Reviewer’s report

Title: Overnight auto-adjusting Continuous Airway Pressure + Standard Care compared with Standard Care Alone in the Prevention of morbidity in sickle cell disease Phase II (POMS2B): study protocol for a randomised controlled trial

Version: 1 Date: 14 Dec 2017

Reviewer: Maura Marcucci

Reviewer’s report:

Please note that this review was for the original submission.

Howard and colleagues submitted the protocol of a randomized controlled trial evaluating the effect on cognitive functions of auto-adjusting continuous positive airways pressure (APAP) on the top of standard of care, compared to standard of care, in paediatric and adult patients with sickle cell anaemia (SCA). The research question is clinical relevant; the protocol is well written and compliant with methodological standards of conducting and reporting research. I suggest that the Journal considers the manuscript for publication, after the authors have addressed the following points:

* The rationale for trying to affect the cognitive performance by reducing low daytime and night-time oxygen saturation (SpO2) using a continuous positive airways pressure (CPAP) in SCA patients could be better explained. Obstructive sleep apnoea (OSA) is more frequent in SCA patients, but OSA is not an inclusion criterion. It is not clear whether there is any effect that is expected on oxygen saturation (or directly on cognitive function) from a CPAP also in patients with SCA but no OSA, and if so, through which mechanisms. Including everyone and not only patients with OSA or low SpO2 at baseline might raise ethical concerns, and might dilute the effectiveness of the interventions, if there is no biological plausibility. At the end of the discussion the authors write "Based on our previous findings that many patients with sickle cell disease have minimum oxygen saturation overnight lower than the minimum documented in healthy asymptomatic children in the general population, we have elected to recruit both patients with evidence for obstructive sleep apnoea and those with more severe desaturation into this trial. This decision will allow comparisons of the magnitude of benefit across these groups." The sentence does not provide a satisfactory rationale and is also a bit inconsistent with the eligibility criteria, since: i) patients with "severe desaturation" are in fact excluded (at least those with "overnight oximetry showing mean overnight saturation of <90% for <30% of the night"); ii) in case of desaturation or "severe desaturation", CPAP therapy is not expected to be necessarily more effective than oxygen therapy alone, if there is desaturation but no specific conditions that would respond to a CPAP; iii) in fact, based on its eligibility criteria, the study will include also patients with no desaturation, neither mild nor severe.
In case of the inclusion of patients for whom there is no known or expected plausibility for the interventions to work might be justified by practical reasons.

In any case, the authors are invited to make the rationale for the study intervention and for the eligibility criteria clearer.

* **Primary outcome and expected effect size.**

Authors are invited to:

- provide a rationale for using the Wechsler scale as the instrument to measure cancellation (related to visual attention and processing speed). Please, provide details for the test and the psychometric characteristics of the scale

- explain what the BRIEF questionnaire consists in

- provide the rationale for sizing the study on an expected effect size of 2.3 points (or 2.4?) as difference in cancellation performance. This is close to the effect size found in a pilot study in children. Is there any evidence about the clinical relevance of this effect size and on whether the same clinical relevance is expected in children and adults? Does the limited study duration represent a reason not to expect any greater effect?

* **Blinding.** Please provide information on blindness of other study personnel (e.g. statistician).

* **References.** Please, conform all references and the ways they are cited in the text to the journal requirements

Close

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