Abstract

Background Outcome of patients with hepatic venous outflow tract obstruction (HVOTO) has improved with newer treatments, including anticoagulants, radiological interventions and liver transplant. In India, however, liver transplant and radiological interventions are costly and have limited availability. Hence, patients often opt for anticoagulation alone. We followed up a group of such patients to determine the clinical outcome with such treatment.

Methods Consecutive patients with HVOTO, treated with oral anticoagulation and supportive medical therapy but no radiological or surgical intervention, were followed up for at least 12 months. Diagnosis of HVOTO was based on color Doppler, and either angiography or magnetic resonance venography. Warfarin dose was adjusted to maintain international normalized ratio (INR) between 2.0 and 3.0. Patients with secondary HVOTO and those with baseline INR >2.0 were excluded. Response was defined as absence of ascites and/or encephalopathy, normal AST/ALT, bilirubin <1.5 mg/dL, and no portal hypertension related bleed after starting therapy.

Results Of 43 patients (mean [SD] age=28.7 [8.4] years; 20 men), 26 (61%) had a response during a median follow up of 23 (range 15-33) months. The response first appeared within 2 months of the start of treatment in 18 patients and between 2 and 5 months from the start of treatment in eight patients. Seven patients died of progressive liver failure (6 patients) or GI bleed (1 patient). Nine patients had anticoagulation-related complications. On univariate analysis, short duration of symptoms, high serum albumin, low baseline INR, and low baseline Child-Pugh’s (CP) or Clichy scores predicted response. Presence of hepatic encephalopathy, portal vein thrombosis, obstruction of all hepatic veins, low albumin, high INR, high serum bilirubin, high baseline CP score, Murad score and adverse Clichy index were associated with higher mortality rate. However, on multivariate analysis, only low CP score was associated with response, and no factor was found to predict death.

Conclusions More than half of patients with HVOTO show response with only supportive medical therapy and anticoagulants. This occurs more often in patients with low CP score. Some patients may have delayed response.

Key words Budd-Chiari syndrome · chronic liver disease · portal hypertension

Introduction

Management of hepatic vein outflow tract obstruction (HVOTO) has drastically changed over the last 30 years, with the advent of radiological intervention techniques such as trans-jugular intrahepatic porto-systemic shunt (TIPSS) and liver transplantation. In addition, several underlying prothrombotic conditions have been identified. A step-wise management protocol, consisting of anticoagulation, followed by radiological intervention, and then liver transplantation, based on non-response to the previous step, has been proposed.

HVOTO is being recognized more often in India. However, most Indian patients cannot undergo a therapeutic radiological intervention or liver transplant, because of their high cost and limited availability. Hence, many patients opt for only supportive medical therapy and anticoagulants, though the natural history of disease with such treatment remains unknown. There is increasing acceptance for use of anticoagulation in all patients with HVOTO, though the issue remains controversial.
Survival with medical therapy alone has varied from 10%-77%.[12-14] We followed up a group of patients who received anticoagulant therapy alone.

Methods

Sixty consecutive adult patients with HVOTO (Fig. 1) seen over a period of two years underwent a detailed clinical and laboratory evaluation, including liver biochemistry, international normalized ratio (INR), hemogram, abdominal ultrasonography, upper gastrointestinal (GI) endoscopy, HBsAg, anti-hepatitis C virus antibody, anti-nuclear antibody and serum ceruloplasmin level. Child-Pugh (CP) score, Murad score, Murad class and Clichy score were calculated at baseline. Clichy score >5.4, CP score, Murad score and Murad class were tested as adverse prognostic scores. All patients underwent testing for factor V Leiden (FVL) mutation and anti-phospholipid antibody (APLA). Levels of protein C, protein S and antithrombin III were estimated in patients with normal serum albumin and INR. If hemogram was abnormal, a bone marrow examination was done to look for myeloproliferative disorders (MPD). After diagnosis, all patients were offered radiological intervention or surgery, if these were technically feasible. Forty-three patients who could not undergo these procedures, either because of technical reasons or cost consideration, were offered treatment with anticoagulants. The treatment was begun with heparin, which was gradually replaced with warfarin over the next three days. Diuretics and other supportive therapy were prescribed, as required. Patients with history of variceal bleeding and those with large esophageal varices at endoscopy underwent variceal band ligation before anticoagulant treatment was begun.

INR was monitored every week till the target [2.0-3.0] was achieved on a stable dose of warfarin. Patients were then followed every month with clinical evaluation, INR and liver function tests, for at least 12 months. Response was defined as absence of detectable ascites and encephalopathy during a clinical visit, no portal hypertension-related bleed since the start of therapy, normal serum AST/ALT levels and serum bilirubin below 1.5 mg/dL.

Patients with HVOTO secondary to hepatocellular carcinoma, metastatic cancer or liver abscess, and those with INR >=2.0 before the start of treatment were excluded. The institutional ethics committee approved the study, and patients gave informed consent.

