Assessment of Safety and Efficacy of Transjugular Liver Biopsy As a Diagnostic Method in Adult Patients with Congenital Bleeding Disorders with HCV Infection

M. Nassiri Toosi MD[1],
H. Ghanaati MD[2],
F. Azmoudeh Ardalan MD[3],
H. Agdarkosh MD[1],
S. R. Safai MD[4],
M. Lak MD[5],
M. Managhchi MD[5],
N. Karimi MD[5],
H. Foroutan MD[1],
H. Ghofrani MD[1],
M. Farahvash MD[1],
S. M. Alavian MD[6],
S. Shirani MD[4],
H. Saberi MD[5].

1. Department of Gastroentrology and Hepatology, Imam Khomeini Hospital, Tehran University of Medical Sciences,Tehran,Iran.
2. Department of Radiology, Medical Imaging Center, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran.
3. Department of Pathology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran.
4. Department of Hematology and Oncology, Vali-Asr Hospital, Tehran University of Medical Sciences, Tehran, Iran.
5. Iranian Hemophilia Center, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran.
6. Department of Gastroentrology and Hepatology, Baghiyyatollah Hospital, Baghiyyatollah University of Medical Sciences, Tehran, Iran.
7. Department of Radiology, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran.
8. Department of Radiology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran.

Corresponding Author:
M. Nassiri Toosi, Apt#24, ASP Building, 1431 Shariati St., Tehran, Iran.
Tel: +98 21 2602523
Fax: +98 21 2605908,
E-mail:
mohsen_nasiri@yahoo.com

Background/Objectives: Liver biopsy in patients with congenital bleeding disorders (CBD) and hepatitis C virus (HCV) infection is still a challenge between risk of procedure and effect of biopsy result on management.

Materials and Methods: We did transjugular liver biopsy (TJLB) on 12 patients with CBD with chronic HCV infection and elevated liver enzymes to determine its safety, efficiency and therapeutic consequences.

Results: All patients were men, with a median age of 29.5 years (14-54 years). Eleven patients had haemophilia A (10 severe, one moderate) and one patient had factor XIII deficiency, with no titer of inhibitor. HCV genotyping was carried out with type 1a (7 patients), type 1b (2 patients), type 3 (2 patients) and genotype 1a and 1b (1 patient). HIV and HBV co-infection was negative in all patients. We used the modified Ross needle with 100% transjugular access rate to the hepatic veins and 92% success rate in tissue obtaining. The specimen obtained was satisfactory but limited for histopathologic diagnosis in 54.5%. Mild hepatitis was revealed in 4 patients (36.4%), moderate hepatitis in 5 (45.4%) and extended fibrosis or cirrhosis in 2 (18.2%). There were 2 procedure-related complications (16.6%). The major limitation of technique was low number of portal area in liver biopsies.

Conclusion: TJLB with some limitations is useful in patients with CBD. Transjugular approach to liver biopsy is a safe and effective alternative to the percutaneous approach in patients with CBD and could be requested to determine their liver prognosis and considered for diagnostic liver biopsy prior to anti-HCV therapy.

Keywords: congenital bleeding disorder, liver, biopsy, hepatitis

Introduction

Since patients with hemophilia require replacement coagulation factors, they are at an increased risk of contracting a number of blood-borne infections such as HCV, HBV, and HIV. The prevalence of HCV infection among patients with congenital bleeding disorders ranges from 86 to 98%.[1] The long-term effects of this infection in the hemophiliac population are as yet unclear. It is further suggested that at least 50% of patients develop chronic hepatitis 10-20 years after infection, and perhaps up to 20% of them may develop cirrhosis.[2,3]

The challenge for those who care for this population is to define the extent of liver disease in order to determine the prognosis and to plan appropriate treatment strategies. Liver biopsy, a necessary component of the evaluation of patients with chronic liver disease particularly in those infected with HCV genotype 1, provides direct histological assessment of liver inflammation and fibrosis. Consequently, the *2002 National Institutes of Health (NIH) Consensus Development Conference on HCV* recommends that HCV-infected patients undergo pretreatment liver biopsy to assess the degree of hepatic fibrosis and inflammation.[4]

