Format for ANSWERING REVIEWERS

December 10, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7066-review.doc).

Title: Dexmedetomidine vs propofol in intensive care unit patients

Author: Valeria Fadda, Dario Maratea, Sabrina Trippoli, Andrea Messori

Name of Journal: *World Journal of Anesthesiology*

ESPS Manuscript NO: 7066

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 reviewers:

COMMENTS OF REVIEWER N. 00506105
Although the TSA has not found anything new other than what was established by the meta-analysis, as a letter to the editor, it is good to reinforce the point that further analysis also have not established clear benefits of dexmedetomidine. I feel the paper should be accepted Minor comments Core point "Hence, the therapeutic role of dexmedetomidine is still uncertain." Sweeping statement – may be 1)'**therapeutic role of dexmedetomidine in ICU is uncertain'** Although the figure has been explained, **2) a little more explanation regarding why the 'Z' line is within the Favors 'T" segment in Panels A and C while it is in Favors "C" segment in Panel B may be helpful for people who do not understand TSA very well**
ANSWER TO REWIER 00506105
1-2) Suggested changes have been inserted in the text

COMMENTS OF REVIEWER N. 00502975
The submitted manuscript is constructed properly and meets criteria of World Journal of Anesthesiology editorial board. It brings some data regarding to comparison dexmedetomidine and propofol in intensive care unit patients. These sets of data are very pertinent. The grammar, punctuation and language in some place needs to be reviewed. References are actual and permit. **References do not follow the instructions for World Journal of Anesthesiology authors. Several reference numbers are not in square boxes. The conclusion is missing.**
ANSWER TO REWIER 00502975
1-2) Suggested changes have been inserted in the revised version of the paper

COMMENTS OF REVIEWER N. 00506142
This is a re-analyzing report for the data of the meta-analysis of Xi et al. By using 'trial-sequential analysis (TSA)', the authors demonstrated that dexmedetomidine showed no proof of incremental effectiveness (for length of ICU stay and incidence of delirium) or proof of no incremental effectiveness (for duration of mechanical ventilation) compared to propofol. And they suggest that the therapeutic superiority of dexmedetomidine over propofol is still uncertain. The authors should be commended for a well-written paper and thorough statistical analysis. However, there are some factors that go into

determining if a manuscript will be accepted. 1. Including me, most reader may not be familiar with the statistical method of 'trial-sequential analysis (TSA)'. **I would recommend including a sentence of more detail description about the TAS (especially, limitations of this statistical method).** 2. According to the parent study (meta-analysis of Xi et al), dexmedetomidine significantly reduces the incidence of delirium comparison with propofol. Because of different pharmacological mechanism (lack of GABA agonistic action), this finding has been repetitively demonstrated in previous many laboratory or clinical studies. **In this regard, the authors should state the possible reasons of the conflicting result.**

ANSWER TO REWIER 00506142:

1. In general, the main advantage of trial sequential analysis (TSA) is represented by its ability to re-interpret a non-significant meta-analysis and, in particular, to differentiate its results between the case of inconclusiveness (.i.e. no proof of difference) and the case of demonstrated non-inferiority/futility (i.e. proof of no difference). Another advantage of TSA is that this technique estimates the "optimal information size" for the comparison under examination and so indicates how many patients would be required to draw a "proven" conclusion and to consequently avoid an inconclusive result; this second characteristic is of particular value in those case where the TSA has provided an inconclusive result based on the available data.

As regards the limitations of TSA, in the first place this new statistical technique –broadly speaking- shares virtually all the limitations that are already known for meta-analysis.

In addition, one specific limitation of TSA is related to its need to declare a pre-specified margin for the clinical benefit, i.e. a threshold that differentiates between a clinically irrelevant benefit and a clinically relevant one. This margin, which is generally based on a mixture of subjective and objective judgement, has thus far been widely used for power calculations that are required for designing a randomized study and determining its sample size. Furthermore, the use of a pre-specified margin is also required for conducting a non-inferiority or an equivalence statistics, and it is well known that equivalence studies and non-inferiority studies are increasingly being carried out in recent times.

2. As pointed out in our previous response, the results from meta-analysis and TSA are not conflicting. TSA pointed out that the results of the meta-analysis have been overestimated , because of the low sample size.

COMMENTS OF REVIEWER N. 00069137

The authors have written a very interesting and timely commentary, with novel results. It is of note that the literature on dexmedetomidine is relatively young, and other studies are indeed in progress that could change these results. It is well written. Minor comments. The references need to be checked, in case the "epub" for forthcoming papers is not in accordance with journal guidelines. Some reference numbers are not in square braquets, in paragraph 1 of text body. **1) How did the authors acquire the data from reference 1 to analyze?** 2**) How were the outcome measures chosen? Was it arbitrary?** (1 day hospitalizarion, 6 h intubation, 40% difference etc..) **3)The authors could numerically mention the number of patients needed to reach conclusions even if its in the figures**. **4) It could be explicitly stated that not all of the studies reviewed had the same outcome measures (for example for delirium, not all 10 studies had this as outcome) 5)It is also worth stating explicitly that the comparator is propofol but other comparators, such as benzodiacepines, have different results.**

ANSWER TO REWIER 00069137

1) The data for the analysis have been extracted from the fulltext paper of Xia et al.

2) The outcome measures chosen to identify the intervention effect used to run the analysis have been settled taking in account the mean difference values deriving from the meta-analysis.

3-4-5)we incorporated the suggested changes in the text

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

Sincerely yours,

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