

A call for a more rigorous screening of postoperative delirium

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Provenance: This is an invited article commissioned by the Academic Editor Dr. Hao Zhang (Department of Anesthesiology, Rocket Force Characteristic Medical Center of PLA, Beijing, China).

Comment on: Wildes TS, Mickle AM, Ben Abdallah A, *et al.* Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery: The ENGAGES Randomized Clinical Trial. JAMA 2019;321:473-83.

Submitted Jul 01, 2019. Accepted for publication Jul 12, 2019.

doi: 10.21037/atm.2019.07.32

View this article at: <http://dx.doi.org/10.21037/atm.2019.07.32>

With the publication of the “Electroencephalography Guidance of Anesthesia to Alleviate Geriatric Syndromes (ENGAGES)” trial, Wildes and colleagues presented the results of a prospective, randomized, controlled, single-center trial aiming to analyze whether intraoperative electroencephalography (EEG) guidance could reduce the rate of postoperative delirium (POD) (1). Patients above 60 years were randomized to “Electroencephalography-guided minimization of anesthetic administration” (EEG-guided group) (n=614) or “usual anesthetic care” (n=618), after stratification for cardiac *vs.* noncardiac surgery and positive *vs.* negative recent fall history. They found that volatile agents could be significantly reduced by 14% in the EEG-guided group, leading to a reduction in EEG Burst suppression ratio of 46%. Surprisingly, this did not result in a lower incidence of POD in the EEG-guided group. This is in direct contradiction to prior RCTs (2-4) and substantial clinical experience, resulting in guideline recommendations in the ESA guideline 2017, American Geriatrics Society 2016, and UK’s National Institute for Health and Care Excellence (5-7). We here like to give a short overview; about the concerns we have with the data presented by Wildes and colleagues. Our concerns can be subdivided in three subheadings: (I) insufficient POD screening; (II) inadequate EEG guidance and (III) misappropriate presentation of important results, causing a misguidance of the readers on this subject.

Insufficient POD screening

Our main concern is that delirium monitoring in this trial was not in line with ESA’s 2017 guideline recommendation on POD (5). Delirium can occur soon after emergence from anesthesia, which is why screening should start as early as in the recovery room. Instead, POD monitoring in this trial was initiated on day 1 after surgery, most likely more than 24 h after the end of the surgical procedure/anesthesia. This is a crucial issue, especially since the analysis seeks to examine the relationship between depth of anesthesia and POD, and this unobserved gap between cause and effect can potentially compromise the results. It is also important to consider that their preferred instrument, confusion assessment method (CAM), was shown to have a low sensitivity for hypoactive POD (sensitivity =0.43) (8), which is the main form of delirium observed in elderly patients (9).

Another reason for the unexpected results may be the frequency and time points of delirium screening. The authors performed a single screening per day in the afternoon. However, delirium has a fluctuating course, and clinical experience shows a characteristic increase of delirious symptoms in the morning (“sun-uppers”) and in the late night (“sun-downers”), hence it is of importance to screen for POD once per shift in the morning and evening (5). Admittedly, these preferred time points have not been widely published, but may have been nevertheless

inferred from their considerable clinical experience. We feel that it would have been particularly valuable to include the early POD rates, within the first postoperative day, i.e., first evening and first morning. The inadequate frequency was supplemented by chart reviews, but also here one must consider that, as reported by Rudolph and Marcantonio (10), chart review detects only about 7% of the delirious patients that would have been found by using an adequate methodology.

Ineffective EEG guidance

Anesthesia-induced alpha-band power decreases significantly with age (11,12), which is believed to reduce the accuracy of bispectral index (BIS) and other processed EEG based index level when applied to older patients. Additionally, while elderly patients have a higher risk of developing Burst Suppression during general anesthesia, at the same time, the “Burst-Suppression ratio” indicated in the EEG monitors underestimate the absolute duration of EEG suppression (13), again making existing processed-EEG monitors uniquely ill-suited for older patients. Based on these facts, we also advocate that in future, anesthesiologists should be trained to read EEG waveforms and spectra to detect Burst Suppression periods, particularly in older patients, to avoid reliance on processed-indices that are known to be inaccurate in this population.

However, EEG data analysis in the ENGAGES study revealed a reduction in Index level below 40 [EEG guided group 32 (9/81) *vs.* usual care group 60 (19/132); difference, OR -28, 95% CI, -38 to -18] and a reduction in EEG Burst-Suppression ratio of 46% in the EEG-guided group. These findings did not result in a statistically significant difference in the incidence of POD between the groups. Having a detailed look at EEG based read outs of the ENGAGES trial, we found patients tended to spend large proportions of time with BIS <40, with wide variability even in the EEG-guided group. When compared to the data in the CODA trial this suggests, that EEG-guidance was poorly performed [Time (min) with BIS <40, normalized by mean surgery time: CODA trial: EEG-guided median 3.4/interquartile range (IQR) =2.6 and routine care 12.5/IQR =18.4; ENGAGES trial: EEG-guided 7.3/IQR =16.4 and routine care 13.6/IQR =25.7]. If the CODA trial showed that EEG-guided anesthesia could significantly reduce POD, the ENGAGES trial seems only to suggest that ineffective EEG-guided anesthesia will not reduce delirium.

In future thoroughly, EEG data analysis indicating a correlation with POD in older patients should focus on raw EEG data analysis, adjusted for age and anesthetic agents and dosage. Three studies are actually on their way (clin trials: NCT03879850; NCT03124303; ANZCTR ID: 12617001354370).