Furthermore, hepatic histological assessment is important to suggest the likelihood of disease progression, to determine the urgency for treatment, to predict responsiveness to antiviral therapy, and to provide a baseline for future histological comparisons.[4]

Liver biopsy is not warranted in those with hemophilia because of perceived high morbidity and mortality risks from bleeding. An early study estimated that mortality was as high as 1% and morbidity 12.5%.[5] More recently, it has been suggested again that liver biopsy is unsafe.[6] Transjugular liver biopsy is the technique of choice in patients with contraindications for percutaneous biopsy essentially because of massive ascites, massive obesity, suspected vascular tumor or peliosis hepatis and severe coagulopathy.[7] Recent guidelines proposed that liver biopsy, if necessary in hemophiliacs, should be performed by the transjugular liver biopsy prepared by adequate factor replacement.[8]

We reviewed our experience with transjugular liver biopsies over a one-year period to study both the technical aspects of performance of TJLB at our institution and also to determine whether the histological results helped with further management of hemophiliacs with chronic HCV infection.

Materials and Methods

Patients

Twelve chronic hepatitis C (HCV) infected patients with congenital bleeding disorders (CBD) with laboratory evidence of elevated liver enzymes 1.5 times more than upper limit of normal for more than six months,who were referred for pre-treatment liver assessment, underwent transjugular aspiration liver biopsy (TJLB) between December 2002 and December 2003 in a Tehran University affiliated hospital, Tehran, Iran. They were from 236 patients with inherited coagulation defects registered at the Iranian Hemophilia Center.

Patient's Information and details of underlying bleeding diatheses, factor inhibitor, viral status, liver function tests, prothrombin time, serum bilirubin, biochemical tests, CBC (hemoglobin and platelet), abdominal ultrasound (liver status, collateral and spleen size), esophagoscopy (in cases with stigmata of cirrhosis) was collected. Each patient's clinical course was characterized by: (1) pre- and post-biopsy hemoglobin; (2) pre- and post-biopsy abdominal ultrasound; (3) the factor replacement regimen for hemostasis prophylaxis; (4) Ross modified needle transseptal liver biopsy; (5) peri-procedure clinical courses and complications recording; and (6) histologic examination of the liver tissue.

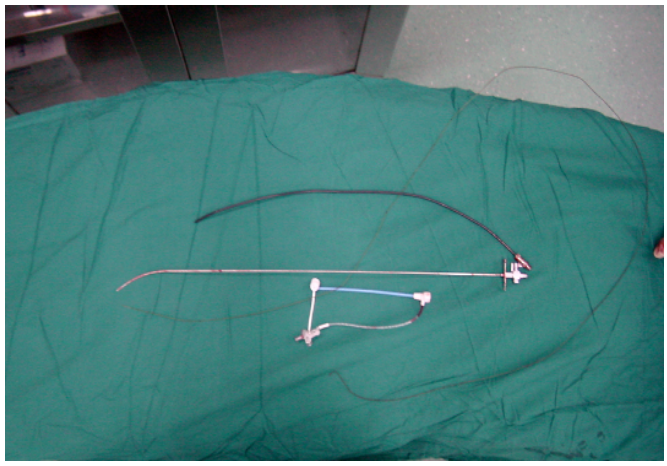

Figure 1: Transjugular liver biopsy set (From Cook Company)

