Author’s response to reviews

Title: Impact of PReOperative Midazolam on OuTcome of Elderly patients (I-PROMOTE): study protocol for a multicentre randomised controlled trial

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Author’s response to reviews:

Dear Reviewers,

Dear Editor,

Thank you for your encouraging and helpful comments and giving us the opportunity to revise our manuscript. We have revised our manuscript according to your suggestions.
Reviewer reports:

Reviewer #1: This is potentially important study on the postoperative effects of routine midazolam premedication in the elderly. The design of the trial is well thought through and discussed in every detail in the manuscript. In fact the paper has important learning qualities for the readers.

I only have two minor comments:

1. Is intubation an inclusion criterion? The 7th inclusion criterion is: "Planned extubation at the end of surgery". However, in point 5 it is stated that "surgery duration ≥30 minutes". Several interventions in this category (even laparoscopic hernia repairs) can be done with laryngeal mask. Please clarify this issue.

Response: We apologize for this unclear statement. We totally agree with you. No, intubation is not mandatory as an inclusion criterion. Patients with laryngeal mask airway may be included as well. It will be recorded in the database, whether an intubation or laryngeal mask airway was used.

When we defined this inclusion criterion, we thought about the long surgeries, where the patients are transferred intubated to the ICU. That’s why we used this misleading expression. We have added now the information to the inclusion criterion #7 as follows: “Planned extubation at the end of surgery (This criterion is also comprising the removal of a laryngeal mask)”. On page 15 within the description of visit 2 we have added the explicit information that the attending anaesthesist has to decide which kind of airway device he wants to use, as follows: “Anaesthesia will be conducted according to the clinical routine, this includes also the kind of anaesthesia and used airway device.”

2. There are a lot of secondary end points. It seems to me that these are a bit too ambitious, although it is also obvious that the study team would not like to overlook any potentially important outcome detail. It is just a gut feeling of mine, nothing more.

Response: Yes, we agree with you. This is for our opinion the first and only very large RCT within this topic in the elderly patients and we aim to investigate as many important outcomes as possible. It was difficult to decide whether frailty assessment, postoperative delirium, functional or cognitive recovery, health-related quality of life or the mortality or serious complications within the first 30 postoperative days are not important enough to be assessed in this study. Of note, the analyses of the secondary outcomes will be considered exploratory.
Finally, I would like to congratulate the team for this robust work.

Response: Thank you!

Reviewer #2:

Dear authors,

You have proposed a study to evaluate the use of postoperative patient satisfaction after premedication with preoperative administration of 3.75 mg midazolam.

The manuscript is written sufficiently, the length is acceptable and the statistical methods are mentioned and enough

Please give your statement to the following points:

1. Title
   - no problem

2. Abstract
   - no problem

2. Introduction
   - Please specify the clinical message that the authors want to send

Response: Thank you for your comment. At the moment we don’t have enough high quality evidence to convince the reader to use benzodiazepines only on individual basis in the elderly patients. We think that this study will provide important and useful new evidence for the clinical handling of benzodiazepines in this patient group. We have added in the “Aims and objectives” section on page 6, line 134-135: “We aim to generate clinically relevant decision-support for premedication with benzodiazepines in elderly patients.”

3. Methods/design Inclusion/exclusion criteria: Well explained

Primary endpoint: well explained
Allocation/randomization: please, better specify

Response: We have revised the section –Allocation- on page 9-10 as follows: “Sequence generation for randomisation will be carried out computer-based by the biostatistician APK of the Department of Medical Informatics RWTH Aachen University Hospital. A randomisation stratified by study centre will be implemented. Sequences will be generated using a 1:1 ratio of the treatment arms and a permuted block randomisation. To ensure allocation concealment, the block sizes and allocation sequence will be concealed from all investigators and staff throughout the study until after the database lock. Allocation sequence list will be provided only to the pharmacy directly by the biostatistician. The Department of Pharmacy, University Medical Center Johannes Gutenberg-University Mainz, Germany will provide sealed, opaque containers containing the assigned treatment to each centre. These containers will be labelled with the ascending unique randomisation numbers. After the recruitment and enrolment of a patient by an investigator, the investigator is obliged to take the next consecutive medication container with the ascending randomisation number at visit 1, see below and Fig. 1. The investigator will assign this unique randomisation number together with the respective medication container to this enrolled patient. In practice this means: The medication container will be handed out to the independent nurse, who is responsible for this next patient (see description of intervention below).”

Sample size/power and calculation and statistical plan: well explained

- Please better specify if there are missing data

Response:

We have revised the sentence in the –Retention- section on page 19, line 450-451, to make clearer that we do not expect significant missing data: “We do not expect a high loss to follow-up or missing data for the most outcomes (including the primary outcome), as the most assessments are finished on the first postoperative day.”

Furthermore, we have added now to the section - Statistical methods—outcomes- on page 19 line 465-468 that the test EVAN-G for the primary outcome “patient satisfaction” has strictly to be performed, to avoid missing data. We have added to the following text: “All reasonable efforts will be made to evaluate the primary endpoint in all study subjects regardless of adherence to the study protocol. If it is not possible to perform the EVAN-G test on the first postoperative day, the test has to be performed on the next possible day.” Additionally on page 20, line 483, we have added “based on the baseline characteristics” at the end of the following sentence: “Secondary analyses will be performed to explore gender specific treatment effects, and the robustness of the results of the primary analysis will be explored by repeating the analysis on the per protocol data set and by imputation of missing primary endpoint data based on baseline characteristics.”

4. Discussion
- please specify the aim of the study and clinical message that the authors want to send

Response: We have added on page 25 in lines 598-601 in the discussion the following: “I-PROMOTE aims to gain first evidence for this vulnerable patient group regarding the premedication effect on patient satisfaction and other outcomes. We think that the results of this study will be useful for justification of waiving of indiscriminate premedication with benzodiazepines in the elderly patients.”

5. Tables

- no problem

6. References

Please check the journal's guidelines

Response: Thank you! We have checked and corrected all references and we refer now to the cited websites in the text with a reference.

Trial registration: OK