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Assessment of laboratory tests and intraoperative bleeding in patients with liver cirrhosis undergoing tooth extractions

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Objectives. The objective of this study was to quantify intraoperative bleeding in patients with cirrhosis and correlate it with clinical characteristics and laboratory coagulation tests.

Study Design. A case-control study was carried out with 74 patients with cirrhosis who were submitted to preoperative coagulation tests (complete blood count, platelet count, prothrombin time/international normalized ratio, thrombin time, activated partial thrombin time, platelet aggregation, fibrinogen, protein C, protein S, antithrombin, and von Willebrand factor level and activity). The levels of nitrogen compounds that can affect the platelet function were determined in saliva and blood by using automated enzymatic-colorimetric assays.

Results. Patients with cirrhosis had changes in almost all coagulation tests. The average volumes of intraoperative bleeding and blood lost per minute in the study group (5.36 mL/min and 0.19 mL/min, respectively) were greater than those in the control group (3.05 mL/min and 0.11 mL/min, respectively; $P < .05$). In the control group, ascites ($P = .012$) and presence of periapical lesion (0.034) were positively correlated with bleeding (mL/min). With regard to coagulation tests and nitrogen compounds, only a positively moderate correlation with the platelet aggregation test was observed.

Conclusions. No patients had hemorrhagic events and it was not possible to correlate a greater amount of bleeding with coagulation tests or nitrogen compounds in the study group. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;000:1−8)

Liver cirrhosis is characterized by replacement of the hepatic parenchyma by fibrous tissue and formation of nodules.[1] Physiologic damage to the liver results in several cirrhotic complications and impairment of other organs and systems (e.g., kidneys, lungs, cardiovascular system, etc.).[2-4]

Hemorrhagic processes are of particular interest because they can increase morbidity and mortality rates. The mechanisms involved in bleeding events include insufficient production of clotting factors, dilation and relaxation of vessel walls due to accumulation of nitrogen compounds (particularly nitric oxide [NO]), a decrease in circulating platelets (as a result of hypersplenic sequestration and decrease in the liver production of thrombopoietin),[5] and a change in platelet function (adhesion) related to the action of NO and ammonia.[6,7] Moreover, there is the possibility that bacterial infections can trigger the release of endogenous heparinoids.[8]

Recommendations for predicting bleeding events in dental surgeries include measurements of prothrombin time (PT), international normalized ratio (INR), and platelet count. Published studies recommend that patients with a platelet count <40,000 or 50,000 and/or INR >3 should not undergo operation; instead, they should be submitted to prophylactic transfusions to avoid intra- or postoperative bleeding. Although these recommendations have been followed, all published studies concluded that it is not possible to correlate the results of these tests with bleeding events in patients with cirrhosis.[9-15] The studies also demonstrated that prophylactic transfusions were not able to prevent bleeding.[10,13-16]

The concept of rebalanced hemostasis, in which the participation of the liver in the production of pro- and anticoagulation factors is recognized, has changed the understanding of coagulation in cirrhosis. In addition to the mechanisms known to act on hemorrhagic events, one can cite the decrease in the levels of disin-

Statement of Clinical Relevance

Dental surgery can be made without prophylactic transfusion of blood or blood products in patients with cirrhosis. Tooth extraction does not seem to be an event important enough to cause concern about the risk of hemorrhage in patients with cirrhosis.

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tegrin and metalloprotease with thrombospondin type 1 motif 13 (ADAMTS 13); an increase in the levels of von Willebrand factor and factor VIII, which would compensate the reduced amount of platelets; and alterations in anticoagulation factors (proteins C and S and antithrombin) and thrombomodulin levels (protein C activator).[16] These changes in the coagulation factors can lead to thrombotic events.[17,18]

On the other hand, because it is possible to identify bleeding events in patients with sufficient amounts of platelets and coagulation factors, it is suggested that there may be a defect in the platelets affecting their adhesion, activation, or aggregation.[19] Medina et al. hypothesized that these platelet alterations in patients with cirrhosis could be associated with an excess of nitrogen compounds because of their poor excretion.[20]

Therefore, the objective of this work was to identify the existence of hemorrhagic events during and after dental extractions in patients with cirrhosis by quantifying the intraoperative bleeding and correlating it with coagulation tests and with salivary and serum levels of nitrogen compounds (NO, ammonia, and urea).