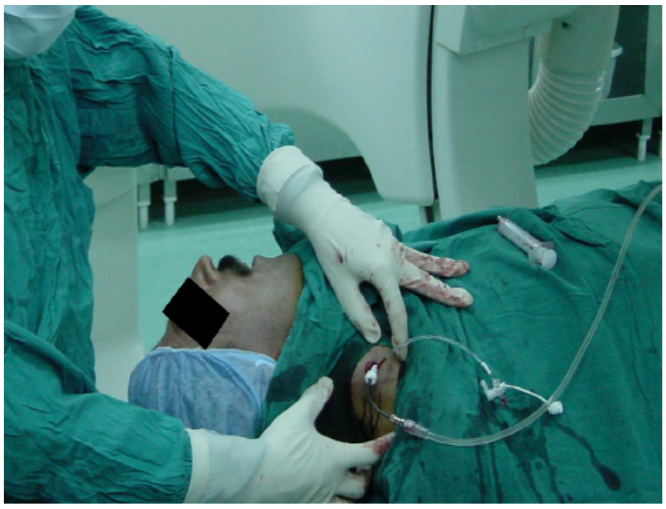

Figure 2: Patient position and entry site

Transjugular Liver Biopsy

We did TJLB with a coordinated multidisciplinary approach with hematology, hepatology, radiology, and pathology services. The ethics and research committee of the University approved the proposal. The informed consent form was taken from all patients.

All biopsies were performed in the angiography suite using a digital subtraction unit. An expert interventional radiologist (HG) performed all procedures using the modified Ross needle trans-septal liver biopsy set (Cook, Bloomington, IN, USA).(Figures1 and 2) A bolus of factor concentrate sufficient to achieve a factor level of 0.8 to 1.0 IU/ml was administered 30 minutes before the procedure. After the procedure, the patients received intermittent factor replacement 25-30 IU/kg every 8 hour in the first day after liver biopsy and the same dose was tapered off every 12 h in the second and third days after biopsy. The patient with factor XIII deficiency was administered cryoprecipitate before and 12h

after the procedure. None of the patients received concomitant tranexamic acid or desmopressin (DDAVP). All patients were administered factor replacement with a goal of achieving 80-100% activity before liver biopsy. If necessary, intravenous midazolam (1–2 mg) was administered for sedation before the biopsy. Prophylactic antibiotics were not prescribed routinely. After local anesthesia, the right internal jugular vein was punctured under direct ultrasound guidance. After tract dilatation, a standard 0.035-inch J-curved guidewire was passed to the inferior vena cava. By using a 5-F Cobra catheter, the guidewire was manipulated to the right or middle hepatic vein. The right hepatic vein was catheterized under fluoroscopic guidance, and a venogram confirmed catheter position.(Figures 3 and 4) The Cobra catheter was then removed, and a 9-F stiffening curved sheath guide catheter with an angled tip was passed over the guidewire into the hepatic vein. A stiffer guidewire was then advanced through the catheter and an angled sheath with an inner metal cannula was inserted into the right hepatic vein. A 16-gauge core biopsy needle, connected to a syringe filled with contrast media, was advanced through the sheath. The catheter and needle were advanced to a wedged position at the centre of the right hepatic lobe. Wedging was confirmed by the absence of reflux after injection of 2 ml of contrast medium into the needle. The needle was then flushed with 5 ml of saline. The patient was asked to hold his breath; the needle, with a strong suction on the syringe, was rapidly advanced 15 mm beyond the tip of the catheter and withdrawn. The hepatic tissue specimen was retained within the needle. Our protocol was to repeat the needle pass to obtain sufficient tissue cores, for a maximum of four times. Finally, the contrast was introduced into the guiding sheath to ensure that no abnormal extravasation of contrast had developed. All devices were then removed and manual digital pressure exerted over the neck puncture site to secure hemostasis. Subsequently, the head of the patient was elevated to 30–45 degrees for 4h to aid hemostasis. Patients were hospitalized and controlled after their liver biopsies for 24h. We did a control abdominal ultrasound in the next day after biopsy for all patients.

