November 09, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: manuscript 5511 review.doc).

Title: LIVER BIOPSY ANALYSIS OF TWO SPECIALISTIC TEAMS RESULTS

Authors:

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Name of Journal: *World Journal of Gastrointestinal Pathophysiology*

ESPS Manuscript NO: 5511

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

Format has been updated

Revision has been made according to the suggestions of the reviewers and are listed below in order

Answer to Reviewer#1:

1)

1.1) As suggested by the reviewer, in order to explicit the intrinsic limit of our study we added the following sentence:

"Unfortunately, the smaller number of procedures performed by IR team, might have lead to the underestimation of differences between the two groups, posing a potential bias intrinsic of the retrospective nature of the study, limiting the power of data analysis."

We appreciated the comment of Reviewer #1 and as requested, data comparing rate of complications separately in the sub groups with regular admission and day hospital were extracted and the following sentence added:

"We performed subgroup analysis on the rate of adverse events observed in the RA setting, and no difference in the G (6/48) vs RI (7/38) team were shown (p= 0.548). Subgroup analysis performed on the rate of adverse events observed in the DH setting also did not show any significant difference between the two groups, G (10/119) vs RI (3/21) (p= 0.413)".

1.2) The 2001 New England Journal of Medicine review on hepatic biopsy suggested that at least 6 to 8 portal tracts were considered to be acceptable for diagnosis. The following 2009 AASLD guidelines suggested that the presence of fewer than 11 complete portal tracts should be noted in the pathology report, with recognition that diagnosis, grading and staging may be incorrect due to an insufficient sample size. Thus, we choose to define as acceptable for diagnosis a minimum of 6 portal tracts. However, we examined the question posed by Reviewer #1, and data analysis showed that overall 30.7% of bioptic samples had ≥ 11 complete portal tracts, 52/151 (34%) and 11/54 (20%) G vs RI respectively. However, bioptic samples with of ≥ 6 complete portal tracts, were overall 157/205 (76.6%), 118/151 (78.1%) and 39/54 (72.2%) G vs RI respectively. We incorporated these data to the text and add a short comment in the discussion.

We added to results: Overall 30.7% (63/205) of bioptic samples had ≥ 11 complete portal tracts, 34% (52/151) and 20% (11/54) G vs RI respectively. Bioptic samples with ≥ 6 complete portal tracts were overall 76.6 % (157/205), 78.1% (118/151) and 72.2% (39/54) G vs RI respectively.

We added to the discussion: A further possible limitation of our data is represented by the percentage of samples with a number ≥ of 11 of complete portal tracts (30.7%). As suggested by the 2009 AASLD guidelines, the presence of <11 complete portal tracts should be noted in the pathology report, with recognition that diagnosis, grading and staging may be incorrect due to an insufficient sample size. Nevertheless, presence of 6 portal tracts have been previously considered to be acceptable for diagnosis [ref. 12 in the text], and overall 76.6% (157/205) of samples obtained were above this limit. Thus, since we choose the latter numeric parameter, we acknowledge that reduced number of portal tracts obtained might have affected the accuracy of diagnosis. However, the significantly higher mean number of portal tracts obtained by the biopsy samples performed by G team suggests a higher opportunity of better diagnostic findings.

1.3)To respond to question 3 by Referee#1 we added the following table.

Table (4) : Occurrence of adverse events following liver biopsy by setting and team performing the procedure.

	Regular admission	Day Hospital	Team G	Team RI
Total number of adverse event	13	13	16	10
Pain moderate to severe % (number/total)	77% (10/13)	70% (9/13)	68% (11/16)	80% (8/10)
Relevant biochemical abnormalities * % (number/total)	15% (2/13)	31% (4/13)	25% (4/16)	20% (2/10)
Nausea/vomiting % (number/total)	7% (1/13)	(0/13)	6% (1/16)	(0/10)

*: mild increase of white blood cells (4 cases); mild hemoglobin decrease < 2 gm/dl from baseline (1 case); thrombocytopenia (1 case).

Answers to Reviewer#2:

2.1/2.2) We thank the Referee for the interesting question, but from the analysis of our data it doesn't seem to emerge that a possible bias in the choice of one team over the other could have been guided by the patients clinical profiles, since there were no differences in coagulative profiles, BMI and prevalence of comorbidities between those managed either by the G or the IR team. Biopsy was indeed performed either by the G or IR teams basically for opportunity-guided reasons, prevalently by the service providing the quickest availability of the procedure. The G team personal is part of the GI department, which articulates on regular admission and day hospital facilities, and usually performs liver biopsy on its own patients, but this personal is not always available to perform the procedure, being employed in different activities (ward, clinical care, clinic, endoscopy, consultation for in-hospital patients). On the other hand, the IR team is part of the radiology department which does not have dedicated beds, and provides services to other departments and sections on regular basis. So opportunity for the patient to undergo liver biopsy following the fastest track possible is the main reason to opt for the procedure to be done by either team.
According to the Reviewer's suggestion we modified the text as follows:
"In addition, even with the limitations inherent to the retrospective nature of our analysis, since the patients had similar coagulative profiles, BMI, and prevalence of comorbidities, there were no elements suggesting a preferential choice of one team over the other. The main reason that guided the choice of one team over the other was the availability of either team at the time the procedure was ordered"

2.3) As suggested by the reviewers we pointed out the limits of our study adding the following sentence: "Unfortunately the smaller number of procedures performed by IR might have lead to underestimate the difference between the two groups, an intrinsic bias of the retrospective nature of this study which in turn limited the power of data analysis."

2.4) Subgroup analysis were performed and results added as described in answer to Reviewer's #1 question #1.1

2.5) As requested by the Reviewer, we analyzed the adverse event ''pain'' which alone or in association with other symptoms accounted for nearly 73% of all adverse events recorded. A further analysis was performed isolating the event "pain". No significant differences between G and RI teams emerged (p= 1). Following the Referee's suggestions we added the following sentence in the text:

"A subanalisys was performed separating the adverse event pain from the other signs and symptoms developing after the performance of this procedure. Again, no differences were observed between the results obtained by the G and the RI team (p= 1). Apart from pain, the most common adverse events were biochemical abnormalities such as a mild increased white blood cell count and a mild hemoglobin decrease (< 2gm/dl) from baseline, registered in a limited number of patients".

As indicated above we added a table summarizing the different rates of adverse events.

2.6) See Answer 2 to Referee #1

2.7) As part of our University teaching and research mission, our Hospital proposes an informed consent acquisition for the use of clinical data for research purposes at the time of admission, both in the DH and RA setting; this consent allows the use of clinical data in the respect of the patients' anonymity.
To answer this question we added the following sentence in the method section:

"All the patients gave informed consent for the use of clinical data at the time of admission''.

References and typesetting were corrected

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

Sincerely yours,

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