Retrograde Transvenous Obliteration of Gastric Varices using Sodium Tetracycl Sulfate: Technical Considerations and Results from a Single Institution Retrospective Study

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Introduction

Retrograde transvenous obliteration (RTO) with the assistance of a balloon (BRTO) or a vascular plug (PARTO) is an established method for treating gastric varices (GVs) secondary to portal hypertension. Most of the available studies on RTO have used lipiodol along with sclerosing agents like ethanolamine oleate or sodium tetracycl sulfate (STS). We evaluated the safety and efficacy of RTO for treating GVs using STS as a sclerosant without lipiodol.

Materials and Methods

Sixteen patients (nine men, age range 16–74 years) were included in this retrospective study. Twelve patients presented with acute bleeding, two with chronic bleeding, one with large varices without bleeding, and one with refractory hepatic encephalopathy (HE). BRTO was attempted in 14 patients and PARTO in 2 patients. The technical and clinical success and complications of RTO were studied.

Results

The RTO procedure was technically successful in 14 (14/16, 87.5%) patients, with 13 (13/14, 93%) obtaining clinical success. One patient died due to the early recurrence of bleeding. Three patients had minor intraprocedural complications.

Conclusion

Retrograde gastric variceal obliteration using STS is safe and technically feasible with high technical and clinical success and low complication rate.
retrograde transvenous obliteration (BRTO) of GVs involves accessing the GRS to temporarily occlude its outflow using a balloon catheter and injecting a sclerosant within the varix in a retrograde manner to induce thrombosis and thereby obliterate the varices. A schematic diagram depicting a BRTO procedure is shown in (Fig. 1). In addition, BRTO has also been described to be of value in cases of recalcitrant hepatic encephalopathy (HE) by occluding the GRS. The authors report their experience on the use of sodium tetradecyl sulfate (STS) as the sclerosant during RTO of GVs in 16 patients with portal hypertension over a 4-year period.

Materials and Methods

Institutional ethical committee approval was obtained for this retrospective evaluation of patient records with consent waiver. Between February 2016 and April 2020, 16 patients had undergone RTO, of which 14 underwent BRTO and 2 underwent plug-assisted retrograde transvenous obliteration (PARTO) (Table 1). In patients who presented with acute upper gastrointestinal (GI) bleed, the procedure was performed within 2 hours to 3 days of clinical presentation. The time duration of procedure after endoscopy depended on the hemodynamic stability and presence of active bleeding on endoscopy. The exclusion criteria for RTO is the presence of gross ascites and main portal vein (MPV) thrombosis.

Patients and Clinical Presentation

Sixteen patients (9 men and 7 women), with a mean age of 50.9 years (age range 16 to 73 years) had undergone BRTO at our hospital over a 4-year period. Of these patients, 12 presented with an acute upper GI bleed, 2 had previous episodes of upper GI bleed with large (> 2 cm size) GVs on endoscopy but were asymptomatic at the time of BRTO, 1 patient underwent the procedure prophylactically because of large GVs, and 1 had refractory HE.

The cause of liver cirrhosis in the patient group (n = 16) was as follows: hepatitis B virus (n = 6), chronic alcohol abuse (n = 4), nonalcoholic steatohepatitis (NASH) (n = 4), extrahepatic portal venous obstruction (EHPVO) (n = 1), and cryptogenic (n = 1). Twelve patients were in Child B stage, 2 in Child C and 2 in Child A. All patients referred for bleeding had undergone upper GI endoscopy for confirming the diagnosis. Endoscopic N-butyl cyanoacrylate (NBCA) glue injection had been attempted in one patient prior to referral for RTO, but no clinical improvement was noted after the same.

BRTO was attempted in 14 and PARTO was attempted in 2.

Contrast-enhanced computed tomography (CECT) of the abdomen was performed in all patients on a 128 slice CT scanner (Somatom Flash, Siemens, Erlangen, Germany) using iohexol 300 mgI/mL as intravenous (IV) contrast material, which was injected by a pressure injector with 50 to 60-second scan delay, to assess for the following: liver volume, presence, anatomy and number of GRS, size of GVs, any large systemic efferent collaterals apart from GRS, patency of MPV and splenic vein (SV), and presence and severity of ascites.