Histological Review

The specimens obtained from each attempt (needle pass) were collected in a contained formalin bottle. For each specimen two H&E, one Masson's trichrome, and one reticulin stained slide was done. A single histopathologist (FAA) independently reviewed the specimens. These parameters were assessed with regard to the number of attempts (needle passes) per case, number of tissue cores per biopsy (number of fragments per section, per case and per pass), sample size and adequacy for histological diagnosis (area of liver tissue per section, per case and per pass), number of portal tracts (per section, per case and per pass), and histological diagnosis. The presence and degree of steatosis were assessed as well. Histological change was also assessed according to the METAVIR score, which allows grading activity from A0 (no activity) to A3 (major activity) and fibrosis from F0 (no fibrosis) to F4 (cirrhosis).[12] Thereafter, liver disease was classified as mild hepatitis (A≤1 and F≤1), moderate hepatitis (A> 1 and F1 or 0, or any A and F2) and extended fibrosis or cirrhosis (any A and F3 or 4).[9] The values of serum ALT, AST, platelet, INR, and albumin at the time of liver biopsy were compared between histology results of F≤2 as early fibrosis with F3 or 4 as extensive fibrosis or cirrhosis.

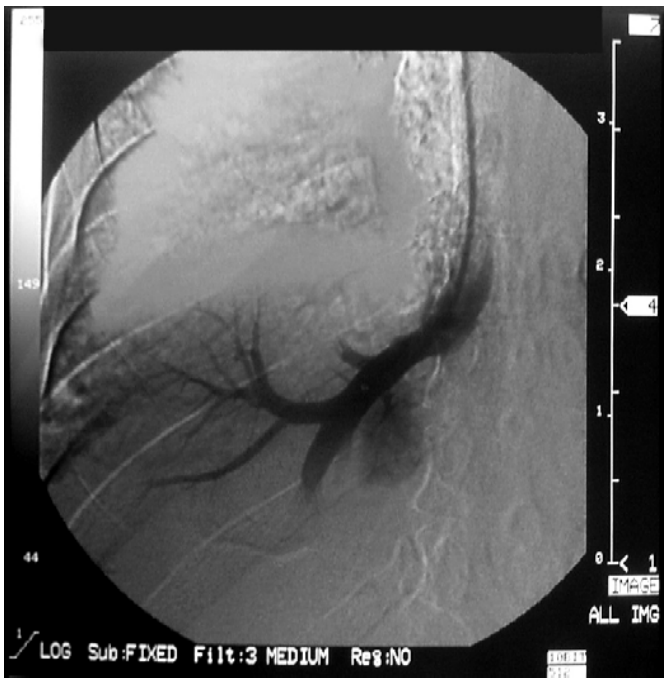

Figure 3: Prebiopsy hepatic venography

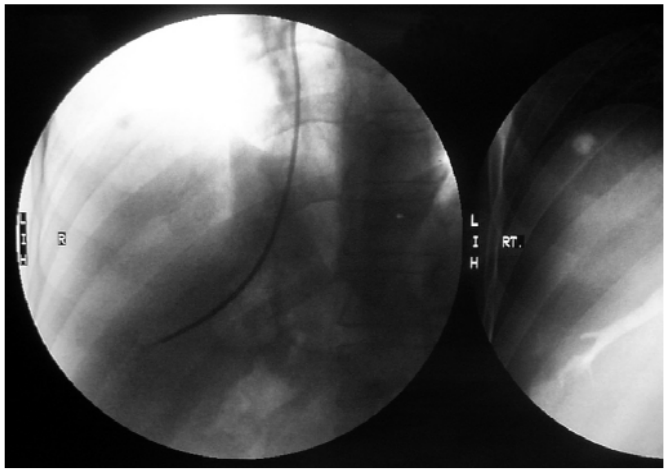

Figure 4: Fluroscopic control of the needle during biopsy

Table 1: Demography, baseline clinical and biochemical status and results of hemophiliac patients underwent transjugular liver biopsy

