October 25, 2012

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 5589-review.doc).

Title: The Effect of The Transversus Abdominis Plane Infiltration on Postoperative Quality of Recovery in Morbid Obese Patients undergoing Laparoscopic Gastric Banding: A Randomized, Double Blinded, Placebo Controlled, Pilot Study

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Name of Journal: *World Journal of Gastrointestinal Surgery*

ESPS Manuscript NO: 5589

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

Referee 1

"The subject of use of TAP blocks is topical and it's use in laparoscopic surgery has been investigated with promising results. It is appropriate to study its efficacy in the cohort of patients that the current study has set out to. The methodology, blinding and statistical methods used are appropriate. The volumes of intervention and control group drugs show discrepancy between that published on the clinical trials website and the study itself (30 ml vs 20 ml)."

Thank you for your complements regarding our manuscript

"It is very disappointing that the authors chose to stop recruitment at 19 cases although their aim was for 50 participants. This study is grossly underpowered rendering any results inconclusive. The authors' stress on positive trends have limited value in the context of meaningful scientific results. The authors stress on the importance of limiting opioid consumption as a means for reduction in unwanted side effects although the results show that the TAP group experienced more nausea. None of the other opioid side effects were investigated."

Since surgeons stop doing gastric banding in our hospital ,we were forced to stop the trial (it was not a choice). However, we believe that our results have important implications. Although not "statistically" significant, it is beyond question that the difference on quality of recovery is clinically significant. We apologize for a mistake in the table that is now corrected; only one patient in the TAP block had nausea in the PACU (10%) compared to three in the control group (33%). In addition, only a patient in the control group had

vomiting In the PACU compared to no patients in the TAP block. Recently, patient reported outcomes have replaced the simple reporting of side effects in perioperative medicine. We believe that is more important to report that patient reported better quality of recovery as the opioid consumption decreased (Spearman's Rho=-0.49).It has alos been shown that not all opioid related side effect are clinically important(Myles PS, Wengritzky R. Simplified postoperative nausea and vomiting impact scale for audit and post-discharge review. Br J Anaesth. 2012 Mar;108(3):423-9.))

More importantly, since the TAP block is more difficult to be performed in obese patients , these patients are often denied that analgesic benefit. We believe that our results will encourage practitioners to offer that option to patients.

"There's a plethora of topographical errors and many references cited are irrelevant to this study."

Two native English speakers independently reviewed and corrected typographical errors as requested by the referee

Referee 2

"The design of the study is good and the subject is of clinical relevance. However, the population is so limited that I doubt we can draw any other conclusion than "a study on a wider population is required"... I think that the authors should try to finish the inclusions with another center or change the nature of the paper to a cases report."

Thank you for your comments regarding the study design. Unfortunately we had to stop the trial due to forces beyond our control. The manuscript is now a brief report and not a full article as suggested by the referee.

"The real importance of parietal pain after laparoscopic surgery needs to be discuss. Indeed, the parietal pain after laparoscopic surgery is weak and is successfully treated by a TAP block. But the visceral pain, which can be important after gastric banding, is not really influenced by a TAP block".

We added a sentence to discuss the referee's important comment "It is important to note that the transversus abdominis block successfully treats parietal pain but visceral pain is not treated by a TAP block. This is likely the reason why even patients in the TAP block group required the use of systemic opioids. Nevertheless, it seems that the reduction in the parietal pain is an important step to improve quality of recovery in patients undergoing laparoscopic gastric bending"

" In the TAP group, 9 patients out of 10 had nausea versus 6 out of 9 in the control group, how can you explain this?"

We apologize for that mistake which has now been corrected. Only one patient(out of ten) in the TAP group reported nausea in the PACU.

"The structure and the writing of the paper should be corrected because some points are not in accordance with author guidelines, for example: - replace conclusions part by discussion - 2nd paragraph of the conclusion: replace particular by particularly The

other writing mistakes should be easily found by a meticulous re-reading of the paper."

Corrected as suggested by the referee. The manuscript has been reviewed by two native English speakers to correct additional mistakes.

Referee 3

"ClinicalTrials.gov Identifier: NCT01075087 The stated objective of the study in the study is to estimate an effect size for TAP infiltration on quality of recovery in morbidly obese patients undergoing laparoscopic gastric band surgery. The study is described as a pilot study. A hypothesis is offered. The methodology appears to be strong. The study is prospective, randomized and blinded. The method of randomization is stated. The performance of the block itself is appropriate."