BRTO Procedure

The right common femoral vein was accessed using a micropuncture set (Cook Medicals, USA) under local anesthesia and ultrasound guidance. Additional right internal jugular and left common femoral venous accesses were obtained for the two patients who underwent PARTO. A large-bore sheath (10 or 12 Fr sheath, Cook Medicals, USA) was advanced into the infrarenal IVC, and a 5 Fr catheter (Cobra 1/Davis/Headhunter 1, Cook, Medicals, USA) with a glidewire (0.035” diameter, Terumo, Japan) was used to access the LRV and subsequently the GRS. The catheter was exchanged for an occlusion balloon catheter (7.5 Fr Swan Ganz, Edwards Lifesciences, USA) in 13 patients. A 27 mm Equalizer occlusion catheter (Boston Scientific, USA) was used in one patient with a very large shunt measuring 25 mm.

An occlusion venogram was obtained and was assessed for adequacy of sealing by the balloon, contrast filling the varices, and systemic communication to inferior phrenic veins/pericardiophrenic veins (Fig. 2A). If pericatheter leak into the renal vein was noted, the balloon was deflated, placed in another location, and the process was repeated.

Coils/gelfoam slurry was injected to block any systemic efferent veins other than GRS. If the coiling of these veins was needed, it was performed using a microcatheter (Progreat, Terumo, Japan).

After confirming adequate stasis of contrast material within the varices with no systemic runoff, sclerosant injection was started (Fig. 2B). We compared the variceal filling on occlusion venogram with the corresponding preprocedure coronal CT venogram (Fig. 2C). The embolization mixture consists of an equal volume of STS (3% w/v sodium tetradecyl sulfate, Samarth Life Sciences, Mumbai, ...
India) and nonionic contrast material (Iohexol 300 mg I/mL) along with a few pledges of gelfoam (absorbable gelatin sponge, USP, Reliance life Sciences, Ahmedabad, India), which were mixed using the Tessari method by way of a three-way connector.

The necessary amount of sclerosant to be injected was estimated using the initial volume of contrast material that was used to obtain the occlusion venogram. An average of 9.5 mL of STS was used in each procedure which along with an equal volume of contrast material was a total volume of 20 mL of embolization mixture. Any reflux into the MPV and SV was avoided. The balloon was kept inflated in place for approximately 6 hours and was removed under fluoroscopic guidance.

The technical success of BRTO was defined as the ability to cannulate the GRS with successful inflation of a balloon for the required period. The authors failed to do BRTO in 2/16 patients due to failure to secure a good position for occluding the GRS with the balloon.