Age	HCV genotype	ALT	AST	Platelet (X1000)	INR	Albumin	Factor defeciency	Hb before biopsy	Hb after biopsy	Time of biopsy (min.)	METAVIR scoring		Complications
											Activity	Fibrosis	
28	1a	117	49	197	1	5.6	VIII <1%	17.7	17	20	_	_	None
20	1a	92	47	144	1	4.7	VIII <1%	16.7	16.2	20	0	1	Liver hematoma, abd. Pain
31	1b	82	30	152	1	4.2	VIII <1%	16.7	16.2	25	0	1	None
21	1a	109	56	167	1.2	5.3	XIII <1%	15.9	15.8	20	1	1	None
20	3a	152	72	153	1	4.2	VIII <1%	17.1	15.1	30	1	1	None
49	1a	54	48	226	1.2	4.2	VIII <1%	16.7	15.9	20	2	1	None
31	3a	102	43	176	1.3	4.5	VIII <1%	15.6	15.1	15	2	1	None
41	1a	50	32	188	1.2	4.3	VIII <1%	17.4	16.1	20	3	1	None
20	1a,1b	69	54	153	1.1	4.8	VIII <1%	17.4	17.4	15	3	1	None
14	1b	153	92	150	1.3	4	VIII 5%	14	12.5	25	2	2	None
54	1a	78	72	39	1.5	3.6	VIII <1%	14.5	14.5	35	3	3	Carotid puncture
48	1a	126	181	46	1.3	3.6	VIII <1%	15	15.6	20	2	4	Abdominal pain

Results

Procedure-Related

All patients were men, with a median age of 29.5 years (range 14–54 years). Their inhibitor titer was not high. Eleven patients had factor VIII deficiency. All had elevated liver enzymes and positive HCV-RNA (polymerase chain reaction test). Patients' demographics, baseline clinical status and laboratory findings are summarized in Table 1.

Transjugular access to the hepatic veins was successful in all cases (100%). Average procedure time, from start of the procedure to getting the patient off the fluoroscopy table, was 22 min (range 15–35 min). The number of passes ranged from one to four (mean 2.25). Tissue specimens were obtained from 11 (92%) of the patients. The clinical course of each patient is depicted in Table 1. Regarding the complications related to the biopsy at the time of the procedure, there was one case of carotid puncture, whit no instant consequence and the procedure proceeded with correct approaching into the internal jugular vein. The patient did well in follow-up. None of the patients experienced any bleeding during or after the procedure. No significant post-biopsy hemorrhage was noted. Among the patients, post-biopsy hemoglobin decreased by a mean of 0.6% (range 0.6–2%). The rest of the procedure was very well tolerated by most of our patients. Only two patients experienced mild to moderate abdominal discomfort and pain on day post-biopsy. On post-biopsy abdominal ultrasound, one of the patients with abdominal pain had intrahepatic hematoma; more abdominal imaging was not performed for the patient due to rapid resolution of symptoms. Both episodes of abdominal discomfort resolved spontaneously. Post-biopsy abdominal ultrasound was normal in all other 11 patients.

Duration of Stay and Follow-up

There was not any major complication during the overnight stay. All patients were discharged after an overnight stay. All patients were seen in 1 week to review the results of their biopsies. None of them were noted to have any bleeding complications, even the patient with liver hematoma on ultrasound.

Biopsy Results

Twenty seven specimens from twelve patients were evaluated. Each specimen represented one attempt (or pass). The number of attempts ranged from one to four for each patient with a median of 2 per patient. Satisfactory samples for histopathologic analysis were obtained in all except one case (with three attempts), with a 92% success rate. The biopsy was not repeated in that patient and he was treated with a combination of interferon and ribavirin. The results of 11 liver biopsies were reported.

The number of fragments per patient ranged from 2 to 20 with a median of 10. Fragmentation of samples was not found to be a problem in any case. The length of liver tissue for each patient ranged from 2 to 32 mm with a median of 14 mm. The number of portal triads per patient ranged from 2 to 13 with a median of 5. Histopathologic evaluation was limited in six cases because of the small number of portal tracts (less than six portal tracts) (9). All tissue specimens were deemed satisfactory for histologic analysis and diagnosis. Mild macrovesicular steatosis (up to 5%) was observed in 4 patients (36%). The results of necroinflammatory grade and stage of fibrosis are summarized in Tables 1.

Histological score could be evaluated in all successful procedures. Mild hepatitis was recorded in 4 patients (36.4%), moderate hepatitis in 5 (45.4%), and there was evidence of extended fibrosis or cirrhosis in 2 (18.2%).

