

September 15<sup>th</sup>, 2013

Dear Editor,

Please find the attached manuscript revisions in Microsoft Word format : 3951-edited.doc

**Title:** Treatment of Gastric Varices with Partial Splenic Embolization in a Patient with Portal Vein Thrombosis and a Myeloproliferative Disorder

**Authors:** Robert J Gianotti, Hearn Charles, Kenneth Hymes, Hersh Chandarana, Samuel Sigal

**Name of Journal:** World Journal of Gastroenterology

**ESPS Manuscript #:** 3951

We would like to thank the reviewers for their helpful comments and suggestions.

- 1) The format of the manuscript has been updated.
- 2) The questions and comments of the reviewers have been addressed and the manuscript has been updated according to their helpful suggestions.

**Reviewer #1**

**It should be further emphasized (in the title also) that even if PSE was effective in preventing new episodes of rebleeding, it was followed by a severe complication.** If the editors will allow us to exceed the 12 word minimum for the title, we suggest the following:

Treatment of Gastric Varices with Partial Splenic Embolization in Patient with Portal Vein Thrombosis associated with a Myeloproliferative Disorder: an effective but potentially high-risk therapy.

**Page 2: since the patient already had portal vein thrombosis and portal hypertension in 2008, did she receive primary prophylaxis with beta-blockers between 2008 and 2010?**

The patient was lost to follow-up during this period and was not receiving primary prophylaxis with beta blockers. We added this to the case description.

**Page 3: further details on the secondary prophylaxis with nadolol should be added, since this treatment failed: dose and degree of beta-blockade in terms of arterial pressure and heart rate should be given.**

Information about the response to beta-blocker therapy has been added. She was treated for 2 months with reduction in heart rate from 90 at hospital discharge to 65 at follow up. Due to the patient's great anxiety about the potential for rebleeding, PSE was performed.

**Page 3: cyanoacrylate glue injection is considered an effective treatment for bleeding gastric varices (McAvoy NC, Hayes PC. Nat Rev Gastroenterol Hepatol. 2010), and is briefly commented in the discussion. However, the case report should better elucidate why this option was not considered: was it available in the hospital where the patient was treated?**

Glue injection was not considered because it was not available. This has been added to the case description.

**Page 3: elective PSE of 30-40% of the splenic parenchyma was planned and performed, but resulted in a much larger spleen infarction. More details regarding how the spleen volume to be embolized was calculated and how embolization was performed should be added.**

The volume of splenic parenchyma embolized was based on fluoroscopic findings at the time of the procedure. The details of this procedure have been added to the body of the manuscript as follows: "Elective PSE to limit venous inflow into the portal circulation was performed with micro-catheter injection of 100-500 micron microspheres at the hilar aspect of the splenic artery. Completion splenic angiogram demonstrated embolization of 30-40% of the splenic parenchyma with sparing of the superior and inferior portions of the spleen (Figure 2)."

**How long the hospitalization due to the complication of PSE lasted? This should be taken into account when evaluating an elective treatment (cost/effectiveness analysis).**

The hospital stay lasted 7 days. This has been added.

**Page 5: it is stated in the discussion states that evident MPD was not present before PSE. This is not true, since in a patient with JAK2 mutation, complete thrombosis of the portal venous system and a spleen size of 18 cm, white blood cell count of  $8.2 \times 10^9/L$ , and platelet count of  $398 \times 10^9/L$  are clearly much higher than expected and compatible with evident MPD. In this setting, an acute increase in WBC and platelets after PSE should be foreseen and treatment with hydroxyurea should be initiated before PSE. Warning regarding this aspect, and description of other possible complications of PSE should be better underlined in the discussion.**

This is a very important point that was discussed on Page 4 and 5. We have further emphasized this point as follows: "...Following the procedure, the patient developed "post-embolization syndrome". This syndrome is a common side effect of any solid organ embolization and includes abdominal pain, fever and vomiting. Importantly, greater than 70% infarction is associated with longer symptom duration and higher complication rates, especially splenic abscess formation<sup>22</sup>. Typically, this common syndrome is treated conservatively with intravenous fluids, anti-emetics and pain

control. We speculate that reduced hypersplenism further unmasked the underlying thrombocytosis related to the MPD which led to a self-perpetuating process of excessive splenic auto-infarction. This phenomenon is similar to the unmasking of latent essential thrombocytosis that has been described in a patient undergoing splenectomy to control variceal bleeding in the presence of a large mesenteric clot burden<sup>23</sup>. A subsequent decrease in splenic blood flow led to a remarkable reduction in portal pressure as demonstrated by the nearly complete resolution of gastric variceal burden.

There are currently no published guidelines for the management of gastric varices in the presence of extensive portal and splanchnic thrombosis in MPD in which TIPS or BRTO are not possible. Our case demonstrates that partial splenic embolization can be an effective strategy in this otherwise difficult clinical scenario. Unmasking of an underlying thrombocytosis and “post-embolization syndrome” should be anticipated with measures taken to limit the extent of embolization including pre-procedure hydroxyurea, and to closely monitor for and rapidly treat the ensuing thrombocytosis<sup>24</sup>.

#### **Reviewer#2**

**Partial splenic embolization (PSE) is used as an adjunctive therapy for portal hypertension in patients who does not respond to beta blocking agents and/or variceal band ligation. There are lots of studies in the literature that include cirrhotic patients and give the long term results of bleeding esophageal varices. The outcome of bleeding gastric varices was also given in lesser studies that include the therapy of PSE coupled with balloon occluded retrograde transvenous obliteration (BRTO). This case is unique in that it gives the long term results of a bleeding gastric varices patient who has abundant thrombosis due to myelofibrosis in whom BRTO could not be done and only PSE was performed for therapy. The discussion section is too long for a case report, I think that the first paragraph is unnecessary.**

We have reduced and combined the first paragraph with the second.

#### **Reviewer #3**

**Anticoagulation in these patients is controversial, specially the length of the treatment. The patient was treated with warfarin for less than one year (months?) and she had a myeloproliferative disorder with V617F in the JAK2 gene. Was she treated again after discontinuation?**

The patient was lost to follow-up. The authors first assumed her care when she presented with variceal bleeding. Warfarin was restarted after recovery from the partial splenic embolization.

**Simultaneous combined BRTO and PSE have been found successful for portosystemic shunts, as allow a reduction in the volume of hazardous sclerosing agent used. Although in this patient it was not possible to carry out, what is the clinical practice about BRTO and PSE in clinical practice?**

If technically possible, this procedure would have been performed. This statement was added on page 3 and 5.

**Some studies indicate that has better long-term outcome and is associated with lower complication rates and a shorter hospital stay than PSE. This consideration should be discussed.**

These studies are referenced on Page 6. In our case there was not a patent spleno-renal shunt and BRTO could not be performed.

**Was splenic artery coil embolization considered in this case?**

Coils are not suitable for partial splenic embolization (PSE) as they do not lead to embolization at the parenchymal level.

We would like to thank you for considering our manuscript for publication in the World Journal of Gastroenterology. We hope that we have adequately addressed the reviewers' concerns and that the manuscript is now acceptable for publication. We apologize for the delay in returning our revisions due to the Summer Holiday.

Sincerely,

Robert J Gianotti, MD