### Table 1  Demographic and clinical details of the patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Cause of cirrhosis</th>
<th>Indication for BRTO</th>
<th>Hemodynamic status</th>
<th>CPS</th>
<th>STS volume used (mL)</th>
<th>Technical success</th>
<th>Follow-up period (days)</th>
<th>Clinical result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>73</td>
<td>M</td>
<td>HBV</td>
<td>Electively for chronic bleeding</td>
<td>Stable</td>
<td>B8</td>
<td>0 (Failed)</td>
<td>No</td>
<td>Lost to follow up at 7 days</td>
<td>NA</td>
</tr>
<tr>
<td>2</td>
<td>69</td>
<td>M</td>
<td>HBV</td>
<td>Acute bleed</td>
<td>Stable</td>
<td>A6</td>
<td>8</td>
<td>Yes</td>
<td>945</td>
<td>No rebleed</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>M</td>
<td>HBV</td>
<td>Acute bleed</td>
<td>Unstable</td>
<td>B8</td>
<td>9</td>
<td>Yes</td>
<td>975</td>
<td>No rebleed</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>F</td>
<td>NASH</td>
<td>Acute bleed</td>
<td>Unstable</td>
<td>C10</td>
<td>10</td>
<td>Yes</td>
<td>770</td>
<td>No rebleed</td>
</tr>
<tr>
<td>5</td>
<td>74</td>
<td>F</td>
<td>NASH</td>
<td>Acute bleed</td>
<td>Stable</td>
<td>A6</td>
<td>11</td>
<td>Yes</td>
<td>190</td>
<td>No rebleed</td>
</tr>
<tr>
<td>6</td>
<td>60</td>
<td>M</td>
<td>Alcohol</td>
<td>Acute bleed</td>
<td>Stable</td>
<td>B8</td>
<td>8</td>
<td>Yes</td>
<td>120</td>
<td>No rebleed</td>
</tr>
<tr>
<td>7</td>
<td>55</td>
<td>M</td>
<td>NASH</td>
<td>HE</td>
<td>Stable</td>
<td>B9</td>
<td>12</td>
<td>Yes</td>
<td>1082</td>
<td>No episode of HE</td>
</tr>
<tr>
<td>8</td>
<td>37</td>
<td>M</td>
<td>Alcohol</td>
<td>Acute bleed</td>
<td>Stable</td>
<td>B7</td>
<td>10 (PARTO)</td>
<td>Yes</td>
<td>1062</td>
<td>No rebleed, mild ascites present</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>M</td>
<td>Alcohol</td>
<td>Acute bleed</td>
<td>Stable</td>
<td>B8</td>
<td>9</td>
<td>Yes</td>
<td>360</td>
<td>No rebleed, died after 1 year due to myocardial infarction</td>
</tr>
<tr>
<td>10</td>
<td>16</td>
<td>F</td>
<td>EHPVO</td>
<td>Electively due to large varices</td>
<td>Stable</td>
<td>B7</td>
<td>13</td>
<td>Yes</td>
<td>914</td>
<td>No rebleed, features of hypersplenism present</td>
</tr>
<tr>
<td>11</td>
<td>62</td>
<td>M</td>
<td>Alcohol</td>
<td>Acute bleed</td>
<td>Unstable</td>
<td>B9</td>
<td>7</td>
<td>Yes</td>
<td>0</td>
<td>Died due to rebleed at 2 hours</td>
</tr>
<tr>
<td>12</td>
<td>30</td>
<td>F</td>
<td>Cryptogenic</td>
<td>Electively for chronic bleeding</td>
<td>Stable</td>
<td>B8</td>
<td>8</td>
<td>Yes</td>
<td>530</td>
<td>No rebleed, banding done for oesophageal varices at 6 months, mild ascites present</td>
</tr>
<tr>
<td>13</td>
<td>16</td>
<td>M</td>
<td>HBV</td>
<td>Acute bleed</td>
<td>Stable</td>
<td>B7</td>
<td>11 (PARTO)</td>
<td>Yes</td>
<td>410</td>
<td>No rebleed</td>
</tr>
<tr>
<td>14</td>
<td>33</td>
<td>F</td>
<td>HBV</td>
<td>Acute bleed</td>
<td>Stable</td>
<td>B9</td>
<td>0 (Failed)</td>
<td>No</td>
<td>21</td>
<td>Endoscopic glue injected at day 4, rebleed at day 21 and later died</td>
</tr>
<tr>
<td>15</td>
<td>67</td>
<td>F</td>
<td>HBV</td>
<td>Acute bleed</td>
<td>Stable</td>
<td>B8</td>
<td>8</td>
<td>Yes</td>
<td>120</td>
<td>No rebleed</td>
</tr>
<tr>
<td>16</td>
<td>40</td>
<td>F</td>
<td>NASH</td>
<td>Acute bleed</td>
<td>Stable</td>
<td>A6</td>
<td>9</td>
<td>Yes</td>
<td>150</td>
<td>No rebleed</td>
</tr>
</tbody>
</table>

Abbreviations: BRTO, balloon-occluded retrograde transvenous obliteration; CLD, chronic liver disease; CPS, Child–Pugh score; EHPVO, extrahepatic portal venous obstruction; HBV, hepatitis B virus; HE, hepatic encephalopathy; NASH, nonalcoholic steatohepatitis; PARTO, plug-assisted retrograde transvenous obliteration; STS, sodium tetradecyl sulfate.
Statistical Analysis

The probability of overall survival rates, ascites-free survival rates, and bleed-free survival rates were estimated using the Kaplan–Meier method. Statistical analysis was performed using the statistical package SPSS 21.0 for Windows (SPSS Inc., Chicago, IL, USA). The pooled estimates of technical success and 1-year overall survival rates were calculated using R software (R: A language and environment for statistical computing, https://www.R-project.org/).

Results

A technically successful procedure could be performed in all but two cases (technical success rate 14/16; 87.5%). One of the failed cases was later managed by endoscopic glue injection 3 days post-BRTO attempt. The other case did not agree for any further endoscopic/vascular procedure. However, on telephonic follow-up at 3 months, he did not have any recurrence of GI bleeding.

