

Dear Editor,

We would like to thank the reviewers for their thoughtful comments and constructive suggestions. Our response is as follows.

Response to Reviewers

Name of Journal: World Journal of Clinical Cases

Manuscript NO: 42765

Title: The Safety of Applying Midazolam-Ketamine-Propofol Sedation Combination under the Supervision of Endoscopy Nurse with PCA Pump in Colonoscopy

Reviewer's code: 00504462

1. Dear Sir, I read with great interest your manuscript and I must congratulate you, as this is very important topic. However, even your objectives and results are very well presented, there is not a good explanation of why you chose ketamine instead of phentanyl.

Response: Thank you very much for pointing out the significance of the study. We have added the following information about why ketamine was chosen instead of fentanyl to the second paragraph of the Introduction.

“Both fentanyl and ketamine provide anaesthesia, analgesia, and anxiolysis. The delayed peak levels and prolonged duration of action of fentanyl are significant disadvantages. After intravenous administration, it reaches its peak level in 4-6 minutes and its duration of action ends in 20-40 minutes. Ketamine also has a good safety profile with the advantage of preserving spontaneous breathing and protective airway reflexes^[8, 9]. In our study, these features are important for sedation safety, since sedation is performed by non-anaesthesia personnel.”

2. Ketamine has as you mention important side effects, but there were others you did not. There are some delay side effects that you did not mention, but you did not mention if you did a follow up of your patients.

Response: In our study, since we focused on the safety of sedation and patient satisfaction under the supervision of the endoscopy nurse, we talked about the most frequently seen complications such as life threatening complications (cardiovascular and respiratory) and

nausea-vomiting and headache, which may affect patient satisfaction very much. As you mention, there are some delayed side effects. We have added the following information related to delayed side effects of ketamine to the last paragraph of the Materials and Methods.

“Side effects such as hypotension, bradycardia and desaturation, which require serious and rapid intervention, and frequently encountered side effects such as nausea, vomiting, and headache, which may adversely affect patient satisfaction, included in the patient follow-up form as main substances. Apart from these side effects, endoscopy nurse was especially informed about complications related to ketamine such as emergence reactions, hypertension, tachycardia, visual hallucinations, vivid dreams, tonic-clonic movements, diplopia, and nystagmus. However, in the patient follow-up form, these side effects were not mentioned separately, were included under the title of other side effects.”

We have also added the following information to Discussion section.

“Complications such as emergence reactions, hypertension, tachycardia, visual hallucinations, vivid dreams, tonic-clonic movements, diplopia, nystagmus, increased intracranial pressure, and increased intraocular pressure are among the complications associated with ketamine ^[31]. Even 24 hours after application, side effects such as severe confusion, hallucinations, unusual thoughts, or extreme fear can be seen ^[32].”

We have also added the following information to the Materials and Methods section.

“Patients were questioned for possible delayed side effects when they were contacted 2 days after the colonoscopy to determine method preference.”

3. Also, there were some grammar mistakes you need to correct. Hope to hear from you soon. Sincerely

Response: Grammar mistakes are corrected now. Thank you very much for your good wishes and for reviewing our paper and for your kind suggestions.

Reviewer’s code: 03725478

1. In the introduction I believe that the parentheses part can be excluded - Gastrointestinal endoscopy practices are increasing worldwide. Particularly during colonoscopy, patients do not want to be awake because of severe abdominal pain, cramps and bloating as well as embarrassment (they feel uncomfortable)

Response: The parentheses part has been removed from the specified sentence.

2. In statistical methods put what is considered as significant in the study

Response: We have added the following information to statistical methods section.

“In all analyses, the p -value <0.05 was considered as statistically significant.”

3. I was struck by the more use of drugs in the nurses group without having any further complications, the explanation was for the longer examination time, so it fits 2 questions. Was the number of participants not insufficient for this type of study? Were the exams done by the same endoscopist?

We have added the following information to the Materials and Methods

“Colonoscopy was performed by two experienced endoscopists who were trained in the same center on the same dates.”

We have added the following information to the Discussion

“Therefore, this difference may be due to the small number of patients or the fact that the procedure was performed by two different endoscopists.”

4. Lower pressures were recorded in the nurses' group, was it necessary to use some drugs to normalize the pressure?

Response: For the prevention of hypotension, the information was explained in the Materials and Methods as "The nurse trained for sedation was informed about possible side effects such as desaturation ($<90\%$), hypotension (systolic <90 mm-Hg), and was also trained to perform the necessary interventions 250 cc of fluid loading in case of hypotension".

Since there was no long-term hypotension in our study, there was no need for drug treatment. Ephedrine is used in our clinic for these possible conditions. However, the lack of information about the ephedrine application in the Materials and Methods has been overlooked. We have added the following information to the Materials and Methods.

“If hypotension is continued, 5-10 mg IV ephedrine will be administered.”

5. - Regarding desaturation, the authors report 4 patients in the group of nurses who had this complication. What measures were needed to normalize saturation?

Response: For the prevention of desaturation, the information was explained in the Materials and Methods as “The nurse trained for sedation was informed about possible side effects such as desaturation ($<90\%$) and was also trained to perform the necessary interventions (such as jaw-thrust and head tilt chin lift manoeuvres in case of desaturation ...”. In addition to these manoeuvres, maintenance of the airway have been provided by the endoscopy nurse using the

oropharyngeal airway, but this statement was not specified. The sentence has been modified as "... interventions (such as jaw-thrust and head tilt chin lift manoeuvres *or using oropharyngeal airway* in case of desaturation".

We have also added the following information to the Materials and Methods.

"In cases where peripheral oxygen saturation does not increase or continues to decline (below 85), the anaesthetist will intervene. In the case of long-term desaturation, the materials required for emergency airway management (bag mask ventilation, intubation, etc.) will be available in the endoscopy room to provide respiratory support."

6. When authors begin the sentence in the discussion with an author's citation, I recommend placing the citation at the end of each sentence and not after each author's name

Response: All citations has been placed at the end of each sentence.

7. Cite guidelines after the sentence: In guidelines for propofol administration of non-anesthesia personnel, it has been stated that ASA III and over patient procedures, long complex procedures, and difficult airway conditions require an anaesthetic personnel

Response: Guidelines has been cited.

8. With regard to conclusion I do not think it is safe and not proven by the study to say that sedation is safe for use in the 2 groups, since the n of the study is too small for this type of drawing

Response: Conclusion has been modified as follows.

"This study demonstrated that the combination of midazolam-ketamine-propofol could be performed under the supervision of both anaesthetist and endoscopy nurse with a PCA device in colonoscopy sedation of low-risk (ASA I-II) patients with similar side effects. There is a need for further studies with ASA III-IV patients and also with more patients."

Thank you very much for reviewing our paper and for your kind suggestions.