MATERIALS AND METHODS

Ethics

This study was approved by the research ethics committee of the Clinics Hospital of the University of São Paulo School of Medicine according to protocol number 2181425 and conducted according to the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) recommendations for observational studies. The study was performed in accordance with the Declaration of Helsinki and all participants read, understood, accepted, and signed a written informed consent form before their inclusion in the study.

Sample calculation

The sample size was calculated using Epi-Info (Centers for Disease Control and Prevention (CDC), Atlanta, Georgia (US) software, version 7.2.0.1, and based on the results of Lillis et al.[21] and Medina et al.[20] A sample consisting of 64 individuals per group was obtained for a power of 80%, significance level of 5%, control group probability of 0.4%, and study group probability of 12.5%. The sample size was increased by 10% to minimize possible losses, thus resulting in an ideal sample of 71 individuals in the study group and 71 individuals in the control group.

Study design and methods

For this observational case-control study, patients over 18 years old who needed dental extraction were selected consecutively. Patients taking anticoagulant or antiplatelet drugs were excluded from the study.

The study group included patients with cirrhosis who were on the liver transplantation waiting list (study group) and the control group include normoreactive (healthy) individuals.

Moments before the surgical procedure, blood and saliva were collected for tests. In the study group, the following tests were performed: complete blood count, platelet count, PT/INR, thrombin time (TT), activated partial thrombin time (aPTT), platelet aggregation adenosine 5′-diphosphate ((ADP), adrenalin, arachidonic acid, and ristocetin), fibrinogen, protein C, protein S, antithrombin III levels, von Willebrand factor levels and activity, and nitrogen compounds (NO, ammonia, and urea) in the blood and saliva. In the control group, only blood count and coagulation tests (PT, aPTT, and TT) were performed because these were included in the routine protocol followed at the hospital where the study was conducted.

The levels of NO, ammonia, and urea (in blood and saliva) were determined using automated enzymatic-colorimetric assays, respectively, EnzyChrom Nitric Oxide Synthase Assay, EnzyChrom Ammonia Assay Kit, and EnzyChrom Urea Assay Kit (BioAssay Systems, Hayward CA, USA) according to the manufacturer's recommendations. The samples were read on a Stat Fax reader (model 2100, Awareness Technology).[22]

Allpatients were submitted to dental extractions according to the technique established by Peterson et al.[23]

During the procedure, the whole blood was aspirated from the alveolus and collected into a container (in milliliters) according to the methodology established by Buhatem Medeiros et al.[24] During the procedure, the dental alveolus was irrigated with saline solution and a portable vacuum suction pump was used to aspirate the fluids (blood and saline solution). Bleeding was measured by subtracting the amount of saline solution from the final amount of aspirated fluid. The suction handpiece of the dental equipment was used only to aspirate saliva, which was discarded and not considered. Procedure time (in minutes), amount of blood lost by the patient (in milliliters), and amount of blood lost per minute (in milliliters per minute) were recorded. At the end of the procedure, 3-0 nylon suture was placed. If the patient had abnormal bleeding, a paste made by mixing tranexamic acid tablets and saline solution was placed in the extraction socket.

A mean blood loss >0.6 mL/min was considered abnormal bleeding.[24] The criteria established by Lockhart et al. were used to define abnormal postoperative hemorrhage.[25]

Standard postoperative recommendations were given to all patients after the procedure and they were also provided with analgesics (dipyrone or acetaminophen for a maximum of 3 days).

