

May 16, 2016

Re: Resubmission of manuscript No. 25885

The Editors

World Journal of Hepatology

Dear Editors,

Thank you for the opportunity to revise our manuscript. We appreciate the careful review and constructive suggestions. It is our belief that the manuscript is substantially improved after making the suggested edits.

Following this letter are the editor and reviewer comments with our responses in italics. Changes made in the manuscript are both highlighted in yellow and noted with track changes. Thank you for your consideration.

Sincerely,

Marie L. Borum, MD, MPH, EdD

REVIEWER #1:

1. This paper is essentially a case report with a review of the scarce literature (all case reports) about radiologically performed mesocaval shunt, a rather complex procedure. The title seems to be excessively optimistic and emphatic: to see “the light at the end of the tunnel” of the prevention of the rebleeding of esophageal varices may be too clear-cut, considering that only 6 (plus that reported in the paper) patients have been described until now. The manuscript is a continuing discussion, without methods and results, as it should be usual, and few informations are available about the only patient that it has been apparently treated by the authors. Moreover, looking at Table 1, the long term outcome after mesocaval shunt might be questioned: one patient had an occluded shunt at 12 months, although no rebleeding was observed at 14 months. The follow up of the shunt in the other patients is at 1 (2 patients), 2 (without rebleeding at 10 months) 3 and 6 months.

*Thank you for these observations. We re-wrote the title to better reflect the state of endovascular mesocaval shunting, changing from “The Light at the the End of the Tunnel: Mesocaval Shunting for Refractory Esophageal Varices in Patients with Contraindications to Transjugular Intrahepatic Portosystemic Shunt” to “Could There Be Light at the End of the Tunnel? Mesocaval Shunting for Refractory Esophageal Varices in Patients with Contraindications to Transjugular Intrahepatic Portosystemic Shunt.”*

2. The last patient was not complaining liver cirrhosis but likely a thrombosis of the superior mesenteric and splenic vein due to a pancreatic tumor, quite a different pathogenesis of esophageal varices, with different evolution, and should not be included in this series, except may be to show the feasibility of the operation.

*Thank you for this comment. We annotated our description of this case to highlight that its inclusion is to reflect procedure feasibility and acknowledge that the underlying pathophysiology may be different.*

3. In two cases thrombosis of the shunt was observed and they were managed by “shunt revision”. Could the authors explain in details the revision procedure? Although re-canalized, the shunts had an incidence of thrombosis of 33%. This should not be under evaluated in the discussion.

*Thank you for this observation. We added a paragraph to the “potential pitfalls” section to go into more detail on how the thrombosed shunts were managed and to underscore this rate of complication in our reviewed case series.*

4. The authors state that, given the limited numbers of patients who have undergone percutaneous or endovascular mesocaval shunt placement, there are no data to evaluate

rates of hepatic encephalopathy with these shunts vs TIPS or surgical shunt creation. However, a high incidence of encephalopathy is commonly reported either after surgical or after radiological shunt, being not different in their physiopathology, and at least it should be reported if encephalopathy has been observed and in how many patients. T

*Thank you for this comment. We added citations and are in agreement with you that the rate of HE is likely similar amongst mesocaval shunts and TIPS. We also made it more clear in the text and table 1 that the cases reviewed unfortunately did not give data regarding the presence or absence of HE.*

5. The paper would be more fitted for a journal of operative radiology than for a gastroenterology journal. Indeed, the technical details, which are the main core of the paper, are not easy to understand for not highly specialized radiologists. Actually, only very skilled in referral centers are likely able to perform such a technically demanding procedure, a fact that should be emphasized. The authors are focusing on the not commonly available surgical experience to perform portocaval shunt, but the expertise concerning pure radiologically performed mesocaval shunt is certainly even less available. As for many other new coming technological advances in the modern medicine, it would be better to say that for now this procedure is feasible.

*Thank you for this analysis. We added a notation that institutions will need interventional radiology expertise to perform this procedure and underscored throughout the paper that this procedure is feasible and promising but does not have robust data at this point.*

6. No any conclusions can be taken about the long term outcome (thrombosis is one of the major drawbacks of TIPS, a comparable procedure) and safety. This issue should be sincerely discussed, considering that the procedure has required in some patients the passage of a needle, and of a guide wire afterward, through the colon or other hollow viscera (and even pancreas) before arriving to the vessels. Apart from the risk of perforation, the risk of infection in a patients with impaired immunity like cirrhotic patients, may not be negligible and this risk should be well pointed out before recommending these maneuvers.