Misappropriate presentation of important results

The suspected shortcomings in EEG-guidance are highlighted by comparing delirious patients versus those without delirium (irrespective of the allocation in the EEG-guided group or usual care group). In the ENGAGES study, EEG suppression and periods with BIS indices <40 were prolonged in POD patients. However, these findings were not discussed within the manuscript, but obviously supporting the findings of the former RCT trials showing a clear correlation between periods of deep anesthesia and the occurrence of POD in elderly patients (2-4).

The suspected shortcomings in POD detection are highlighted by the significant decrease in 30-day mortality in the intervention group (EEG guided group 0.65% *vs.* usual care group 3.07%; $P=0.004$). The authors casually mention these findings, which are again in line with several studies (3,4,14-16). Moreover, it is known that the development of POD is related to an increased mortality in elderly patients (17,18).

In conclusion, we are very much concerned that the tremendous benefits of intraoperative EEG-guidance in anesthesia, several of which were also confirmed in this study, were not sufficiently discussed and valued in the presented manuscript. Although the effect of EEG-guidance on POD could not be observed, possibly due to the aforementioned methodological concerns, we feel that the significant decrease in anesthetic use and reduced mortality rate in the EEG-guided group must not be overlooked, and should be granted due attention and exposure.

We are sincerely grateful to Wildes and colleagues, as well as to other teams in the scientific community, for their tremendous effort in tackling this challenging condition. A similar terminology to define perioperative neurocognitive disorders will improve the comparability of research results and unify POD screening recommendations (19). Each piece of evidence is valuable and brings us closer to preventing or limiting the effects of delirium in our patients, ultimately improving their outcome and quality of life.

Acknowledgments

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

- Wildes TS, Mickle AM, Ben Abdallah A, et al. Effect of Electroencephalography-Guided Anesthetic Administration on Postoperative Delirium Among Older Adults Undergoing Major Surgery: The ENGAGES Randomized Clinical Trial. *JAMA* 2019;321:473-83.
- Chan MT, Cheng BC, Lee TM, et al. BIS-guided anesthesia decreases postoperative delirium and cognitive decline. *J Neurosurg Anesthesiol* 2013;25:33-42.
- Radtke FM, Franck M, Lendner J, et al. Monitoring depth of anaesthesia in a randomized trial decreases the rate of postoperative delirium but not postoperative cognitive dysfunction. *Br J Anaesth* 2013;110 Suppl 1:i98-105.
- Whitlock EL, Torres BA, Lin N, et al. Postoperative delirium in a substudy of cardiothoracic surgical patients in the BAG-RECALL clinical trial. *Anesth Analg* 2014;118:809-17.
- Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. *Eur J Anaesthesiol* 2017;34:192-214.
- Berger M, Schenning KJ, Brown CH 4th, et al. Best Practices for Postoperative Brain Health: Recommendations From the Fifth International Perioperative Neurotoxicity Working Group. *Anesth Analg* 2018;127:1406-13.
- American Geriatrics Society Expert Panel on Postoperative Delirium in Older Adults. Postoperative delirium in older adults: best practice statement from the American Geriatrics Society. *J Am Coll Surg* 2015;220:136-48.e1.
- Radtke FM, Franck M, Schneider M, et al. Comparison of three scores to screen for delirium in the recovery room. *Br J Anaesth* 2008;101:338-43.
- Robinson TN, Raeburn CD, Tran ZV, et al. Motor subtypes of postoperative delirium in older adults. *Arch Surg* 2011;146:295-300.
- Rudolph JL, Marcantonio ER. Review articles: postoperative delirium: acute change with long-term implications. *Anesth Analg* 2011;112:1202-11.
- Purdon PL, Pavone KJ, Akeju O, et al. The Ageing Brain: Age-dependent changes in the electroencephalogram during propofol and sevoflurane general anaesthesia. *Br J Anaesth* 2015;115 Suppl 1:i46-57.
- Koch S, Spies C. Neuromonitoring in the elderly. *Curr Opin Anaesthesiol* 2019;32:101-7.
- Muhlhofer WG, Zak R, Kamal T, et al. Burst-suppression ratio underestimates absolute duration of electroencephalogram suppression compared with visual analysis of intraoperative electroencephalogram. *Br J Anaesth* 2017;118:755-761.
- Monk TG, Weldon BC. Anesthetic depth is a predictor of mortality: it's time to take the next step. *Anesthesiology* 2010;112:1070-2.
- Lindholm ML, Träff S, Granath F, et al. Mortality within 2 years after surgery in relation to low intraoperative bispectral index values and preexisting malignant disease. *Anesth Analg* 2009;108:508-12.
- Leslie K, Myles PS, Forbes A, et al. The effect of bispectral index monitoring on long-term survival in the B-aware trial. *Anesth Analg* 2010;110:816-22.
- Pisani MA, Kong SY, Kasl SV, et al. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med* 2009;180:1092-7.
- Witlox J, Eurelings LS, de Jonghe JF, et al. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA* 2010;304:443-51.
- Evered L, Silbert B, Knopman DS, et al. Recommendations for the Nomenclature of Cognitive Change Associated with Anaesthesia and Surgery-2018. *Anesthesiology* 2018;129:872-9.

Cite this article as: Koch S, Radtke F, Spies C. A call for a more rigorous screening of postoperative delirium. *Ann Transl Med* 2019;7(Suppl 6):S192. doi: 10.21037/atm.2019.07.32