All patients were reevaluated 1 week after the procedure and instructed to return immediately in case of bleeding.

Statistical analysis

The resulting data were analyzed using the Statistical Package for Social Science software (SPSS for Windows, version 22.0, SPSS Inc., Chicago, IL, USA). Before the analyses, the Kolmogorov-Smirnov normality test with Lilliefors correction was used for nonparametric data distribution. Descriptive analysis was performed to obtain frequencies, central trend measures, and dispersion. Mann-Whitney *U* test was used for comparison between groups regarding volume of blood loss, laboratory tests, and levels of nitrogen compounds in the blood and saliva. Spearman's correlation test was used to correlate the volume of blood loss with laboratory data. All statistical analyses were performed at significance level of $P \leq .05$.

RESULTS

A total of 204 patients in the study group and 280 in the control group were evaluated according to inclusion/exclusion criteria to reach a final sample of 74 patients in each group.

In the control group, the mean age was 36 years and the majority of patients were female (78.37%), whereas in the study group, the mean age was 55.03 years and the majority of patients were male (74.33%).

The mean model of end-stage liver disease value was 18.58 (minimum = 7, maximum = 40, median = 18). The main etiologies of cirrhosis were hepatitis C virus (35.13%), alcoholism (31.08%), cryptogenic cirrhosis (6.75%), autoimmune hepatitis (5.40%), and primary biliary cirrhosis (4.05%). With regard to cirrhotic complications, all patients had portal hypertension, esophageal varices, and hypersplenism. Ascites was found in 59.5% of patients, upper gastrointestinal bleeding in 27%, hepatic encephalopathy in 9.5%, and spontaneous bacterial peritonitis in 6.8%. The most common comorbidities were arterial hypertension (n = 24), diabetes mellitus (n = 20), nephropathies (n = 7), and osteoporosis/osteopenia (n = 4).

In the study group, laboratory tests showed that the level of protein S was within the normal range but the levels of fibrinogen, hemoglobin, platelets, antithrombin III, and protein C were decreased and those of PT/INR, aPTT, TT and levels and activity of von Willebrand factor were increased. The mean values of each exam were compared with the reference values. When groups were compared, all tests in the study group that had also been performed in the control group showed statistically significant differences (Table I).

Table I. Laboratory tests performed before the dental extractions

Variables	*Study group*				*Control group*				*P**
	n	*Median*	*Minimum*	*Maximum*	*n*	*Median*	*Minimum*	*Maximum*	
Hb (g/dL)	74	11.00	6.50	15.40	74	13.15	10.80	16.20	< .001
Platelets (mm^3)	74	76.500	21.000	263.000	74	265.500	152.000	430.000	< .001
PT (seconds)	74	15.35	10.80	27.60	74	11.85	10.80	13.40	< .001
INR	74	1.30	0.95	2.44	74	1.02	0.94	1.16	< .001
PA (%)	74	65.00	31.00	120.00	74	95.50	83.00	115.00	< .001
aPTT (seconds)	74	33.05	23.50	48.80	74	30.40	23.90	36.40	< .001
R	74	1.13	0.94	1.58	74	1.03	0.87	1.27	< .001
TT (seconds)	74	20.60	14.60	29.50	74	15.00	14.00	16.00	< .001
von Willebrand factor (%)	74	330.50	101.00	816.00					
von Willebrand activity (%)	74	246.50	72.00	526.00					
Platelet aggregation with ADP (%)	16	77.50	19.00	90.00					
Platelet aggregation with adrenalin (%)	16	80.00	39.00	93.00					
Platelet aggregation with arachidonic acid (%)	13	78.00	22.00	88.00					
Platelet aggregation with collagen (%)	16	80.50	10.00	94.00					
Platelet aggregation with ristocetin (%)	13	80.00	10.00	98.00					
Antithrombin III (%)	74	54.50	14.00	116.00					
Fibrinogen (mg/dL)	74	196.00	107.00	478.00					
Protein C (%)	74	48.00	13.00	128.00					
Protein S (%)	74	66.50	37.00	127.00					