*Thank you for this observation. We emphasized the risk of infection to the procedure and, as above, the frequency with which in-stent thrombosis occurred and the risk of both of these consequences to the patient.*

7. The third major risk, i.e. bleeding, should also not be under evaluated, and no firm conclusion can be taken after few reported patients. It would be interesting to know the coagulation features (including platelets) of the patients submitted to radiological mesocaval shunt

*Thank you for this comment. Unfortunately none of the reviewed cases provided data on the patients' platelet counts or other markers or bleeding. We are in agreement with you that this would affect the safety of the procedure and added a sentence to that affect.*

8. A further important drawback of the manuscript in my opinion is the absence of precise indication criteria to mesocaval shunt. Likely, the procedure seems to be a technical advancement of TIPS and could rise the same concerns.

*Thank you for this observation. We tried to better delineate the ideal candidate for this procedure in the "Introduction," "Discussion: Benefits" and "Conclusion" sections.*

9. A Cochrane review in 2006 [2006 [Cochrane Database Syst Rev. 2006 Oct 18; Portosystemic shunts versus endoscopic therapy for variceal rebleeding in patients with cirrhosis. Khan S, Tudur Smith C, Williamson P, Sutton R] found that all shunts (including TIPS) resulted in a significantly lower rebleeding rate at the expense of a higher incidence of encephalopathy. TIPS were complicated by a high incidence of shunt dysfunction and no survival advantage was demonstrated with any shunt. Can the authors give any answer?

*Thank you for this thoughtful observation. We agree with you that there is not any data to support a mortality benefit from mesocaval shunting and thus it might best be utilized as a bridge to transplant. We included this citation in our updated manuscript and emphasized that this is the scenario where the patient stands to gain the most.*

10. The procedure could be recommended for portal vein thrombosis or as a rescue procedure before liver transplantation. However, it is uncertain whether PVT affects cirrhosis outcome and it has been suggested that TIPS should probably be indicated in liver transplantation candidates, but avoided in patients not suitable for liver transplantation and with an otherwise poor prognosis, i.e. likely the group that the authors define "too sick for transplant. It is debatable if this procedure, which is demanding even in terms of costs (an issue which should be considered) could somewhat help these patients and improve their outcome. Moreover, which patients are not candidates for TIPS in author's opinion?

*Thank you for this observation. As above, we adjusted several sections to emphasize that patients who are awaiting transplant likely stand to have the most benefit from this procedure. We believe that patients who are not TIPS candidates are described in the second paragraph of the "Discussion: Selection of Candidates" section where we outline that patients who lack functional blood vessels for TIPS placement after PVT are not TIPS candidates. Please let us know if our communication is poor here.*

11. TIPS is an accepted rescue therapy for first line treatment failure in acute variceal bleeding. Apparently, no experience have been reported in active bleeding patients. Would the author recommend such a technically demanding procedure in active bleeding patients, especially when refractory to endoscopic therapy?

*We do not believe there is data to support performing this shunting in an actively bleeding patient and added a comment to this effect.*

12. Radiologic pictures are very nice-looking, however is hard to believe that the varices observed in the endoscopic picture could not be successfully managed by ligation.

*Thank you for this comment. We added a line of explanation in the body of the text to let our reader know that our patient was not tolerating endoscopic ligation as she had inpatient admissions for chest pain subsequently.*

13. In conclusion, this manuscript is reporting the feasibility of a delicate and technically demanding procedure. However, the number of reported patients in the literature does not allow any firm conclusion. Indications, risks and outcome should be better and more critically analyzed.

*Thank you for this feedback. Throughout the paper with the above changes, we added qualifications and emphasized the risks of the procedure and the lack of data present for a relatively new approach.*

REVIEWER #2:

1. An interesting review to read, and overall informative. Some work has to be done to present in a suitable fashion. First there are some issues regarding the Language read carefully and rewrite where ever the sentence difficult to read, do not make sense and do correct the grammar.

*Thank you for this observation. We read our paper for grammatical correctness and updated as necessary.*

2. You need to look into table 1 - one should be able to read it without looking to the text to understand what you mean.

*Thank you for this feedback. We re-designed table 1 to make it more readable and added a legend to give more details.*

3. Furthermore the figures need to be worked on - it would for instant be nice if you could indicate where the different veins/stent are located in your figures - it would be much easier to read and comprehended. The legend to figure 2 has to be re-written to be able to explain the figure. Look to what you have been writing in the text - even the explanation in the text is not easy to comprehend - rewrite both is in order.

*Thank you for this comment. We re-wrote the legend for figure 2 with additional labelling in attempt to make the procedure more clear. We also edited the in-text description of the procedure as well in attempt to be more clear.*