Eleven patients required embolization of collateral veins with gelfoam slurry to prevent the runoff of the sclerosant into the systemic circulation. One patient required embolization of the collaterals (►Fig. 4) with coils (Cook Medicals, USA).

The 24-hour postprocedure CT showed significant regression/complete thrombosis in 13/14 completed procedures (thrombosis rate of 92.9%). One patient had a bout of massive hematemesis 2 hours after completion of a successful BRTO which was fatal. Probably, he had rebleed due to the increased pressure within the varices (due to occlusion of GRS which is the efferent for varices by the balloon) before adequate thrombosis could take place.

Follow-up CT at 3 months postprocedure in 13/14 surviving patients following a successful procedure showed no recanalization of GVs. No patient in this group reported any recurrence of GI bleeding in the follow-up period. However, one patient (1/14) developed EVs which were managed by prophylactic endoscopic banding. Further, two patients developed mild increase in ascites (one of them is the patient mentioned above, who required banding for EVs). However, they were managed medically.

The single patient who underwent BRTO for refractory HE showed a decrease in serum ammonia from a preprocedure value of 155 μ/dL to 53 μ/dL at 1-month postprocedure. Also, no recurrence of HE was noted.

The 3-, 6-, 9- and 12-month probability of overall survival rates were 87.5%, 80.8%, 80.8% and 80.8%, respectively. In the same time period, probability of ascites-free survival rates were 92.3%, 82.1%, 82.1% and 82.1%, respectively, and bleed-free survival rates were 87.5%, 87.5%, 87.5% and 87.5%, respectively. ►Fig. 5 shows the Kaplan–Meier curves for these parameters.

Two patients had an intraprocedure rupture of GRS, which was recognized as extravasation of contrast material into the retroperitoneal space. However, the procedure could be completed successfully in both these patients with no intraprocedure hemodynamic instability or postprocedure morbidity. One patient had partial splenic thrombosis in the postprocedure CT without any clinical manifestations. ►Table 2 shows tips and tricks of BRTO procedure.
A 37-year-old man presented with acute upper gastrointestinal (GI) bleed and large gastric varices (GVs) on endoscopy. CPS was B7. (A) The coronal reconstructed image of the CT portal venous phase showed a very large gastrorenal shunt (GRS) (white arrow) measuring 24 to 26 mm draining into the left renal vein (LRV) (black arrow). GVs are seen cranially (arrowheads). Note the constriction in the midpart of GRS (red arrow). (B) Cannulation of the GRS from a right jugular approach demonstrates the difficult anatomy in the form of the large size and an hourglass constriction (black arrow). Left inferior phrenic veins form the systemic runoff (white arrow). (C) Attempts to occlude the shunt using a 27 mm Equalizer balloon failed with the balloon falling into the LRV (black arrow). (D) The shunt was cannulated using a right femoral vein approach and a 10 Fr sheath advanced with its tip (arrow) beyond the constriction. (E) A 24 mm Amplatzer Vascular Plug II was deployed in the GRS with its upper disc being above the constriction. Gelfoam slurry and STS was injected using the 5 Fr catheter present by the side of the plug till stasis was achieved. The plug was deployed in this position. (F) 24-hour CT study shows thrombosis and air foci within the GRS (black arrow).

Table 2  Tips and tricks of BRTO procedure

1. Careful evaluation of CT venogram is required, in case of high clinical suspicion and negative conventional endoscopy to look for perigastric varices communicating with submucosal varices through perforators.

2. The GVs can be ablated in absence of GRS by identifying the efferent channel of GV into the systemic circulation.\(^6\),\(^7\)

3. Significant contrast runoff during occlusion venogram from the varices into the systemic circulation require embolization before sclerosant injection (Fig. 4A-D).\(^4\)

4. In the presence of SVT, BRTO should be preceded by SAE to decrease the portal inflow.\(^4\)

5. The GRS lies medial to the AV. Care should be taken while advancing wire and injecting contrast to avoid AV injury and adrenal hemorrhage.

6. GRS is thin-walled and distended venous channel; therefore, care should be taken during manipulation to avoid inadvertent injury. In most of the cases, GRS rupture due to wire movement is self-limiting without significant retroperitoneal hemorrhage, but it may lead to collapse of the GRS.