Reference values: Hb: 11.5 to 17.5 g/dL; platelets: 140,000 to 450,000/ mm^3; PT: 9.4 to 12.5 seconds; INR: 0.95 to 1.20; PA >70%; aPTT: 25.1 to 36.5 seconds; R: 0.8 to 1.17; TT: 10.3 to 16.6 seconds; von Willebrand factor: 42% to 176%; activity of von Willebrand factor: 40% to 165%; platelet aggregation with ADP (% at 10 minutes): 70% to 100%; platelet aggregation with adrenalin (% at 10 minutes): 70% to 100%; platelet aggregation with arachidonic acid (% at 10 minutes): 70% to 100%; platelet aggregation with collagen (% at 10 minutes): 70% to 100%; antithrombin III: 83% to 128%; fibrinogen: 200 to 393 mg/dL; protein C: 70% to 140%; protein S: 54.7% to 146.1%.

ADP, adenosine 5′-diphosphate; *aPTT*, activated partial thrombin time; *Hb*, hemoglobin; *INR*, international normalized ratio; *PA*, prothrombin activity; *PT*, prothrombin time; *R*, relation patient aPTT /aPTT pool; *TT*, thrombin time.

*Mann-Whitney *U* test.

Table II. Comparison between study and control groups regarding total volume of bleeding, procedure time, and volume of blood lost per minute

	Study group				*Control group*				*P**
	Mean	*Median*	*Minimum*	*Maximum*	*Mean*	*Median*	*Minimum*	*Maximum*	
Total volume of bleeding (mL)	5.36	4	3	30	3.054	3	1	10	< **.001**
Surgery time (minutes)	28.14	27.5	10	50	26.62	25.50	15	40	.319
Volume of bleeding per minute (mL/min)	0.19	0.16	0.08	0.67	0.11	0.10	0.041	0.26	< **.001**

*Mann-Whitney *U* test.
Bold values significance level - $P \leq 0.05$.

Platelet aggregation tests were performed in only 16 patients in the study group because of technical limitations that did not allow their use in patients with <90,000 platelets. Nevertheless, it was found that some individuals had extremely low levels of aggregation (Table I).

Patients underwent simple (nonsurgical) dental extractions after the laboratory tests were performed. The number of teeth extracted in the study group ranged from 1 to 4 and from 1 to 6 in the control group.

The total amount of blood lost was significantly greater in patients in the study group compared with controls, including the total volume per minute (Table II).

Although 2 patients in the study group lost more than 30 mL of blood during the surgical procedure, bleeding was controlled by introducing a paste consisting of tranexamic acid and saline solution into the alveolus. Patients in both groups experienced no abnormal bleeding; that is, blood loss >0.6 mL/min (95% confidence interval of the mean, 0.48-0.75).

After the surgical procedure, patients in both groups were medicated with analgesics; no antibiotics were prescribed. No infectious complications were observed after the procedure and no patient had hemorrhagic complications according to criteria set by Lockhart et al.[25]

Because the amount of bleeding was greater in the study group, we sought to correlate it with clinical characteristics and laboratory coagulation tests. With regard to clinical characteristics, only ascites ($P = .012$) and presence of periapical lesions ($P = .034$) had a positive correlation with bleeding (mL/min).

In addition to a moderate positive correlation in the platelet aggregation test with arachidonic acid, we found no correlation between intraoperative bleeding and laboratory tests in the study group (Table III).