Discussion

Liver biopsy in patients with CBD and HCV infection is still a challenge, for the expenses, morbidity and mortality, risk of procedure and impressive effect

of liver histology assessment on prognosis and treatment strategy. Despite recent reports on low morbidity of percutaneous liver biopsies [10], and due to the former reports of high morbidity (12.5%) and anecdotal fatality rate of 1%, compared to <0.01% in nonhemophiliacs, most physicians are unwilling to consider this procedure in these patients.[6] However, despite the development of noninvasive imaging techniques and the refinements in laboratory testing, liver biopsy is still the single best way of evaluating fibrosis and assessment of histology to plan treatment and to determine prognosis in patients with chronic HCV. Moreover, the information obtained on liver biopsy allows affected individuals to make more informed choices about initiation or postponement of naive antiviral treatment or making decision in non-responder cases.[11] Although TJLB accompanied by adequate factor replacement has been suggested for patients with CBD infected with HCV[11], there are a few, but growing reports of experiences with TJLB in the literature of hemophiliacs. Gupta et al (1997) [12] reported 6 TJLB in the period of 1993-1996, DiMichele et al(2003) [13] have the experience of 13 TJLBs in the period of 2000-2002, and Stieltjes et al (2004)[14] presented 88 TJLBs in the period of 1992-2002 in adult CBD patients with HCV infection without any significant morbidity and no mortality.

Here, we report our 12 experiences of TJLB in CBD patients with HCV infection over one year (2003). There were no major complications in our study and only three patients had minor events directly due to the procedure (carotid puncture 8.3%, liver hematoma 8.3% and abdominal pain 16.7%). Abdominal pain and subcapsular and intrahepatic hematomas are not uncommon post-biopsy findings. Minuk et al showed that by real-time ultrasonography, subcapsular and intrahepatic hematomas could be detected in 23% of patients after percutaneous liver biopsy; none was of clinical significance.[15] All these minor complications were resolved spontaneously without any sequelae. The safety of TJLB has been shown in hemophiliacs previously. Absence of ascites and extensive fibrosis could be related to lower morbidity of TJLB in our hemophiliacs compared to other high-risk indications for TJLB. We come across no procedure-related complication despite the use of less stringent hemostasis prophylaxis and a shorter overnight hospitalization than previously described for hemophilia patients by Gupta et al.[12]

We used the modified Ross needle for biopsy. Corr et al (using a Ross needle) were able to obtain a specimen in 84% of biopsy attempts.[16] The overall success rate of transjugular approach in the literature ranges from 64% to 97%.[17-23] In our study, the technical success rate was 92% and the specimen obtained was satisfactory but limited for histopathologic diagnosis in 54.5% of the cases. Therefore, we think the overall success rate of TJLB does not differ among the types of needles. Adequacy of the specimens has been a concern for TJLB. In this study, although the fragmentation compromised architectural evaluation of samples, scoring was successfully performed in all cases without any problem. The cut-off levels of six portal tracts identified were used in this series as sufficient to grade and stage liver damage in hepatitis C.[9] In this study, the major limitation of the technique was the low number of portal areas in biopsy samples.

Knowing the exact stage of liver fibrosis is crucial for therapeutic decision making and assessing prognosis in chronic HCV infection. The need for liver biopsy in hemophiliacs is a controversial issue. Discussion about this issue could be extended in three aspects. Generally, liver biopsy has been recommended where there is doubt regarding the etiology of chronic liver disease[24] or to provide a baseline in individual patients with chronic HCV infection since there is consensus that patients with moderate to severe liver cell damage should be treated; and also baseline assessment offers a valuable standard for subsequent decision-makings.[25,26] Also, patients with severe fibrosis or cirrhosis need some special consideration in their treatment and management.[27] In this study, liver biopsy results in 55.6% of hemophiliacs fulfilled pretreatment liver assessment and subsequently changed their treatment strategy. The usefulness of a pretreatment liver biopsy requires further study with treatment follow up. We believe that more reports of pretreatment liver biopsy, like this study could help specialists for evidence-based judgment in this regard.

