Pain Ther (2022) 11:743–746
https://doi.org/10.1007/s40122-022-00369-x

LETTER

A Response to: Letter to the Editor Regarding "Neurophysiological Assessments During Continuous Sedation Until Death Put Validity of Observational Assessments Into Question: A Prospective Observational Study"

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Received: February 10, 2022 / Accepted: February 16, 2022 / Published online: March 12, 2022

Keywords: Continuous sedation until death; Pain assessment; Palliative medicine; Unconsciousness; Comfort assessment; Palliative sedation; Neurophysiological monitoring; Wavelet anesthetic value; Analgesia Nociception Index

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To the Editor,

We would like to thank Prod'homme and colleagues for their thoughtful comments on our publication [1]. Their observations have prompted us to further clarify some aspects of this work.

We agree with their first comment, indicating that the available data on ANI monitoring in the palliative population are too limited to consider it as a new golden standard. Indeed, more research is needed. The use of ANI monitoring in this population is still a new development and the primary goal of our research was to assess whether or not clinical observational assessments concur with neurophysiological monitoring. We included both caregiver assessments, assessments by established observational tools and neurophysiological indices of discomfort (ANI), and depth of sedation (WAVcns). Our results showed a poor correlation, which led us to conclude that the validity of observational assessments in this particular patient group needs to be further scrutinized. We would like to reiterate that the medication used to induce continuous sedation until death (CSD) also has an impact on motor responsiveness, while the traditionally used observation scales, as well as clinical assessments, mainly reside on inferences from the patient's responsiveness and may therefore not be entirely reliable. Assessing awareness more independently

from (the assessment of) motor responsiveness may therefore contribute to the quality of assessments of comfort during continuous sedation until death [2]. We further agree that neurophysiological correlates of depth of sedation and discomfort always need interpretation by a skilled caregiver; a correlate is not the same as the object it measures and additional research can help in clarifying different factors involved. In our study, we did not recommend using WAVcns- and ANI-monitoring as standalone measures, but as a top up besides clinical judgement and a tool to be included for guiding treatment decisions so that the principle of proportionality regarding titration of medication can be adhered to as good as currently possible [1, p. 386].

Our use of the term "objective" is meant to indicate that the numerical values of a monitoring device do not depend on a subjective appraisal, as is the case with behavior-based observation scales (and the problems associated with that, such as interrater disagreements, lack of validated tools for use in CSD etc.) [3]. Of course, these monitor values need to be interpreted as well, which is usually the case in medicine when correlates are used. As we mentioned in the discussion section of our publication, our epistemological stance is that for this particular problem (which is related to the hard problem of consciousness) falsification of the hypothesis is not possible, and therefore we have to make inferences based on our results, taking into account the results of other studies where closely related research was carried out. These other studies suggest that (1) neurophysiological monitoring of the level of consciousness by WAVcns, and pain/discomfort by ANI, is more "objective" than behavior based observational tools and (2) that these neurophysiological measures can more reliably detect insufficient sedation and exclude the possibility of significant pain [4, 5].

Further, Prod'homme et al. mention that ANI measures not only pain but is also influenced by stress and anxiety, and can be considered as a vagal tone index. Although studies have shown that pain can be detected by ANI, we do agree that ANI is not restricted to only pain detection. That's why we, throughout our manuscript and on several occasions, used the term 'pain/discomfort'. In a context of continuous palliative sedation until death, and within the concept of total pain, we believe it makes more sense to not only exclude the possible presence of (nociceptive) pain, but also discomfort such as stress and anxiety as well. The suggestion that when ANI is low, both pain-relief and anxiolytic treatments should be adjusted seems to make sense in that regard.

It may be interesting to make the parallelism between the consciousness states potentially encountered during anesthesia, and those seen during end-of-life deep sedation. General anesthesia alters consciousness in a reversible way and, depending on the type of medication, may produce different states of consciousness. These include (1) complete absence of subjective experience (unconsciousness), (2) conscious experience without perception of the environment (disconnected consciousness, like during dreaming), and (3) episodes of oriented consciousness with awareness of the environment (connected consciousness) [6]. During end-of-life deep sedation, recall cannot be assessed afterwards (as with general anesthesia), but unpleasant disconnected consciousness episodes (e.g., nightmares) may potentially occur. This is difficult to assess in a non-communicative dying patient but detecting them and adapt sedation to avoid them could be a goal to further improve comfort in this situation [6]. We consider this as an important argument for also measuring depth of sedation in this context by using a processed EEG monitor (such as the NeuroSense in our study). In addition, as Prod'homme et al. rightly point out, an ANI monitor cannot detect neuropathic pain, and therefore depth of sedation should also be measured, as we did in this study, to allow a broader assessment of pain and discomfort and to ensure that no undetected residual pain (whether nociceptive or neuropathic) can be present or possibly consciously experienced.

Regarding the comment about the complementarity of clinical hetero-assessment by family and caregivers and ANI assessment, claiming that neither is superior to the other, we feel more research is still needed to clarify this. It is still unclear how some of these

assessment methods relate to each other; for example, previous research has shown that family members tend to overestimate pain in a loved one, while caregivers tend to underestimate pain [7]. Other factors such as cultural values and norms regarding pain and dying, and intergenerational differences could play a role as well [8, 9].

The time has indeed come to introduce various monitoring techniques as standard care to support medical decision-making and hetero-evaluation during continuous sedation until death. The final goal regarding comfort assessment during continuous sedation until death should be objective monitoring of both absence of pain and optimal sedation, thereby strengthening hetero-evaluation, which will ultimately lead to better care for the terminally ill patient. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this letter.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Author Contributions. SS: conceptualization and design, writing-original draft. JP: writing-original draft, writing-review and editing. SL: writing-review and editing. OM: writing-review and editing. PT: writing-review and editing. JB: writing-review and editing. RD: writing-review and editing.

Disclosures. Stefaan Six, Jan Poelaert, Steven Laureys, Olivier Maîresse, Peter Theuns, Johan Bilsen, and Reginald Deschepper have nothing to disclose.

Compliance with Ethics Guidelines. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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