysis).

No side effects of the hemostatic materials or complications during the follow-up period were encountered. There were no differences between the hemostatic effects of Celox™ and Surgicel® in patients with cirrhosis (p>0.05).

DISCUSSION

A prospective randomized single-blind design of this study enabled the best possible, yet ethical setting for clinical comparison of Surgicel® and Celox.® The planning of dental treatment in patients with liver disease should be formulated considering the coagulation factors and drug metabolism, as invasive procedures involve the risk of severe hemorrhage (12,19,20). Preoperative tests, including FBC, platelet count, PT, partial thromboplastin time (PTT), and INR, to ensure an intact coagulation system are mandatory (12).

Table 4. SABT* and p-values in post-op reviews

SABT* (Post-op control)	Number of Bleeding Patients	p
4th hour	Celox: 14	
	Surgicel: 9	0.22
10th hour	Celox: 12	
	Surgicel: 10	0.62
1st day 9 am	Celox: 8	
	Surgicel: 7	0.78
1st day 10 pm	Celox: 6	
	Surgicel: 5	0.75
2nd day 9 am	Celox: 6	
	Surgicel: 4	0.50
2nd day 10 pm	Celox: 6	
	Surgicel: 5	0.75
3rd day 9 am	Celox: 3	
	Surgicel: 3	1.00
3rd day 10 pm	Celox: 3	
	Surgicel: 5	0.46
4th day 9am	Celox: 3	
	Surgicel: 4	0.69
4th day 10 pm	Celox: 3	
	Surgicel: 3	1.00
5th day 9 am	Celox: 2	
	Surgicel: 2	1.00
5th day 10 pm	Celox: 2	
	Surgicel: 2	1.00

*SABT: Statistically adjusted secondary bleeding time

Implementing merely local measures of hemostasis (Surgicel® or Celox® packing and suturing) in the absence of medical measures in cirrhotic patients with an INR value higher than 1.4 would definitely constitute an excellent testing tool for these materials. Additionally, the fact that this study does not include a negative control group could be considered as a weakness. However, such a setting would clearly be unethical, as it would increase the risk of bleeding, hence the risk of infection with serious consequences in this group of patients. Therefore, medical management of the patients with an INR value higher than 1.4 was arranged appropriately, in consultation with the same gastroenterologist, and fresh frozen plasma was infused intravenously prior to extractions.

Antibiotics were regarded necessary as cirrhotic patients were expected to bleed, and any infection should better be avoided in this very ill group of patients who have a major metabolic deficit. Accordingly, patients were prescribed prophylactic amoxicillin (500 mg tds). The factors that are cited to support antibiotic prophylaxis include a decrease in the white cell count, the presence of infection in the surgical field, and immunosuppression. Prophylactic administration of antibiotics has been shown to reduce both mortality and the bleeding risk in this cohort (21,22). Conversely, Douglas et al. (20) in their study state that they are doubtful of prophylactic antibiotics' value and that it may in fact be harmful.

A careful extraction technique applied in this study minimized surgical trauma and thus reduced the risk of post-operative bleeding. Similarly, AbuBotain et al. (23) emphasized the importance of minimizing trauma during oral surgical procedures to reduce the risk of post-operative bleeding in patients with progressive familial intrahepatic cholestasis. Lockhart et al. (1) stated that local hemostatic measures, as well as a careful surgical technique and appropriate consultations, are necessary to minimize the risk of secondary bleeding after dental extractions.

Oxidized cellulose, tranexamic acid rinses, astringents (e.g., aluminum chloride), microfibrillar collagen, thrombin-soaked gauze, fibrin sealant and adhesive, electro cautery, absorbable gelatin sponges, and aminocaproic acid to prevent clot lysis have all been suggested as aids

Table 5. P-values by Mann-Whitney U Test

	CHILD* Classification	MELD** Classification	Trauma Score	Hemostasis Time
p	0.601	0.892	0.553	0.155

*CHILD: Child-Pugh; **MELD: Model for End-Stage Liver Disease

to hemostasis in this setting. Several polymeric classes of materials have been used to develop topical hemostatic materials involving collagen, chitin and chitosan (24).