Thank you for your nice comments about our manuscript

"**Primary and secondary end points are not clearly stated. The estimation of sample size is unusual. The primary and secondary outcomes as stated in the online clinical trials registry is opioid consumption. QoR-40 is not mentioned. The TAP dose in the study differs from that listed in the clinical trials registry (30 ml). The study period runs until March 2014. It is disappointing that recruitment is not continuing as the major weakness of this study is that it is underpowered. The clinical meaningfulness of a 10 point difference in a 200 unit scale is unclear to me especially when the scores are 170+ in each group."**

It is currently accepted that a 10 point improvement in quality of recovery is clinically significant since it represents an approximately15-20% improvement in recovery based on the range values observed.

Our group has published several manuscripts using the QoR-40 as the primary outcome and a 10 point difference as clinically significant:

De Oliveira GS Jr, et al.. Systemic Lidocaine to Improve Quality of Recovery after Laparoscopic Bariatric Surgery: A Randomized Double-Blinded Placebo-Controlled Trial. Obes Surg. 2013 Sep 15. [Epub ahead of print]
De Oliveira GS et al..Transversus abdominis plane infiltration and quality of recovery after laparoscopic hysterectomy: a randomized controlled trial. Obstet Gynecol. 2011 Dec;118(6):1230-7.
De Oliveira GS Jr et al.. Dose ranging study on the effect of preoperative dexamethasone on postoperative quality of recovery and opioid consumption after ambulatory gynaecological surgery. Br J Anaesth. 2011 Sep;107(3):362-71.

We have corrected the mistakes in the clinical trial registration. We have always used the QoR-40 as the primary outcome in all our studies. In the current manuscript , both outcomes did nor result in "statistically" significant differences, that could lead to reporting bias.

"What was their experience of GSD in use of TAP block prior to the study. ?"

GSD has performed over 300 TAB blocks. He also published two other manuscripts involving 150 patient in different surgical population (**De Oliveira GS et al.**.Transversus abdominis plane infiltration and quality of recovery after laparoscopic hysterectomy: a randomized controlled trial. Obstet Gynecol. 2011 Dec;118(6):1230-7. And **De Oliveira GS Jr** et al, A dose-ranging study of the effect of transversus abdominis block on postoperative quality of recovery and analgesia after outpatient laparoscopy. Anesth Analg. 2011 Nov;113(5):1218-25.) Added to the manuscript

"The time points at which pain is assessed. It is also stated that in early recovery, the area under the NRS pain scale versus time was calculated. What defined 'early' recovery? How was pain assessed after this?"

Pain was assessed in the PACU every 30 minutes (added to the manuscript). After PACU we used the opioid consumption to estimate the pain burden.

" ? Insufflation pressure. ? Volume of insufflated gas ? Port site locations ? Time breakdown of opioid administration in the post-operative period."

We added the insufflation pressure, port side locations and the time breakdown of opioid administration as requested by the referee. We did not record the volume of insufflated gas but have no reason to think they were different between the subjects since they were randomized.

"Much of the benefit of TAP blocks is seen in the first six hours. It may be beneficial for the authors to analyse the early data."

Only twenty four hour opioid consumption was initially listed as one of the outcomes.In previous studies, we have seen an extended benefit of the TAP block (if done preoperatively) on analgesic outcomes up to 24 hours. We also have meta-analysis in press that confirms this finding.

"There was unfortunately no significant difference between the groups in any of the stated outcomes and this is clearly secondary to failure to recruit adequate numbers of subjects and not due to lack of efficacy of the intervention. The emphasis on positive trending distracts the readers from the lack of statistical significance. If this is truly a pilot study then the authors should generate the sample size calculations based on the data acquired."

A sample size calculation based on our findings was presented in the 6th paragraph of the discussion as requested by the referee.

"The authors place strong emphasis on the importance reduction in opioid side effects but measure few of them. Data on hypoxaemia are not given. Vomiting/retching are not reported beyond PACU."

We only used two sentences to mention the importance of postoperative opioid reduction. The QoR-40 have several measures of opioid related side effects such as nausea, vomiting , dizziness, etc.

"There are a large number of typographic errors."

The manuscript was independently reviewed by two native English speakers in order to reduce the typographic errors.

"Decimalization is inconsistent in the table."

Corrected

"Many of the references seem irrelevant to the specifics of TAP blocks (14,,24,33)."

Those citations were not related to the TAP block but can directly interfere with the outcome(quality of recovery)

References and typesetting were corrected

Thank you again for publishing our manuscript in the World Journal of Gastroenterology.

Sincerely yours,

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