The variable expressing the values of bleeding per minute (mL/min) was dichotomously categorized by using the last quartile (q75) because this measurement represents

Table III. Spearman's correlation showing the relationship between total volume of blood lost and volume of bleeding per minute in the coagulation tests in the study group

Tests	*Total volume of bleeding (ml)*		*Volume of bleeding per minute (ml/min)*	
	r	*P*	*r*	*P*
Platelets (mm^3)	−0.216	.065	−0.200	.088
PT (seconds)	−0.040	.733	−0.120	.307
INR	−0.011	.927	−0.107	.363
PA (%)	0.019	.872	0.106	.370
aPPT (seconds)	0.057	.627	0.014	.906
R	0.036	.760	0.004	.973
TT (seconds)	−0.016	.891	−0.007	.956
von Willebrand factor levels (%)	−0.188	.108	−0.208	.075
von Willebrand factor activity (%)	−0.098	.407	−0.093	.428
Platelet aggregation with ADP (%) (n = 16)	0.046	.866	0.142	.600
Platelet aggregation with adrenalin (%) (n = 16)	−0.056	.832	−0.017	.949
Platelet aggregation with arachidonic acid (%) (n = 13)	**0.424**	**.149**	**0.680**	**.010**
Platelet aggregation with collagen (%) (n = 16)	0.268	.316	0.222	.409
Platelet aggregation with ristocetin (%) (n = 13)	−0.090	.769	0.004	.989
Antithrombin III (%)	0.064	.588	0.016	.895
Fibrinogen (mg/dL)	−0.099	.403	−0.056	.637
Protein C (%)	−0.005	.968	0.096	.418
Protein S (%)	−0.020	.866	0.006	.961

ADP, adenosine 5′-diphosphate; *aPTT*, activated partial thrombin time; *INR*, international normalized ratio; *PA*, prothrombin activity; *PT*, prothrombin time; *R*, relation patient aPTT /aPTT pool; *TT*, thrombin time.
Bold values significance level - $P \leq 0.05$.

Table IV. Comparison of the values of laboratory coagulation tests and nitrogen compounds between patients who had bleeding greater and lower than 0.250 mL/min (last quartile) in the study group

Tests	*Volume of bleeding per minute ≤0.250 mL/min (n = 61)*	*Volume of bleeding per minute >0.250 mL/min (n = 13)*	*P**
Platelets (mm^3)	77,000 (242,000)	73,000 (120,000)	.410
PT (seconds)	15.5 (16.8)	14.3 (6.7)	.198
INR	1.30 (1.49)	1.21 (0.58)	.219
PA (%)	65 (89)	70 (43)	.675
aPTT (seconds)	33.3 (25.3)	32.2 (16.4)	.330
R	1.13 (0.64)	1.14 (0.46)	.921
TT (seconds)	20.7 (12.8)	20.0 (13.5)	.820
von Willebrand factor levels (%)	337 (715)	224 (600)	**.034**
von Willebrand factor activity (%)	247 (454)	214 (410)	.158
Antithrombin III (%)	53 (102)	60 (79)	.532
Fibrinogen (mg/dL)	196 (371)	196 (186)	.707
Protein C (%)	46 (115)	52 (74)	.551
Protein S (%)	64 (90)	70 (57)	.580
Urea in saliva (mg/dL)	27.17 (46.33)	28.42 (8.77)	.362
Nitric oxide in saliva (U/L)	15.37 (46.21)	20..04 (38.93)	.732
Ammonia in saliva (mg/dL)	1.81 (0.79)	1.74 (0.74)	.552
Urea in blood (mg/dL)	38.18 (43.03)	36.25 (13.26)	.251
Nitric oxide in blood (U/L)	6.09 (15.13)	6.30 (7.52)	.851
Ammonia in blood (mg/dL)	1.00 (0.98)	1.01 (0.30)	.820

Results expressed as median and interquartile interval for each variable.
aPTT, activated partial thrombin time; *INR*, international normalized ratio; *PA*, prothrombin activity; *PT*, prothrombin time; *R*, relation patient aPTT /aPTT pool; *TT*, thrombin time.
*Mann-Whitney *U* test.
Bold values significance level - $P \leq 0.05$.

patients in the study group who had a greater volume of bleeding during the dental extraction procedure.

