Author’s response to reviews

Title: Bioelectrical impedance analysis of body composition for the anesthetic induction dose of propofol in older patients

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Version: 1 Date: 12 Aug 2019

Author’s response to reviews:

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Manuscript title: “Bioelectrical impedance analysis of body composition for the anesthetic induction dose of propofol in older patients”

Dear Dr. Anna Melidoni,

The authors would like to acknowledge your efforts and those of the reviewers for the thorough review of the manuscript. Furthermore, the authors would like to acknowledge all the pertinent comments and suggestions provided. Due to the comprehensiveness of the reviews, and bearing in mind the novelty, the significance of the topic and the impact of findings on the field, the authors would like to take this opportunity to address, in the following pages, some of the main comments made by the review board.

Response to the Reviewer #1 comments

1. With regard to the main study, the authors should include the ethical committee approval details in the methods section, followed by a brief description of the goals of the main/overall study.

We acknowledge the reviewer’s comment and in the revised version of the manuscript the Ethical Committee approval details were included in the methods section. In the revised version, we also clarified the purpose of the main study registered at clinicaltrials.gov.
2. The authors should be more open with the readers and mention that they have sliced their data and analysis into 4 sections. They should inform the reader that they have already published the results of a similar comparison in an overlapping sub-group - in the 20 obese and 20 non-obese adults. [Araujo et al. Reliability of body-weight scalars on the assessment of propofol induction dose in obese patients. Acta Anaesth Scand 2018].

We acknowledge the reviewer’s comment and in the revised version of the manuscript we mentioned that sectorial evaluations of the results focusing on the induction and maintenance phases of anesthesia have been conducted during model calibration. In addition, we clarified that the first study, planned to assess the ability of body size descriptors to estimate propofol induction dose in obese patients, has already been published [1].

3. As the current study, and the published one above mentioned above, both include the same group of 20 adult (<65 years) non-obese patients, one would expect the same data for patient demographics (age, gender etc), weight, and propofol dosing and concentration data, to be the same for this group in both papers. Looking at the tables 1 and 2 in the current paper, and the published one in Acta Anaesth, I see small but significant differences. Could the authors please explain why there are differences?

The present study provides secondary analysis of data registered at clinicaltrials.gov under the reference NCT02713698. According to the mentioned data, a total of 60 patients from 3 groups have been included. In group 1 were included patients older than 18 years old, with ASA physical status I to III and BMI<35kg/m2 scheduled for elective nose or ear surgery; in group 2 were included patients older than 18 years old, with ASA physical status I to III and BMI≥35kg/m2 scheduled to undergo laparoscopic gastric bypass surgery; and patients older than 65 years old, with ASA physical status I to III scheduled for orthopedic surgery were included in group 3.

To accomplish the objective of the present sectorial analysis we have evaluated the data from 20 adult patients (18-64 years), with ASA physical status I to III and BMI≤35kg/m2, and 20 older patients (with 65 or more years), with ASA physical status I to III and BMI≤35kg/m2.

In the previous published sectorial analysis [1], we planned to assess propofol induction dose in class II and III obese patients. Consequently, we have analyzed the data from twenty patients with BMI≥35kg/m2 and 20 patients with BMI<35kg/m2. The results of patients older than 70 years old were deemed out of the scope of this manuscript because we aimed to compare groups with the same age range.

As a result, considering the distinctive purposes of the mentioned sectorial analysis, the demographic characteristics of BMI≤35kg/m2 group of the published manuscript are different from the demographic characteristics of adult group of the present submission. For clarity, in the revised version of the manuscript, the identification of adult and older groups were changed to Age<65 and Age≥65 groups, respectively.

4. The sample size analysis seemed to be based on very optimistic parameters - including a correlation co-efficient of 0.7. As it turns out, the actual correlation co-efficients they have observed are far lower. Please discuss the potential effect of this on the confidence we should have in the power of the study.

Sample size considerations accomplished before the beginning of the study were based on association analyses using the Pearson correlation test between propofol induction dose and TBW in adult patients with normal BMI [2] because to the author’s knowledge there was no previous study evaluating this relationship in older patients. To detect a correlation of at least 0.7 (r=0.7) between propofol induction
dose and TBW a sample of at least 13 subjects was calculated to provide 80% power and a 0.05 level of significance.

As exposed in the introduction section, a higher level of heterogeneity in terms of physiology should be expected in a population of older patients in comparison with adult populations [3]. Consequently, we decided to include 50% more patients than the minimum number recommended by the power analysis to account for the increased variability anticipated in older patients.

