

Peer Review File

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Reviewer A

Thank you for the opportunity to review this systematic review. This review describes a very important area of interest and a subject that warrants discussion, specifically; Comparing upper airway awake exploration, drug-induced endoscopy and natural sleep – A systematic review. The authors have done a comprehensive search on the area; however, it requires significant scientific English editing as there are large sections of the review that are extremely difficult to understand.

Reply to Reviewer 1: Thank you for your nice words, we did our best to explain ourselves and asked for help with the English grammar, so now we hope that there are no paragraphs difficult to follow.

Reviewer B

- Thank you for this broad discussion on a very interesting topic comparing NSE (natural sleep endoscopy), DISE (drug-induced sleep endoscopy) and awake nasendoscopy. This is a well conducted and well-written review with a solid methodology. However, the large discrepancy between the 'materials & methods' of the included studies prevents going beyond a narrative review and discussion of the current knowledge without solid conclusions. All information is represented in a concise way with clear tables.

Reviewer 2: Thank you for your deep reading and suggestions. Here you can see the answers to your questions/suggestions.

78:

- The question is raised whether information obtained during DISE justifies the cost, time and risk for the patient undergoing it. Please provide a comment in your discussion section on this concern.

Reply: 78:- The question is raised whether information obtained during DISE justifies the cost, time, and risk for the patient undergoing it. Please provide a comment in your discussion section on this concern.

You're right that if we say the sentence like this we should offer some comments about the cost, etc, but we feel that discussing if DISE is cost-effective is beyond this review, as many more concepts need to be considered (it does change the surgical plan but then it doesn't seem to improve the success rates, to be honest, the metanalysis performed on this subject are disappointing, mostly because they are not critical with the

articles included and they are mixing different things... In order to discuss this properly, we would need another paper, this is why we have rephrased this sentence and now it says: The issue therefore is whether a pharmacologically induced sleep state can mimic natural sleep, and if performing a sleep endoscopy during this induced sleep state confers additional information to the one obtained during awake exploration.

127-128:

- It should be nuanced that Ordonez et al. did compare propofol induced sleep with zolpidem induced sleep, since it is not fully 'natural sleep'. Eg. Zolpidem might increase arousal threshold and pharyngeal muscle responsiveness (Carberry et al.).

- What are your insights about using other drugs such as remifentanil solely as a sedative or in combination with propofol to reduce respiratory depression during sleep endoscopy? Do you think Remimazolam might be another good alternative during sleep endoscopy as already used in other endoscopic procedures? For example, also because of less respiratory inhibition?

Reply: 127-128: - It should be nuanced that Ordonez et al. did compare propofol-induced sleep with zolpidem-induced sleep, since it is not fully 'natural sleep'.

Thank you for the observation, you're right, therefore we have added this: It should be mentioned that Ordonez et al. compared TCI-propofol DISE vs zolpidem-induced sleep, nevertheless, as zolpidem has proven no changes in collapsibility of the UA or in Pcrit and due to its short half-life, its effect does not take place throughout the night, it has been considered that this study could indeed be comparable to natural sleep. (111-114)

What are your insights about using other drugs such as remifentanil solely as a sedative or in combination with propofol to reduce respiratory depression during sleep endoscopy? Do you think Remimazolam might be another good alternative during sleep endoscopy as already used in other endoscopic procedures? For example, also because of less respiratory inhibition?

These are my thoughts on this subject: the use of remifentanil in addition to propofol can cause a higher desaturation, although it reduces sneezing (Cho, J. S., Soh, S., Kim, E. J., Cho, H., Shin, S., Kim, H. J., & Koo, B.-N. (2015). Comparison of three sedation regimens for drug-induced sleep endoscopy. *Sleep and Breathing*, 19(2), 711–

717. <https://doi.org/10.1007/s11325-015-1127-9>.) Although other articles showed that

was OK Kim, Y., Park, H., Shin, J., Choi, J. H., Park, S. W., & Kang, H. Y. (2018). Effect of remifentanil during drug-induced sleep endoscopy in patients with obstructive sleep apnea. *Sleep and Breathing*, 22(4), 919–923. <https://doi.org/10.1007/s11325-018-1738-z>. Nevertheless, discussing this

topic goes beyond the scope of this review, this is why we don't mention it. Regarding Remimazolam, no experience, sorry.

195, 229- Static and dynamic fiberoptic with maneuvers.

- Interesting overview of the differences between DISE and awake nasendoscopy. Apart from the general consensus that awake examinations underestimate degree of collapse, the heterogeneity in scoring systems between the different studies and the different body positions (supine-nonsupine), as mentioned, make it difficult to compare and get a uniform conclusion. The lack of uniformity in scoring should be mentioned in the discussion section.

