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Reviewer A

I reviewed the manuscript entitled " End-tidal capnographic monitoring during flexible bronchoscopy under fentanyl and midazolam sedation" by Dr. Minami, et al. This study conducted a retrospective study to 1) investigate the frequency of apnea episodes by end-tidal capnography under fentanyl and midazolam sedation during bronchoscopy. The results demonstrated that apnea episodes were recorded in 85 patients (100%). The authors concluded that endtidal capnography was effective for detecting the occurrence of apnea in patients undergoing a bronchoscopic examination under fentanyl and midazolam sadation. The study contents are important in clinical practice, however, there are several concerns (some of them seem serious) as an original article as follows.

Major comments;
1. Study design
Comment 1.
Because this research is a retrospective study as described in the manuscript, the authors should show participant more precisely. How many patients were excluded? Were these 85 patients surely consecutive all cases who undergo bronchoscopy in your hospital between august 2017 and march 2018, or not?

Reply 1:
-> Thank you for the good suggestion. These were 85 patients surely consecutive all cases who undergo bronchoscopy in our hospital between august 2017 and march 2018.Thus, we added the following sentences in the Study design (Page 6, Line 8-9).

Changes in the text:
They were surely consecutive all cases who undergo bronchoscopy in the hospital.

Comment 2.
2. Research question
The author should clarify research question and novelty of this study more.

Reply 2:
-> Thank you for your good comments. In this study, the research question is that the occurrence of apnea episodes during bronchoscopic examinations under fentanyl and

midazolam sedation and the efficiency of capnographic data, by cap-ONE YG-227T (NIHON KOHDEN, Tokyo, Japan). The novelty of this study is that cap-ONE YG-227T (NIHON KOHDEN) detected the occurrence of apnea in patients undergoing a bronchoscopic examination under fentanyl and midazolam sedation. Apnea episodes were recorded in 85 patients (100%), although clinical problems did not occur. Thus, we describe about the following sentences in the introduction (Page 5, Line 18 and Page6, Line 1-2) and discussion (Page 10, Line 10-13 and Page10, Line 18; Page 11 Line 1-4).

Changes in the text:
Here, we retrospectively revealed the occurrence of apnea episodes during bronchoscopic examinations under fentanyl and midazolam sedation by end-tidal capnography.

In our study, cap-ONE YG-227T (NIHON KOHDEN) detected the occurrence of apnea in patients undergoing a bronchoscopic examination under fentanyl and midazolam sedation. Apnea episodes were recorded in 85 patients (100%), although clinical problems did not occur.

This device comprises the mainstream capnometer cap-ONE (TG-980P; Nihon Kohden), nasal adapter, oxygen cup, and mouthpiece. The nasal adapter collects exhaled nasal flow into a measurement cell, while the oxygen cup delivers oxygen through the patient's nose and has a sponge to scatter oxygen for accurate CO2 monitoring (19)

3. Analysis as an original article
Comment 3.
The aim of this study was "to investigate the frequency of apnea episodes by end-tidal capnography under fentanyl and midazolam sedation during bronchoscopy". The conclusion was "End-tidal capnography was effective for detecting the occurrence of apnea in patients undergoing a bronchoscopic examination under fentanyl and midazolam sedation". Which results or analysis demonstrated the effectiveness of detecting the occurrence of apnea in patients undergoing a bronchoscopic examination under fentanyl and midazolam sedation. Regrettably, the manuscript might be just report (or letter), but not original research article.
Reply 3:
-> Thank you for an important suggestion. In this study, it is a first report about efficiency of cap-ONE YG-227T (NIHON KOHDEN, Tokyo, Japan) for detecting the occurrence of apnea bronchoscopic examination. We added and described the following sentences in abstract (Page4, Line 3), methods (Page 7, Line 18 and Page8, Line1) and discussion (Page 11, Line 4-5 and Line10-12, Page10, Line 18-Page 11 Line 1-4).
, respectively

Changes in the text:
End-tidal capnography, cap-ONE YG-227T was effective

This device was used for end-tidal capnographic monitoring (Fig. 1C).
thus, the device was effective for detecting the occurrence of apnea.