In the last quartile, we identified 13 patients who experienced bleeding >0.250 mL/min, whereas 61 experienced less bleeding. We also found a statistically significant difference in the distribution of the von Willebrand factor levels (Table IV).

To assess the hypothesis that nitrogen compounds can interfere with coagulation in patients with cirrhosis, we evaluated the patients in the last quartile (n = 13) in relation to bleeding per minute and quantification of nitrogen compounds (Table IV). We also performed a correlation test between these compounds and total volume of bleeding per minute (Table V). No correlation was found.

DISCUSSION

Two groups of patients, 1 group with liver cirrhosis and 1 control group without cirrhosis, were recruited for this study. We assume that case-control studies may show selection bias, especially when they are unpaired, because the selection of controls is generally influenced by the availability of resources and time. However, pairing of characteristics, such as sex and age, did not influence the results of this study. Both groups had comparable characteristics in their totality and met the main objective of this study.

The demographic characteristics of the groups reflect the main inclusion criteria; that is, in the study group the patients had liver cirrhosis and in the control group the patients were healthy. Moreover, although there

Table V. Spearman's correlation test showing the relationship between total volume of bleeding per minute and nitrogen compounds in the blood and saliva of patients in the study group

	Total volume of bleeding (mL)		*Volume of bleeding per minute (mL/min)*	
	r	*P*	*r*	*P*
Urea in saliva (mg/dL)	−0.101	.398	−0.083	.490
Nitric oxide in saliva (U/L)	−0.009	.943	−0.111	.352
Ammonia in saliva (mg/dL)	0.028	.818	0.033	.785
Urea in blood (mg/dL)	−0.130	.276	−0.153	.199
Nitric oxide in blood (U/L)	−0.147	.217	−0.017	.889
Ammonia in blood (mg/dL)	−0.086	.472	0.030	.805

were differences in sex and age between the groups, they are not recognized as modifiers of bleeding. However, there were a greater number of patients with decompensated cirrhosis (59.5% with ascites). Decompensated cirrhosis can be defined by the development of clinically evident complications of portal hypertension (e.g., ascites, varicose hemorrhage, hepatic encephalopathy) or of hepatic insufficiency (e.g., jaundice).[26] Decompensation has been associated with an increase in hemorrhagic events.[27]

In dentistry, despite the few studies published so far, it seems that conventional coagulation tests (PT/INR and platelets) and prophylactic transfusion of blood and blood products are considered of little use. However, these studies are very heterogeneous because they have different designs and some used blood and blood products prophylactically, and none used a control group.[9-14,20]

The lack of a control group affects the perception on the occurrence of abnormal bleeding.[9-14,20] Hemorrhages are more extensive and the absence of this type of bleeding event does not mean that there may not be an abnormal bleeding event that requires treatment. In our study, we defined not only what could be considered a bleeding event intra- and postoperatively but also a control group to compare the amount of blood lost during the surgical procedure. With this methodology, it was possible to observe that patients with cirrhosis had significantly greater blood loss during dental extractions compared with controls, although there were no hemorrhagic events. The amount of blood lost was divided by surgical time in order to determine a more reliable value. Thus, we believe that the risk of bias can be minimized because the number of teeth extracted is directly related to procedure time. This observation shows that it is necessary to be aware of local bleeding control in patients with cirrhosis, which can be performed in a relatively simple and inexpensive way by means of suture and tranexamic acid paste.

It was expected that patients in the study group would show discrepant laboratory results owing to the greater blood loss compared with controls. Although almost all mean values of coagulation tests were out of the reference ranges, we found that the results pointed to the concept of rebalanced hemostasis because there were changes in procoagulation (platelets, PT/INR, aPTT, von Willebrand factor, fibrinogen) and anticoagulation (antithrombin III, protein C) tests. We also observed a greater preservation of primary hemostasis, which was relatively balanced because the decrease in platelets seems to be compensated by an increase in von Willebrand factor levels and activity. In addition, platelet adhesion and aggregation were preserved, although platelet aggregation tests were not performed in some patients because of technical limitations. Secondary hemostasis also showed signals of a certain balance because it was found that the levels of PT, aPTT, and TT (representing a decrease in the coagulation factors of intrinsic, extrinsic, and common pathways) were increased, whereas the levels of antithrombin III and protein C were decreased.