7. During the injection of the sclerosant, reflux of the contrast into the SV and PV must be watched out for and avoided.

Abbreviations: AV, adrenal vein; BRTO, balloon-occluded retrograde transvenous obliteration; GRS, gastrorenal shunt; GV, gastric varices; PV, portal vein; SAE, splenic artery embolization; SV, splenic vein; SVT, splenic vein thrombosis.

Fig. 4 (A) Initial occlusion venogram shows the GRS (white arrow) with fast systemic runoff into the left inferior phrenic vein (black arrow). (B) Coiling of the latter performed using two 3 mm size pushable coils. (C) Repeat venogram after coiling and gelfoam injection show good opacification of the gastric varices (GVs). (D) Sclerosant contrast stasis within the GVs.
**Discussion**

Upper GI endoscopy is the first-line diagnostic and therapeutic procedure for bleeding varices (EVs and GVs); however, it is not very effective for controlling bleeding from GVs. A transjugular intrahepatic portosystemic shunt (TIPS) is commonly performed to decompress the portal venous system if endoscopic interventions fail to arrest bleeding from varices. However, its efficacy in controlling bleeding GVs is much inferior compared with bleeding EVs. Occurrence or worsening of hepatic encephalopathy in 20 to 30% of patients who undergo TIPS is also an important factor for consideration.

BRTO is an established form of treatment for GVs as an alternative to TIPS. Olson et al described the first attempt at balloon-occluded sclerotherapy of GRS for GVs, and Kanagawa et al developed the modern form of this technique. During the past two decades, the technique for BRTO has evolved and it is presently a well-established minimally invasive treatment for GVs (both to control emergent bleeding or electively) as well as patients with medically refractory HE.

The presence of EVs is not considered a contraindication for BRTO, since they can be easily managed by endoscopic band ligation in case they bleed/increase in size on close endoscopic follow-up. However, RTO of GVs is known to worsen EVs and ascites. In our study, only one of the 14 patients required treatment for EVs (endoscopic banding) at 1-month endoscopic follow-up after BRTO. In the presence of splenic vein thrombosis (SVT), BRTO can be performed after partial splenic artery embolization (SAE).
One of the important components of RTO procedure is the choice of sclerosant used. Ethanolamine oleate was used in Japan but its use outside Japan is minimal, primarily because of its adverse effects such as hemolysis, hemoglobinuria and hemolysis-induced renal failure as well as the lack of availability of an effective antidote. The various other sclerosants used over the years are absolute alcohol, N-butyl cyanoacrylate, STS, and polidocanol. The latter two are surfactants that cause endothelial damage with subsequent thrombosis of the vessels.

Chang et al described safe use of STS liquid sclerotherapy in 17 patients for BRTO. Our results and complication rates are similar to those reported in their study, with a technical success rate of 87.5% and a clinical success rate of 92.9%. Poold analysis of the published Indian studies revealed a clinical success rate of 100% (95% CI: 0.95 to 1.0; both fixed and random effect model) (Fig. 6). To our knowledge, there are two other large studies from the Indian subcontinent, describing the role of BRTO in patients with bleeding GVs or HE. The sclerosant used by authors in both these studies was a mixture of air, STS, and lipiodol in a ratio 3:2:1. In our study, no lipiodol was used and this entails cost saving. Intraprocedural balloon rupture is also not seen in any of our cases.

The limitations of our study include the retrospective design and small sample size. The results need to be followed-up by doing a prospective study with the recruitment of a larger sample size. With the advent of EUS-guided coil and glue injection being done for GVs, a randomized study should be done to compare the efficacy and safety profile of the two procedures.

In conclusion, RTO is a safe and effective minimally invasive treatment in a select group of patients with GVs who have active or intermittent bleeding, are at high risk of bleeding due to the size of varices, or have refractory HE.

Fig. 6 Pooled analysis of the clinical success rate for balloon-occluded retrograde transvenous obliteration (BRTO) from published Indian studies.

Fig. 7 Pooled analysis for survival rate at 1 year following balloon-occluded retrograde transvenous obliteration (BRTO) from published Indian studies.
Conflict of Interest
None declared.

Acknowledgment
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References