Review

Risk of Bleeding in End-Stage Liver Disease Patients

Undergoing Cardiac Catheterization

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Patients with end-stage liver disease frequently have baseline coagulopathies. The international normalized ratio is in common use for the estimation of bleeding tendency in such patients, especially those undergoing an invasive procedure like cardiac catheterization. The practice of international normalized ratio measurement—followed by pharmacologic (for example, vitamin K or fresh frozen plasma) or nonpharmacologic intervention—is still debatable. The results of multiple randomized trials have shown the superiority of the radial approach over femoral access in reducing catheterization bleeding. This reduction in bleeding in turn decreases the risk and cost of blood-product transfusion. However, there is little evidence regarding the use of the radial approach in the end-stage liver disease patient population specifically. In this review, we summarize the studies that have dealt with cardiac catheterization in patients who have end-stage liver disease. We also discuss the role of the current measurements that are used to reduce the risk of bleeding in these same patients. ***(Tex Heart Inst J 2015;42(5):414-8)***

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Multiple pathologic processes play an important role in the hemostasis of patients with end-stage liver disease (ESLD).[1-4] Most of the coagulation factors are decreased in the presence of ESLD. The exceptions are factor VIII and von Willebrand factor, which typically increase in quantity, because their chief producers are extrahepatic sites.[1,2] The decrease in coagulation factors that accompanies ESLD is also balanced by a parallel decrease in the natural anticoagulants, such as protein C and protein S, which usually maintains a net balanced hemostasis.[1]

Because both pro- and antifibrinolysis proteins are synthesized predominantly in the liver, they also decrease in the presence of ESLD.[3,4] As a consequence, ESLD patients can present with a wide spectrum of hemostatic abnormalities, depending on the net balance of these processes.[1]

The international normalized ratio (INR)—originally established to evaluate the degree of anticoagulation achieved by vitamin K antagonists—is also commonly used to evaluate the activity of the intrinsic pathway coagulation factors.[5] Multiple studies[6-12] have discussed the use of the INR to evaluate the bleeding tendency in patients with ESLD. When Tripodi and colleagues[6] compared in vitro the blood samples of 134 cirrhotic patients with those of healthy members of a control group, thrombin generation was found to be higher in the cirrhotic group (0.8 vs 0.17), even though the INR was higher in the cirrhotic group (1.2 vs 0.9; P <0.001).[6] Accordingly, the INR has been shown to correlate poorly with bleeding in studies that involve invasive procedures, including liver biopsy and paracentesis.[7-12]

Cardiac catheterization is commonly performed in ESLD patients as a part of the pre-transplant evaluation.[13] The American Association for the Study of Liver Disease recommends performing a left-sided heart catheterization (LHC), a right-sided heart catheterization (RHC), or both, as a confirmatory test for evaluation before transplantation in patients with abnormal noninvasive-test results (class II recommendation).[13] However, the routine incorporation of cardiac catheterization as part of the pre-transplant evaluation is uncertain (appropriate-use score of 5 out of 9, according to the American College of Cardiology's (ACC's) appropriate-use criteria for diagnostic catheterization).[14] Measurement of INR before cardiac catheterization is in fact recommended by the ACC[15] for patients with known hepatic disease. However, there is a paucity of data regarding the efficacy of INR in ascertaining bleeding risks in ESLD

patients before they undergo cardiac catheterization. Similarly, the benefits of administering, before cardiac catheterization, fresh frozen plasma (FFP), vitamin K, or recombinant factor VIIa (rFVIIa) to decrease the incidence of bleeding are not well established.

Methods

We used the Medline database in conducting our review of the literature. The MeSH keywords "end stage liver disease," "liver diseases, alcoholic," "blood coagulation disorders," "liver transplantation," "cardiac catheterization," and "bleeding" were used in our search. Studies were included if they were conducted on ESLD patients who were undergoing cardiac catheterization with postprocedural bleeding as an outcome. We found 7 retrospective studies that considered the topic of INR and post-catheterization bleeding in ESLD patients (Table I[16-22]).