However, the result for protein S were within the normal reference range, which is surprising because we expected that protein S would be decreased.[28] Proteins C and S help regulate clotting by acting jointly with thrombin on a feedback basis. Thrombin combines with thrombomodulin to activate protein C, which in turn combines with protein S, and together they degrade the blood coagulations factors VIIIa and Va (these activated factors are needed for production of thrombin). The final effect is to delay the production of new thrombin and inhibit the formation of more clots.[29] Fibrinogen plays several important roles in the maintenance of primary and secondary hemostasis and is converted by thrombin into an insoluble fibrin network, which, together with platelet aggregates, induces hemostasis in response to endothelial disruption.[30] Decreased levels of fibrinogen were observed in about 40% of the patients with cirrhosis, and this decrease is linked to a worsening clinical state.[31]

This scenario regarding coagulation was expected despite not being presented or considered by studies in the field of dentistry.

Another objective of this study was to identify clinical characteristics or laboratory tests that could be correlated with a greater blood loss in patients with cirrhosis.

Clinically, ascites and presence of periapical lesions were positively correlated with bleeding, as expected, because the former condition is one of the clinical characteristics of decompensation and ascitic fluid has fibrinolytic activity.[32] In addition, periapical lesions are characterized by a local inflammatory process,[33] which in turn is known to promote an increase in bleeding.[34]

The same association could not be observed for laboratory coagulation tests. In fact, none of the tests correlated positively or negatively with bleeding, except platelet aggregation with arachidonic acid, even when we selected patients with a greater amount of bleeding (i.e., those in the last quartile). The correlation with platelet aggregation with arachidonic acid, despite its biological plausibility, was interpreted as being merely casual because the number of patients was small and other platelet aggregation tests did not provide the same results.

The most innovative question raised by Medina et al. regarding the participation of nitrogen compounds, which are present in blood and saliva, in the bleeding process of patients with cirrhosis could not be demonstrated in the present study.[20] In fact, none of the nitrogen compounds were found to be correlated with bleeding in the study group.

It is estimated that this occurred because the volume of platelets was enough to generate thrombin needed in the initiation phase, although they were extremely low in some cases. Thrombin amplifies the coagulation process by activating other platelets, thus increasing their adhesion and activating factors V, VIII, and XI. Our results are corroborated by in vitro studies, which report that 20,000 to 30,000 platelets would be enough to produce thrombin for the initiation process.[35]

The process leading to increased bleeding in patients with cirrhosis seems to be complex and multifactorial, in which the generation of thrombin plays an important role in primary and secondary hemostasis. In fact, thrombin seems to prevent possible defects in platelet activation, adhesion, and aggregation during the initiation phase, whereas little changes in protein C and no change in protein S interrupt the feedback system with thrombin. Moreover, thrombin is fundamental for the transformation of fibrinogen into fibrin and for the activation of fibrin stabilizer factor. It was found that thrombin generation tests were normal or slightly decreased in patients with cirrhosis.[36]

In the present study, none of the laboratory tests were positively or negatively correlated with greater blood loss in patients with cirrhosis. It is possible that tests measuring thrombin generation could be more effective in predicting hemorrhagic events in patients with cirrhosis, but they are complex and expensive for use in dental surgery.[37,38]

Patients with cirrhosis undergoing dental extraction experienced more bleeding than patients without cirrhosis. However, the amount of bleeding was not severe enough to rate it as a hemorrhagic event. Laboratory coagulation tests or presence of nitrogen compounds in the blood or saliva were not correlated with bleeding in these patients.

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