Association of clinical response with various predictors was assessed using Fisher’s exact test, chi square test and Mann-Whitney test. Predictors showing significant association (p<0.10) with outcome in univariate analysis were entered into a multivariate logistic regression model. Separate analyses were done by including CP score, serum albumin levels or INR to avoid collinearity. SPSS software (version 16.0) was used for data analysis.

Results

Table 1 shows the demographic and clinical characteristics of the 43 patients enrolled in the study during a 2-year period. Among these, a radiological intervention was technically not feasible in six, and the remaining 37 could not afford such a procedure.

All the patients were symptomatic; the duration of symptoms was less than 1 month in three patients, 1-6
months for 21 patients and more than 6 months in 19 patients. Five patients were in Child class A, 28 in class B and 10 in class C. Four patients belonged to Murad class 1, none to class 2, and 39 to class 3. Twenty-six patients had Clichy score exceeding 5.4. Twenty-seven (62.7%) patients had obstruction of all three hepatic veins and 16 had obstruction of two hepatic veins. Thrombosis at additional sites was found in 25 patients (inferior vena cava 17, portal vein 7, deep limb veins 4 and cortical sinus 2). Five patients had FVL mutation, four had APLA and two had MPD (both polycythemia rubra vera). Forty-two patients had ascites, and five had hepatic encephalopathy. Median (range) AST and ALT levels at baseline were 55 (24-345) IU/dL and 43 (21-398) IU/dL, respectively; one or both of these were elevated in 36 patients.

The study subjects were followed up for a median period of 21 (range 15-33) months. Of the 43 patients receiving anti-coagulants and supportive treatment, 26 (60.5%) showed response beginning at different time points, including 13 by the end of first month, 18 by the end of 2 months, and 8 others between 2 and 5 months. No patient showed a response thereafter. Patients with symptom duration upto 8 months were more likely to have a response (19 of 26) than those with a shorter symptom duration (7 of 17; \( p=0.04 \), OR 3.88 [95% CI 1.06-14.19]; Table 1). Response was associated with a CP score less than 10 (20 of 26, \( p=0.47 \); OR 2.3 [1.01-5.27]) at baseline. On multivariate analysis, a CP score \( \leq 9 \) was the only factor significantly associated with response. Demographic features, other clinical features, bilirubin levels, presence of prothrombotic conditions, involvement of the IVC, portal vein thrombosis, Clichy score, Murad score and Murad class had no association with response.

Follow-up Doppler studies were done in 14 patients who had a response. Seven had complete and three had partial recanalization of the hepatic veins. Seven patients died during follow-up – 6 of progressive liver failure within the first 4 months of admission, and one of refractory GI bleed after 15 months. Death was more common in patients with encephalopathy (3/5; \( p=0.02 \), RR 7.7 [95% CI 1.56-30.04]), jaundice (6/17; \( p=0.01 \), RR 2.81 [1.57-5.00]). Low albumin, high INR, high bilirubin, high baseline CP score, high Murad score, adverse Clichy index (\( p=0.02 \), RR1.89 [1.39-2.58]), block in all hepatic veins (\( p=0.02 \), RR 1.8 [1.34-2.41]) and presence of portal vein thrombosis (\( p=0.008 \), RR 6.86 [1.95-24.15]) were also associated with death. On multivariate analysis, none of these factors showed significant association with death.

Nine patients had complications related to oral anticoagulation – menorrhagia in four, GI bleed in three, and hemoperitoneum in two. One patient with GI bleed died. Four of the five patients with severe bleeding had CP score of 9 or more.