Pharmacologic Approaches to Reducing the Risk of Bleeding after Cardiac Catheterization

Role of Fresh Frozen Plasma Administration. In 2005, Vaitkus and colleagues[16] conducted a retrospective study involving 79 ESLD patients who underwent RHC and LHC from 2002 through 2004. The mean INR was 1.49 ± 0.44, and approximately 40% of the patients had an INR >1.5. Only 4 patients (5%) were given FFP before the procedure, and one patient (1.3%) had a major adverse outcome in the form of a pseudoaneurysm. The authors concluded that cardiac catheterization was feasible in ESLD patients, with an acceptably low risk of post-catheterization bleeding and without the routine administration of FFP before the procedure.[16]

In 2009, Sharma and associates[17] published a retrospective case-control study that matched (for left-sided heart catheterization) 88 ESLD patients with a control group of 81 patients who had no known history of liver disease. The primary sequelae were vascular, with major bleeding in accordance with the criteria of the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE)-2 trial.[23] The mean INR was 1.6 ± 0.1 in the ESLD group, in comparison with 1.1 ± 0 in the control group. Major bleeding occurred more frequently in the ESLD than in the control-group patients (14.8% vs 3.7%). Five patients in the ESLD group had a pseudoaneurysm, versus 1 patient in the non-ESLD group. Forty percent of ESLD patients were given FFP 24 hours before and after the catheterization. Although the study showed a statistically significant higher incidence of major bleeding (P=0.014), this was driven mainly by the periprocedural increase in the transfusion of blood products. The incidence of life-threatening intracranial and retroperitoneal bleeding was nil in both groups, which might be attributed to the prophylactic administration of FFP.[17]

Pillarisetti and coworkers[18] conducted a retrospective study that compared 43 ESLD patients with similar patients (without a history of liver disease). The mean INR in the ESLD group was 1.4 ± 0.2, compared with 1.1 ± 0.2 in the control group. Only 3 of 12 patients with INR >1.6 in the ESLD group were given FFP. One patient from the ESLD group developed minor groin bleeding, and no patients from either group received packed red blood cells after transfusion. The study showed an overall low incidence of FFP administration to ESLD patients before cardiac catheterization, and a low risk of major bleeding after the procedure.[18]

Another retrospective study, by Townsend and colleagues,[19] involved 240 ESLD patients who underwent either RHC or LHC. Patients were divided into 2 major groups, LHC and RHC, and each group was further divided into high (>1.5) and low (≤1.5) INR groups. Only 7% of the RHC and LHC patients received FFP before the procedure. The primary outcome was the reduction in postprocedural hemoglobin in each group. The change in hemoglobin was not significant in either the RHC group (10.5 vs 10.5 g/dL, P=0.83) or the LHC group (11.1 vs 11 g/dL, P=0.83). In addition, the reduction in hemoglobin between high and low INR groups was not significant in either LHC or RHC patients, indicating that high INR levels did not necessarily mean a higher risk of bleeding in ESLD patients.[19]

Role of Vitamin K Administration. The use of vitamin K to correct coagulopathy in ESLD patients is debatable. The main purpose behind vitamin K administration in such a population is to replenish vitamin K deficiency that might occur because of malnutrition or cholestasis.[24] A study by Saja and associates[25] illustrated a modest improvement of vitamin K-dependent procoagulants after the administration of intravenous vitamin K to ESLD patients.[25] The use of vitamin K for correction of other bleeding sequelae, such as gastrointestinal bleeding in ESLD patients, is a common practice but is not supported by solid clinical evidence.[26]

Role of Recombinant Factor VIIa Administration. Recombinant factor VIIa, which is produced in vitro by recombinant DNA technology, had been used off-label for treatment of postsurgical bleeding in ESLD patients.[27] Multiple trial investigators have evaluated the efficacy of rFVIIa in preventing bleeding after liver biopsy and liver transplant surgery.[28-32] The primary outcome in most of the trials was the number of packed red blood cells transfused.[28,29,31,32] There was no difference in the number of blood units administered to rFVIIa and non-rFVIIa groups. Meanwhile, the results of another study[29] showed that the risk of thromboembolism was 20% in the rFVIIa group versus 10% in the non-rFVIIa group. It appears from these studies that the role of rFVIIa as an intervention to minimize the bleeding risk in patients with ESLD before cardiac catheterization remains questionable.

