February 21 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: **8998**-review.doc).

Title: Predictors of double balloon endoscopy outcomes in the evaluation of gastrointestinal bleeding.

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Name of Journal: *World Journal of Gastrointestinal Endoscopy*

ESPS Manuscript NO: 8998

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer (highlighted in yellow)

(1) Please read our responses below and highlighted in yellow in the text.

1o.- "Most patients had overt GI bleeding with melena in 34 (63%) and hematochezia in 13 cases (24.1%)." how many were active or nor active at the time of the performance of DBE and VCE? ,and what were the rate of positive findings of VCE and DBE in both situations?

- Active GI bleeding at the time of DBE was defined as overt bleeding within one week from DBE while non-active GI bleeding was defined as overt bleeding beyond one week from DBE. This has been clarified in the text.
- Based on this definition: 20 cases (*36.4%)* had active bleeding at the time of DBE, 23 (41.8%) were not active and 11 (20%) had occult GI bleeding. Positive diagnostic yield was seen in in 10 (50%) active GI bleeding cases, 16 (69.5%) non-active cases, and 4 (36.3%) occult GI bleeding cases. This data has been inserted into the edited manuscript on page 8.
- *We did not collect information on GIB activity at the time of VCE so we cannot include that in our analysis.*

2o.- " The time lapse between VCE and DBE was within a week in 15 cases (28.8%), between one week a..." Could you show us the DBE rate of positive findings and positive therapeutic treatment in these different groups.

These results have also been placed in the edited manuscript. (Table 3)

Time from VCE to DBE	Less than 1 week	1 week to 1 month	1 month to 1 year	More than 1 year
DBEs with positive diagnostic yield /total number of DBEs	8/15 (53.3%)	3/6 (50%)	15/25 (60%)	3/6 (50%)

DBEs that led to therapy/total number of DBEs	7/15 (46.7%)	2/6 (33.3%)	13/25 (52.0%)	2/6 (33.3%)

3o.- The authors gave us the time lapse between DBE and VCE ,but it would be very important to know the time lapse between VCE and the beginning of the OGIB episode , and the time lapse between DBE and the episode OGIB, and the DBE rate of positive findings according to the different times of the performance of DBE

These results have also been placed in the edited manuscript . (Table 3)

Time from onset of GI bleed to VCE	Less than 1 week	1 week to 1 month	1 month to 1 year	More than 1 year
VCE with positive findings /total number of VCE	10/10 (100%)	2/3 (66.7%)	11/14 (78.6%)	15/18 (83.3%)

Time from onset of GI bleed to DBE	Less than 1 week	1 week to 1 month	1 month to 1 year	More than 1 year
DBE with positive findings /total number of DBE	2/8 (25%)	3/3 (100%)	9/14 (64.3%)	17/27 (63%)
DBE leading to therapy/total number of DBE	1/8 (12.5%)	3/3 (100%)	7/14 (50%)	14/27 (51.9%)

4o.- "The majority of patients had chronic GI bleeding of more than 1 month duration (75.5%)" . So at least 24,5 % of GI bleeding could be considered the first episode of OGIB (not chronic), could you show us what the results of DBE were in this group of first episode of OGIB?

- Acute GI bleeding was defined as GI bleeding within one month of VCE or DBE.
- 5 of 12 cases (41.7%) with acute GI bleeding at the time of DBE had positive diagnostic yield on DBE. This has been added to the edited manuscript in results section and highlighted.

5o.- It is surprising that VEC had a high diagnostic yield of 83,6% and hardly a 54,3% with DBE (VCE false positives ?) .In different studies the rate of positive findings of VCE is very similar to the DBE (nearly 56% , meta-analysis,Triester S, Am J Gastroenterol 2005;100:2407-18) Could the authors consider and comment other explanations different to the time lapse between VCE and DBE and the length of the enteroscope introduced ; what about VCE false positives? the type OGIB episode (acute or chronic OGIB?, active or inactive overt OGIB?

- Respectfully, the study mentioned above did not compare DBE to VCE, instead it was a metaanalysis comparing VCE to other modalities such as push enteroscopy, small bowel barium radiography..etc. This will lead to different results.
- There was a high rate of positive VCE findings that led to non-diagnostic DBE in our study and this has been highlighted in the manuscript. These lesions could be classified as falsely positive VCE findings and were mainly polyps (88%), followed by ulcers (50%) and AVMs (35%). This is consistent with a previous

multicenter prospective study showing acceptable concordance between DBE and VCE for AVMs and inflammatory lesions, but not for polyps or masses. Endoscopy. 2009 Jul;41(7):587-92. This was revised in the edited manuscript in discussion, paragraph 3 (page 10).

- This also can be explained by healing over time of ulcers or inflammatory lesions. Furthermore, protruding or bulging lesions may be falsely seen as polyps or masses on VCE but then flattened by air insufflation when endoscopically visualized. Lastly, one cannot exclude the possibility of falsely negative DBE due to missing lesions or inadequate insertion depth. More information has been added to the manuscript in discussion in page 11-12.
- We do not have data on the activity of GI bleed at the time of VCE, so we cannot assess whether more active GI bleed at the time of VCE explained the higher rate of positive findings at the time of VCE as opposed to DBE.
- The same number of cases had acute GI bleed at the time of VCE and DBE based on our classification of acute GI bleed, however more findings were seen with acute GI bleed at the time of VCE. This could be due to increased detection rate on VCE due to shortened interval to onset of GI bleed. This was revised in the edited manuscript in discussion in page 11-12.

6o.- The logistic regression analysis try to identify patient′s factors related with a negative DBE (45,7% of patients had a non diagnostic DBE), assuming that the DBE was truly negative, without missed lesions . But this study did not have a follow up (the authors said " It was hard to evaluate rebleeding rates post DBE in our study since most patients were seen at the time of DBE for the first time. However.." . So before performing the logistic regression study, the issue of the missed lesions have to be fully excluded with an adequate follow up to assure there were not new and undiagnosed OGIB episodes in these patients DISCUSSION page7 first paragraph " Surprisingly, acute GI bleeding in the short period prior to DBE was associated with non-therapeutic intervention." I cannot understand the meaning of this sentence, what does "in the short period prior to DBE" mean ?, could you better explain it

Those were revised in the discussion section as highlighted.

- As mentioned in discussion, the possibility of having positive findings beyond our insertion depth could not be excluded. However our DBE cases evaluated the majority of the small intestine and reached areas suspected to have positive lesions based on VCE, so we expect that our DBE insertion depth was adequate. Only 4 cases were referred for repeat DBE due to ongoing GI bleed. As this institution is only one of 2 referral centers in the state to perform DBE (located approximately 250 miles apart). One would assume that repeat DBE requests would again come to our institution for continued bleeding to attempt total enteroscopy through a combined approach. Follow up laboratory and clinical data would be helpful to collect in a future prospective study.

- “In the short period prior to DBE” meant “Active GI bleeding in the week prior to DBE” This was clarified in the edited manuscript.

(2) Overall this is a good article. In the last paragraph of the introduction it states that there over a 1% risk with balloon endoscopy but that it is safe. I don't know how you can make that statement-safe relative to what? I have no other comments

- *We removed the word safe from the manuscript.*

(3) No revisions were requested.

Thank you again for publishing our manuscript in the *World Journal of Gastrointestinal Endoscopy*

Sincerely yours,

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