On the other hand, hemophiliacs have comorbidity mainly with joints and liver disease needing medical attention. The prognosis of liver involvement can affect their life planning. In this way, minimal or no fibrosis on liver biopsy may reassure about a favorable prognosis. Even though, it is suggested that some patients with chronic HCV infection could be treated without liver biopsy, but determination of liver prognosis could be the main concern of some hemophiliacs with other comorbid diseases.

It is worth mentioning that we need to know about liver injury and treatment of special groups of hemophiliacs like children with chronic HCV infection, through further research. It has been reported that children with hemophilia had less liver injury than children who had acquired HCV through blood transfusion or maternal–fetal transmission.[28] On the other hand, the result of a trial of IFN treatment in children with chronic hepatitis C and hemophilia was less encouraging[29], and it is suggested that interferon therapy should be offered to children

with hemophilia who are infected with HCV genotype 2.[30] In this study, we did TJLB in one 14-year-old hemophiliac and reported the liver biopsy result. Considering the prevalence of HCV infection in children with hemophilia and the importance of making decision for interferon therapy in a child of growing age, we believe it is justifiable to do broader research on children with hemophilia and biopsy-proven chronic HCV infection.

Conclusion

We have now demonstrated that the transjugular approach, with adequate hemostasis prophylaxis, is well-tolerated, safe and effective enough to procure diagnostic liver tissue from patients with severe congenital bleeding disorders and HCV-related liver disease. Based on our experience, we suggest that HCV-infected patients with congenital bleeding disorder cared for in hemophilia treatment centers with the required expert multidisciplinary support, should be considered for diagnostic liver biopsy prior to anti-HCV therapy. We believe that the transjugular approach to liver biopsy with the modified Ross needle is a safe and effective alternative to the percutaneous approach in patients with congenital bleeding disorders. Also, liver biopsy could be requested for hemophiliacs to determine their liver prognosis. Determination of selected special groups of hemophiliacs, who take more benefit from liver biopsy, as the main indications of this procedure, is needed. However, as our experience is limited, the safety and efficacy and indications of this procedure in this population must be further corroborated through the study of larger patient cohorts.