Both oxidized regenerated cellulose and chitosan are known to be biocompatible, and the former has a very well-documented clinical reputation as a hemostatic material. Chitosan on the other hand is known to be a potent hemostatic material; however, its use has been limited to warfare and animal models of major bleeding (3-8,12-15,25,26). No complications or side effects related to the use of Surgicel® or Celox® were detected in our study, demonstrating the safety of these materials for use in patients with cirrhosis after a tooth extraction.

Clinical experience suggests that a significant post-operative bleeding would

- Continue beyond 12 hours
- Cause the patient to seek professional assistance
- Result in the development of a large hematoma or ecchymosis locally
- Sometimes require a blood transfusion (1)

Accordingly, in the present study, patients were followed up for 6 days, including the day of the tooth removal.

Susarla et al. (16) assessed patient satisfaction with a telephone follow-up and compared the frequencies of post-operative complications between the patients undergoing telephone and those undergoing a clinical follow-up after ambulatory office-based dentoalveolar procedures. Results of their study revealed that patient satisfaction with a telephone follow-up was high, and no significant difference was found in the complication frequencies according to the follow-up method. In a similar study by Inverso et al. (17) post-operative complication rates and the costs involved in a third molar extraction were compared between patients reviewed over the phone and those in the clinic. Their study confirms that one should not expect to see a significant difference in the post-operative complication rates, however the cost would decrease when using telephone follow-up compared to clinical follow-up (17). We agree that a telephone follow-up is not only as efficient as clinical follow-up regarding patient satisfaction and detection of complications, but it is also less time consuming.

The trauma score of extractions as used by Bodner et al. (9) is a useful tool since it enables a statistical assessment of the possible relation between the difficulty of extraction and bleeding. Accordingly, Spearman's rho correlation analysis revealed that the trauma score and SABT are correlated in the Surgicel® group only. This could mean that Celox® is more effective than Surgicel® as the trauma score increases. However, as there is no statistical significance between the groups, clinical significance of this finding is questionable in this setting. The CHILD and MELD classifications were valuable in the decision making of the gastroenterologist for medical management of patients with cirrhosis prior to dental extractions. Bleeding was assessed as bleeding immediately after the extraction (bleeding time) and bleeding in the post-operative 5 days (SABT). As a novel parameter, SABT allowed temporal monitorization of bleeding, supporting its value as a parameter of persistent bleeding.

The fact that there was no statistical significance between the patient demographics (age, sex, trauma score, the CHILD and MELD classifications) across the study groups supports that there is no selection bias. The results of this study did not yield any significance between Celox™ and Surgicel®. There would possibly be a significance between a sham topical hemostatic application and the study materials; however, such a setting would undoubtedly be dangerous and unethical with possible legal consequences for treating physicians and dentists.

Results of the present study revealed the safety of the techniques and procedures involved in this setting. Only 1 patient from the Celox™ group returned to the clinic complaining of secondary bleeding that required re-suturing and packing under local anesthesia. Although minimal bleeding continued beyond 3 days in 7 cases, there were no cases of bleeding observed after the 5th post-operative day. Therefore, we can state that dental extractions are safe in patients with cirrhosis after appropriate medical arrangements, transfusion of fresh frozen plasma as necessary, accompanied by suturing and packing with either of the study drugs, namely Celox™ or Surgicel®, as topical hemostatic agents. Dental extractions and other similar minor oral surgical procedures in patients with an acquired coagulopathy can be managed safely in general dental practice. However, a strict adherence to the discussed suggestions in this manuscript is required to avoid complications.

This setting of dental extractions in patients with cirrhosis could serve as a useful model for assessing the efficacy of surgical and/or medical treatments aiming to reduce the risk of post-operative bleeding. Celox™ and Surgicel® are both effective topical hemostatic agents that can safely be used after dental extractions in patients with cirrhosis providing medical management is properly addressed.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ethics Committee of Ege University School of Medicine (Approval Date: 17.01.2011; Decision No.: 10-11.1/19).

Informed Consent: Written informed consent was obtained from the patients who participated in this study.

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