5. In places the authors use the terms FFM and LBW interchangeably, which is confusing, because it is difficult to determine whether they are talking about a LBW measured from bio-impedance, or the FFM estimated by the Janmahasatian equation.

We agree with the reviewer´s point regarding the use of terms FFM and LBW. In the revised version LBWj was used to define LBW values obtained by the Janmahasatian equation and FFM was used to describe LBW values measured by the BCM.

6. The concept of phase angle calculated from the bio impedance measurements is new to me, and will be new to many readers too. Please elaborate on this - perhaps more detail on how it is calculated, and on why it should correlate with a frailty score.

Bioelectrical impedance analysis (BIA) is a reference method for the assessment of body composition by measuring resistance and reactance [4, 5]. Resistance is the opposition offered by the body to the flow of an alternating electrical current, essentially related to the amount of water present in tissues, and reactance is the resistive effect produced by the tissue interfaces and cell membranes [6].

Phase angle can be directly calculated from resistance and reactance \[\arctan(\text{Reactance/Resistance}) \times \frac{180°}{\pi}\] and it reflects the relative contributions of fluid (resistance) and cellular membranes (reactance) of the body [6]. Consequently, phase angle has been interpreted as an indicator of cell mass, membrane integrity, water cell distribution between the intra and extracellular spaces and, it has also been proposed as a biological marker of cell death [5, 8]. Phase angle determination has been suggested as a prognostic indicator in several clinical conditions such as human immunodeficiency virus infection, liver cirrhosis, chronic pulmonary disease, haemodialysis, sepsis and lung, breast, colorectal and pancreatic cancer [5]. More recently, phase angle has also been advocated as an objective indicator to identify frail patients [9, 10].

Frailty is generally defined as a biological syndrome of decrease reserve and resistance to stressors, resulting from cumulative declines of multiple physiologic systems [11]. Since frailty phenotype comprises unintentional weight loss, exhaustion, weakness, slow walking speed and low physical activity, BIA derived phase angle has been proposed as an objective indicator to identify frail patients [9].

In order to improve the clarity, phase angle definition was complemented in the introduction section of the revised version of the manuscript.

7. The variable delay between LOC and blood sampling is a significant weakness, but cannot be changed at this stage.

We agree with the reviewer’s point regarding the delay between LOC and blood sampling. According to the study design, propofol plasma samples were to be collected immediately after LOC. The main reason associated with the mentioned delay was the fact that the sequence of tasks of this observational
The study was performed during the normal routine schedule of the operative room. Notwithstanding the lack of rationale for the delay, the results were shown to illustrate the adequacy of the propofol induction doses for the established endpoint (BIS value and plasma concentration). Additionally, since there is no statistically significant difference between the time of plasma concentration measurements, we compared propofol plasma concentrations obtained in both groups. Consequently, it was verified that propofol plasma concentrations in the older group were higher than in the adult group, despite the lower dose required to attain LOC. These findings could explain the higher mean MAP variation observed during induction of general anesthesia in older patients.

Response to the Reviewer #2 comments

In this novel study, the authors used bioelectrical impedance analysis of body composition and baseline frailty score to predict the induction dosage of propofol in older patients. This study demonstrated that weight-based reduction of propofol is suitable in older patients and provided anesthesiologists understand the dosage in older patients in clinical practice. The weak point in the study is the patients' BMI<35 kg/m². However, there are many older patients' BMI<20 kg/m² and they are suffering hypotension during induction with propofol frequently. Therefore, I suggest further study is need to investigate the differences among BMI<20 vs >20-25 vs 26-35.

We agree with the reviewer’s point regarding the influence of BMI on phase angle. In normal-weight and overweight patients, phase angle increases with increasing BMI, whereas when BMI >40kg/m² there is an inverse association between BMI and phase angle [12]. Furthermore, age and sex related differences were also found to influence phase angle values [13]. Consequently, in order to establish a direct comparison among different studies or different groups of patients, a standardized phase angle value, calculated based on the reference values from a healthy population [12] should be used. The transformation of phase angle values into standardized values (z-score) allows the quantification of individual deviations from sex, age and BMI-specific population averages and to compare patients from a heterogeneous group [14].

In the present study, despite using different BMI classes, standardized phase angle values were used to directly compare the differences between the adult and older group (Figure 2).

Final considerations

The constructive comments made by the reviewers significantly improved the study and the analysis of the results presented in the manuscript. Once again, the authors would like to express their gratitude for your time and consideration, and acknowledge the questions, suggestions and comments that will considerably improve the clarity and robustness of the present submission.

Yours sincerely,
References