### Table 1  Profile of patients treated with anticoagulants and supportive medical therapy, and relationship of various parameters with response and survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=43)</th>
<th>Response (n=26)</th>
<th>No response (n=17)</th>
<th>p value</th>
<th>Alive (n=36)</th>
<th>Dead (n=7)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>28.7 (8.4)</td>
<td>26.9 (8.2)</td>
<td>31.3 (8.9)</td>
<td>0.10</td>
<td>29.0 (8.8)</td>
<td>27.0 (6.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Men</td>
<td>18</td>
<td>10</td>
<td>8</td>
<td>0.36</td>
<td>16</td>
<td>2</td>
<td>0.20</td>
</tr>
<tr>
<td>Duration of symptoms (mo)</td>
<td>6 (1-120)</td>
<td>6 (1-120)</td>
<td>12 (1-48)</td>
<td>0.09</td>
<td>6 (1-120)</td>
<td>6 (1-36)</td>
<td>0.73</td>
</tr>
<tr>
<td>Ascites</td>
<td>42</td>
<td>25</td>
<td>17</td>
<td>0.60</td>
<td>35</td>
<td>7</td>
<td>0.83</td>
</tr>
<tr>
<td>Eenchalopathy</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>0.37</td>
<td>2</td>
<td>3</td>
<td>0.02</td>
</tr>
<tr>
<td>GI bleed (before treatment)</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>0.72</td>
<td>4</td>
<td>3</td>
<td>0.07</td>
</tr>
<tr>
<td>Jaundice</td>
<td>17</td>
<td>8</td>
<td>9</td>
<td>0.15</td>
<td>11</td>
<td>6</td>
<td>0.01</td>
</tr>
<tr>
<td>INR</td>
<td>1.3 (0.2)</td>
<td>1.2 (0.2)</td>
<td>1.4 (0.3)</td>
<td>0.004</td>
<td>1.3 (0.2)</td>
<td>1.5 (0.2)</td>
<td>0.001</td>
</tr>
<tr>
<td>Bilirubin (mg/dL)</td>
<td>2.2 (1.4)</td>
<td>2.0 (1.3)</td>
<td>2.4 (1.5)</td>
<td>0.38</td>
<td>1.9 (1.2)</td>
<td>3.4 (1.5)</td>
<td>0.008</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>2.9 (0.7)</td>
<td>3.1 (0.7)</td>
<td>2.5 (0.7)</td>
<td>0.02</td>
<td>3.0 (0.7)</td>
<td>2.2 (0.4)</td>
<td>0.01</td>
</tr>
<tr>
<td>Murad score</td>
<td>2.0 (0.6)</td>
<td>1.9 (0.5)</td>
<td>2.1 (0.6)</td>
<td>0.25</td>
<td>1.9 (0.5)</td>
<td>2.5 (0.7)</td>
<td>0.003</td>
</tr>
<tr>
<td>Baseline Child-Pugh score;</td>
<td>8 (6-15)</td>
<td>8 (6-14)</td>
<td>10 (7-15)</td>
<td>0.02</td>
<td>8 (6-14)</td>
<td>12 (9-15)</td>
<td>0.001</td>
</tr>
<tr>
<td>(median (range))</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Clichy score</td>
<td>26</td>
<td>13</td>
<td>13</td>
<td>0.07</td>
<td>19</td>
<td>7</td>
<td>0.02</td>
</tr>
<tr>
<td>All HV obstruction</td>
<td>27</td>
<td>17</td>
<td>10</td>
<td>0.66</td>
<td>20</td>
<td>7</td>
<td>0.02</td>
</tr>
<tr>
<td>IVC thrombosis</td>
<td>17</td>
<td>13</td>
<td>4</td>
<td>0.08</td>
<td>16</td>
<td>1</td>
<td>0.14</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>7</td>
<td>2</td>
<td>5</td>
<td>0.07</td>
<td>3</td>
<td>4</td>
<td>0.008</td>
</tr>
<tr>
<td>Presence of prothrombotic condition</td>
<td>11</td>
<td>6</td>
<td>5</td>
<td>0.45</td>
<td>8</td>
<td>3</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Data are shown as mean (SD) or number. INR: international normalized ratio; HV: hepatic vein; IVC: inferior vena cava.
During the study period, 11 other patients with HVOTO underwent radiologic intervention in our hospital. Among them, at the end of one year follow-up, 9 showed response and none had died. Two other patients underwent surgery during the period; of these, one died.

Discussion

In our study, a combination of anticoagulation and supportive medical therapy was associated with occurrence of response in 61% of our patients with HVOTO with baseline INR below 2.0, in whom radiological intervention was not possible either because of a technical reason or high cost. Response usually occurred within two months of starting this treatment, but was delayed till up to 5 months after the start of treatment in some patients. Seven patients died. Factors indicating severe disease and poor liver function were associated with lack of response and mortality. On multivariate analysis, low CP score was associated with response.

In patients with HVOTO, anticoagulants may prevent extension of existing thrombus and formation of fresh thrombus in recanalized vessels or collaterals, and thus help maintain hepatic venous outflow. Anticoagulation has been advocated for all patients with HVOTO. There is a need to identify predictors of response to medical therapy alone, which is what many of our patients receive because of lack of facilities or finances for radiological treatment. Initial results with such medical therapy were disappointing with reported survival rates of less than 30%.

In another study, 10 (77%) of 13 patients treated medically were alive at a median follow-up of 40 months (range 17-176 months), 1 had died, and 2 were lost to follow-up. Plessier et al found clinical response in only 17.6% of patients receiving medical treatment, at the end of 2 weeks. A recent study has shown excellent long-term results with TIPSS. A recent study from India showed good results with vascular stenting in patients with HVOTO, but did not include data on patients on medical therapy alone.

Our data show fair short-term response rates and survival in patients of HVOTO with mild hepatic dysfunction (CP score up to 9) who receive medical therapy alone. Furthermore, survival in these patients may depend on severity of liver dysfunction. Thus, in patients with poor liver function, medical therapy alone may not be acceptable. Our data however do not permit assessment of longer-term survival or morbidity rate with medical management alone.

Though radiological intervention is the mainstay of management of HVOTO, supportive medical management may have a role, especially in patients in whom vascular intervention is not feasible or in those who cannot afford such treatment.

References