References

1. DiMichele D. Hemophilia 1996.Pediatr Clin N Am 1996; 43:709-36.
2. Fattovich G, Giustina G, Degos F, et al. Morbidity and mortality in compensated cirrhosis type C: a retrospective follow-up study of 384 patients. Gastroenterology 1997; 112: 463-472.
3. Darby SC, Ewart DW, Giangrande PL, et al, UK Haemophilia Centre Directors' Organisation. Mortality from liver cancer and liver disease in haemophilic men and boys in UK given blood products contaminated with hepatitis C. Lancet 1997; 350: 1425-1431.
4. National Institutes of Health Consensus Development Conference Statement. Management of Hepatitis C; 2002.June 10-12, 2002. http;//consensus.nih.gov/cons/116/091202116cdc-statement.htm
5. Aledort LM, Levin PH, Hilgartner M et al. A study of liver biopsies and liver disease among hemophiliacs. Blood 1985; 66: 367-72.
6. Lee CA. Investigation of chronic hepatitis C infection in individuals with haemophilia. Br J Haematol 1997; 96: 425–426.
7. Bravo AA, Sheth SG, Chopra S. Liver Biopsy. N Engl J Med 2001; 344 15: 495-500.
8. Makris M, Baglin T, Dusheiko G, Giangrande PL, Lee CA, Ludlam CA, et al. Guidelines on the diagnosis, management and prevention of hepatitis in hemophilia. Hemophilia 2001; 7: 339–345.
9. The French METAVIR Cooperative Study Group, 1994; Bedossa & Poynard, 1996.
10. Ahmed M, Mutimer DJ, Elias E, Linin J, Garrido M, Hubscher S, et al. A combined management protocol for patients with coagulation disorders infected with hepatitis C virus. Br J Haematol 1996; 95: 383–388.
11. Papatheodoridis GV, Cholongitas E. Hepatitis C and no response to antiviral therapy: potential current and future therapeutic options. J Viral Hepat 2004; 11: 287-96.
12. Gupta R, Druy EM, Kessler CM. Safety and potential usefulness of liver biopsy in HIV seropositive hemophiliacs employing a transjugular venous approach. Hemophilia 1997; 3: 201–204.
13. DiMichele D, Mirani G, Wilfredo-Canchis P, Trost DW, Talal AH. Transjugular liver biopsy is safe and diagnostic for patients with congenital bleeding disorders and hepatitis C infection. Hemophilia 2003; 9: 613–618.
14. Stieltjes N, Ounnoughene N, Sava E, Paugy P, Roussel-Robert V, Rosenberg AR, et al. Interest of transjugular liver biopsy in adult patients with haemophilia or other congenital bleeding disorders infected with hepatitis C virus. Br J Haematol, 2004; 125: 769–776.
15. Minuk GY, Sutherland LR, Wiseman DA, MacDonald FR, Ding DL. Prospective study of the incidence of ultrasound-detected intrahepatic and subcapsular hematomas in patients randomized to 6 or 24 hours of bed rest after percutaneous liver biopsy. Gastroenterology 1987; 92: 290–293.
16. Corr P, Beningfield SJ, Davey N. Transjugular liver biopsy: a review of 200 biopsies. Clin Radiol 1992; 45: 238-239.
17. Lebrec D, Goldfarb G, Degott C, Rueff B, Benhamou JP. Transvenous liver biopsy. An experience based on 1000 hepatic tissue samplings with this procedure. Gastroenterology 1982; 83: 338-40.
18. Bull HJM, Gilmore IT, Bradley RD, Marigold JH, Thompson RPH. Experience with transjugular liver biopsy. Gut 1983; 24: 1057-60.
19. Gamble P, Colapinto R, Stronell RD, Colman JC, Blendis L. Transjugular liver biopsy: a review of 461 biopsies. Radiology 1985; 157: 589-93.
20. McAfee JH, Keeffe EB, Lee RG, Rosch J. Transjugular liver biopsy. Hepatology 1992; 15: 726-32.
21. Velt PM, Choy OG, Shimkin PM, Link RJ. Transjugular liver biopsy in high risk patients with hepatic disease. Radiology 1984; 153: 91-3.
22. Corr P, Beningfield SJ, Davey N. Transjugular liver biopsy: a review of 200 biopsies. Clin Radiol 1992; 45: 238-9.
23. Colapinto R, Blendis L. Liver biopsy through the transjugular approach: modification of instruments. Radiology 1983; 148: 306-12.
24. Bravo A, Sheth SG, Chopra S. Liver biopsy. N Engl J Med 2001; 344: 495-500.
25. Krawitt EL, Lidofsky SD, Ferrentino N, et al. Efficacy of peginterferon alfa-2b plus ribavirin in patients with chronic hepatitis C previously unresponsive to interferon-based therapy. Hepatology 2002; 36(suppl. 1):359A.
26. Ghany MG, Kleiner DE, Alter H, et al. Progression of fibrosis in chronic hepatitis C. Gastroenterology 2003; 124: 97-104.
27. Heathcote EJ, Shiffman ML, Cooksley WG et al. Peginterferon-2a in patients with chronic hepatitis C and cirrhosis. N Engl J Med 2000; 343 : 1673-80.
28. Zellos A, Thomas DL, Mocilnikar C, et al. High viral load and mild liver injury in children with hemophilia compared with other children with chronic hepatitis C virus infection. J Pediatr Gastroenterol Nutr 1999; 29: 418–23.
29. Zwiener RJ, Fielman BA, Cochran C, et al. Interferon-alpha-2b treatment of chronic hepatitis C in children with hemophilia. Pediatr Infect Dis J 1996; 15: 906–8.
30. Ko JS, Choe YH, Kim EJ, Lee EH, Jang JJ, Seo JK. Interferon-alpha treatment of chronic hepatitis C in children with hemophilia. J Pediatr Gastroenterol Nutr 2001; 32: 41-4.