TABLE I. Summary of the Clinical Studies Included

Reference	Study Group		Patients (n)		MELD Score (mean)		INR		Type of Cardiac Catheterization	Radial Vascular Access (%)		Primary Outcome	Incidence of Primary Outcome (%)	
	Case	Control	Case	Control	Case	Control	Case	Control		Case	Control		Case	Control
Vaitkus PT, et al.[16] (2005)[a]	ESLD	NA	79	NA	NR	NA	1.5 ± 0.4		RHC + LHC	5	NA	Major bleeding	0	
Sharma M, et al.[17] (2009)	ESLD	No liver disease	88	81	NR	NR	1.6 ± 0.1	1.1 ± 0	LHC ± RHC	5	1	Major bleeding	15	14
Pillarisetti J, et al.[18] (2011)	ESLD	No liver disease	43	43	NR	NR	1.4 ± 0.2	1.1 ± 0.2	LHC ± RHC	2	0	Procedural vascular/ bleeding complications	2	0
Townsend JC, et al.[19] (2012)	High INR	Low INR	RHC, 61	RHC, 96	21	13	1.8 ± 0.2	1.3 ± 0.1	RHC + LHC	0	0	Procedural vascular/ bleeding complications	0	0
			LHC, 23	LHC, 60	22	14	1.7 ± 0.2	1.3 ± 0.4					0	0
Jacobs E, et al.[20] (2014)[a]	ESLD	NA	82	NA	19	NA	1.4 (1.2–1.8)[b]		RHC + LHC	100	NA	Procedure-related major bleeding	2	NA
Huded CP, et al.[21] (2014)	LTC	Non-LTC (normal)	107	964	21	NA	1.7 ± 0.5	1.1 ± 0.2	LHC ± RHC	100	100	Transradial approach failure	10	7
Feng K, et al.[22] (2014)[c]	Trans-radial access	Trans-femoral access	145	189	26	21	1.9 ± 1.2	1.6 ± 0.6	LHC ± RHC	100	0	Procedure-related bleeding complications	0	0

ESLD = end-stage liver disease; INR = international normalized ratio; LHC = left-sided heart catheterization; LTC = liver transplant candidates; MELD = Model for End-stage Liver Disease; NA = not applicable; NR = not reported; RHC = right-sided heart catheterization

[a] Single-arm study
[b] INR reported as mean (range)
[c] ESLD patients undergoing cardiac catheterization

Data are presented as mean ± SD, as number, or as percentage.

Nonpharmacologic Interventions to Reduce the Risk of Bleeding after Cardiac Catheterization

Transradial versus Transfemoral Access. Transradial access has been shown in multiple randomized clinical trials to be a safer approach for LHC, with fewer bleeding and vascular complications.[33-35] The safety of transradial access for LHC in ESLD patients has also been verified by investigators in a few retrospective studies.[20-22] Jacobs and colleagues[20] studied 82 ESLD patients who underwent both LHC through the radial artery and RHC through either the brachial or femoral vein. The baseline INR was 1.4 (range, 1.2–1.8). Two patients (2%) had a major bleeding episode unrelated to the radial artery site, and no patient had any vascular sequela after catheterization.[20]

The investigators in another study[21] compared transradial access in liver-transplant candidates with that of non-liver-transplant candidates. Although the liver-transplant group had a lower platelet count at baseline (75,000 vs 237,000/mm^3, P <0.01) and a higher INR (1.7 vs 1.1, P <0.01), there was no difference in the incidence of vascular and bleeding sequelae (1% in both groups). Of note, the incidence of blood-product transfusion was 3% in the group of liver-transplant candidates, and all transfusions were administered prophylactically before the procedure. The primary outcome of the study was the rate of failure of transradial access, which was similar in both groups (10% in liver-transplant vs 7% in non-liver-transplant candidates).[21]

Feng and associates[22] compared transradial with transfemoral approaches in ESLD patients, in regard to bleeding and vascular sequelae (N=334 patients). The transradial group had a significantly lower hemoglobin level (10.4 ± 1.9 vs 11.1 ± 2.02 g/dL, P=0.001) and a significantly higher INR (1.94 ± 1.16 vs 1.59 ± 0.62, P=0.0001) at baseline. The transradial group had lower incidences of pseudoaneurysm formation (0 vs 3.7%, P=0.019) and hematocrit reduction (5.4% vs 7.8%, P=0.0393). However, there were no bleeding complications in either group.[22] All of these studies illustrate the feasibility of the transradial approach, with its lower incidence of bleeding and procedure-related vascular sequelae. It is worth mentioning that the mean INR levels for the ESLD patients in all the previously mentioned studies were less than 2 and that almost no data exist regarding the subset of ESLD patients with an INR level of more than 2.

Conclusion

The current evidence is derived chiefly from retrospective studies and does not support prophylactic FFP administration in ESLD patients who are undergoing cardiac catheterization. The use of rFVIIa before cardiac catheterization is still questionable and might be associated with a higher frequency of venous thromboembolic events. Transradial arterial access for LHC appears to be a safer approach, with fewer bleeding and vascular complications. Future studies and randomized trials are needed to further determine the best approach to minimizing the bleeding risk in the ESLD patient population.

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