Reply: 195, 229- The lack of uniformity in scoring should be mentioned in the discussion section. Thank you for this suggestion, it's been added.

288:

- The included studies performing NSE only included small sample sizes. Do you think we need more research in the field of endoscopic observed collapse to get more insight into the similarities/differences between NSE and DISE, in particular?

- The abstract and line 73 state that endoscopy during natural sleep is not viable in everyday practice. In a recent systematic review this topic was discussed (Van den Bossche et al.). In line 187-191 other non-anatomical pathophysiological traits are mentioned. What are your thoughts about flow analysis and/or acoustic analysis of snoring as a possible future solution for the problem regarding endoscopy during natural or drug-induced sleep?

Reply: 288-The included studies performing NSE only included small sample sizes. Do you think we need more research in the field of endoscopic observed collapse to get more insight into the similarities/differences between NSE and DISE, in particular?

Thank you for pointing out this limitation that we didn't think about. You're right that more research should be done on this, although it's challenging. Our feeling is that if the patient is not oversedated, the results of DISE are real, the fact that snoring apps show similar results supports us in our reasoning, but the number of studies is small so far and some are contradictory so we cannot be sure.

The abstract and line 73 state that endoscopy during natural sleep is not viable in everyday practice. In a recent systematic review this topic was discussed (Van den Bossche et al.). In lines 187-191 other non-anatomical pathophysiological traits are mentioned. What are your thoughts about flow analysis and/or acoustic analysis of snoring as a possible future solution for the problem regarding endoscopy during natural or drug-induced sleep?

Thanks for this information, we have added this to the discussion: A recent systematic review of the papers on NSE found that the soft palate was the most reported site of upper airway collapse during natural sleep endoscopy, followed by the tongue base, lateral walls, and epiglottis, which is in line with

previous findings during drug-induced sleep endoscopy, nevertheless, more research is needed on this topic. It may be possible that new tools based on the flow appearance or sound analysis will help us to have a reliable notion of what happens during natural sleep without the need for NSE or DISE.

294:

- Would you expect a difference in upper airway collapse during natural REM and non-REM sleep? Generally, DISE only provides non-REM sleep, would this mean that observations during DISE are less reliable than observations during natural sleep?

Reply: 294- - Would you expect a difference in upper airway collapse during natural REM and non-REM sleep? Generally, DISE only provides non-REM sleep, would this mean that observations during DISE are less reliable than observations during natural sleep?

DISE only provides information about NREM sleep, mostly because propofol, which is the drug most widely used, inhibits REM and we cannot observe the patient in that stage of sleep, but also because, although with midazolam REM can be observed according to Genta et al (Critical closing pressure during midazolam-induced sleep. <https://doi.org/10.1152/jappphysiol.00508.2011>), it takes 60-90 minutes to achieve it, therefore it takes too much time. To be honest, most of the patients that show a collapse in REM sleep and have predominant REM sleep apnea, also have some obstructions in NREM, therefore the information obtained during DISE is useful, but we cannot prove it, this is why we would rather not discuss this and say that this is a limitation of the study and DISE.

299:

- Nuance your statement, try to avoid speaking about (No) accurate prediction if the developed models in the different studies are not validated in an external cohort.

Reply: 299- Nuance your statement, try to avoid speaking about (No) accurate prediction if the developed models in the different studies are not validated in an external cohort.

We have tried to do as you said and now it's been changed to: Awake exploration, both static and dynamic, does not have good agreement with the types of collapse that occur in DISE in many patients.

301:

- Would you advise performing a DISE in 'all' patients that are PAP intolerant? When are time, costs and risks for the patient of performing DISE justified? Nuance/explain your statement.

Reply: 301- Would you advise performing a DISE in 'all' patients who are PAP intolerant? When are time, costs, and risks for the patient of performing DISE justified? Nuance/explain your statement.

The goal of this article is not to talk about the risk, costs, or time used for DISE, as we state we wanted to compare natural sleep vs DISE and awake exploration vs DISE. Discussing about if every sleep surgeon should perform DISE in "all" patients is beyond the scope of this systematic review. The conclusion that is made is that "no exploration is better to observe the collapse that occurs in the UA of OSA patients in need of alternative treatments to the standard UA positive pressure". The sleep surgeon who is treating the patient should consider if they need that information to treat the patient, some well-known and respected sleep surgeons don't perform DISE because they think that they don't need that information. What we say is that the information is reliable and that is not the same as awake.