This device comprises the mainstream capnometer cap-ONE (TG-980P; Nihon Kohden), nasal adapter, oxygen cup, and mouthpiece. The nasal adapter collects exhaled nasal flow into a measurement cell, while the oxygen cup delivers oxygen through the patient's nose and has a sponge to scatter oxygen for accurate CO2 monitoring (19)

Reviewer B

I have written with interest the manuscript "End-tidal capnographic monitoring during flexible bronchoscopy under fentanyl and midazolam sedation". I find the topic weary relevant both from the scientific point of view, as well as important clinical impact. However there are two major limitations which in my opinion should be addressed, before detailed revision of the manuscript is being made, and finally before the manuscript is accepted for publication.

Comment 1.
Based on my clinical experiences the average dosage of Fentanyl in a >70yo. population is around 50ug (which is similar as in reviewed manuscript), whereas for Midazolam is approximately 1-2,5mg which is much lower than in reviewed manuscript. Therefore I would expect to see assessment of all subjects with Richmond Agitation-Sedation Scale. Because this relatively high Midazolam doses should be considered as apnea risk factors. However taking into account retrospective character of reviewed paper I do expect that this data may be not available. Missing RASS is acceptable.

Reply 2:
-> Thank you for the good comments. We added the following sentences in discussion (Page 12, Line 7-9)

Changes in the text:
This study has one limitation. We did not see assessment of all subjects with Richmond Agitation-Sedation Scale. This relatively high midazolam and fentanyl doses might be considered as apnea risk factors.

Comment 2.
However, taking into account that that the major research tool described in the manuscript is the cap-ONE YG-227T (NIHON KOHDEN, Tokyo, Japan) end-tidal CO2 readings must be mandatory reported and discussed in all major manuscript sections (methods, results and discussion). Reporting only on apneas without describing and discussing end-tidal CO2 readings may lead to misinterpretation of this weary important results. Taking this into account please include explained above missing data.

Reply 2:
-> Thank you for the good suggestion. I added and described the following sentences.

Changes in the text:
In methods (Page 8, Line 1-3)
The cap-ONE bite block (YG-227T; Nihon Kohden, Tokyo, Japan) can deliver oxygen while measuring mainstream EtCO2 during bronchoscopic procedures.

In results (Page 9, Line 5-7)
the onset of an apnea episode by the cap-ONE YG-227T monitoring device (NIHON KOHDEN) and decline in the SpO2 level of ≥4% from baseline.

In discussion (Page 10, Line 18 and Page11, Line 1-5)
This device comprises the mainstream capnometer cap-ONE (TG-980P; Nihon Kohden), nasal adapter, oxygen cup, and mouthpiece. The nasal adapter collects exhaled nasal flow into a measurement cell, while the oxygen cup delivers oxygen through the patient's nose and has a sponge to scatter oxygen for accurate CO2 monitoring (19); thus, the device was effective for detecting the occurrence of apnea.

Comment 3.
Moreover, taking into account a recent publication "Risk factors of complications during noninvasive mechanical ventilation -assisted flexible bronchoscopy. Adv Med Sci. 2021 Apr 20;66(2):246-253. doi: 10.1016/j.advms.2021.04.001." in which even though the patients were supported with Noninvasive Mechanical Ventilation the doses of sedatives being used in that study were smaller in comparison to reviewed publication (Midazolam [mg] 3.3 ± 1.3 for uneventful and 2.0 ± 1.0 for complicated group p=0.9, whereas a bit lower for Fentanyl [µg] 68 ± 27 for uneventful and 67 ± 29 or complicated group p= 0.66) a role of ventilatory support such as NIV should be mentioned in the discussion part. After making these two amendments I will be more than happy to revise the manuscript again.

Reply 2:
-> Thank you for the good suggestion. Oversedation sometimes could causes severe respiratory depression and oxygen desaturation. I added about a role of ventilatory support such as Noninvasive Mechanical Ventilation in the discussion part (Page 12,

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Line 7-13)

Changes in the text:
In previous report, sedation depth was analyzed to reveal Noninvasive Mechanical Ventilation - Flexible bronchoscopy risk factor (32). It is necessary to be careful for overdose sedation which could cause severe respiratory depression and oxygen desaturation.