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The Use of Indirect Calorimetry in Nutrition Therapy and Its Impact on Clinical Outcomes in Critically ill Patients: A review

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ABSTRACT

Adequate nutritional support is an essential element for achieving favorable outcomes in critically ill patients, which requires an accurate evaluation of energy needs to avoid under or overfeeding. Energy requirements of critically ill patients can be assessed either by Predictive equations (PEs) or by indirect calorimetry(IC) measurements. However, assessment of energy expenditure (EE) is a challenging task in intensive care unit patients because EE during critical illness is widely variable and the current PEs are inaccurate to determine the caloric requirement in these patients. Currently, IC is considered a gold standard for measuring EE as recommended by guidelines. Despite being the most accurate method of measuring EE, adequate data are lacking to validate the beneficial effects of IC-guided nutrition therapy on clinical outcomes in critically ill patients. Because of this, the actual clinical benefits of IC are poorly appreciated, and it is still an underutilized tool among dietitians in clinical practice. Therefore, in many centers, PEs are commonly used instead. The purpose of this review is to summarize the findings of recent studies regarding IC-guided nutrition therapy and its impact on clinical outcomes in critically ill patients.

Keywords: Nutrition therapy; Critical Illness; Indirect Calorimetry; Energy Expenditure; Predictive equations

INTRODUCTION

Critical patients in the Intensive Care Unit (ICU) are at higher risk of malnutrition (Yeh et al. 2015). Which is significantly associated with poorer clinical outcomes such as higher infection rate, increased morbidity, and mortality, longer hospital stay, increased health care costs, and reduced quality of life (Heyland et al., 2011; Sioson et al., 2017; Yeh et al., 2015). Combined with the higher prevalence of malnutrition in ICU (approximately 40 to 80%) (Lew et al. 2017; Wang et al. 2017). Hyper catabolism associated with critical illness may have further deleterious effects on outcomes when patients receive inadequate or inappropriate nutrition support (Delsoglio et al. 2019; Krishnan et al., 2003; Oshima et al., 2017).

The role of nutritional therapy during critical illness has been a focus of great interest in recent years, which is recognized as an essential component in the management of critically ill patients (Lambell et al., 2020; De Waele et al., 2019). Several published studies and two updated international clinical guidelines have shown that nutrition therapy has a positive impact on critically ill patients who meet their defined goals of caloric feeding (McClave et al. 2016; Singer et al. 2019). However, an inappropriate energy assessment can contribute to under- or overfeeding, resulting in deleterious effects (Heyland et al., 2011; Wichansawakun et al., 2014). Therefore, an accurate determination of EE is crucial in critically ill patients to optimize nutritional support and prevent negative effects from inappropriate feeding (Espinoza et al., 2016; Rattanachaiwong and Singer 2018; Wichansawakun et al., 2014). The provision of energy and protein is considered an integral part of optimal nutritional therapy (Ridley, Gantner, and Pellegrino 2015). However, the optimal amount of energy and protein required by critically ill patients to reduce morbidity and mortality is controversial (Wang et al., 2017). Some observational studies have shown that underfeeding or caloric debt is associated with adverse clinical outcomes in critically ill patients (Alberda et al., 2009; Elke et al., 2014; Heyland et al., 2011; Nicolo et al., 2015; Wei et al., 2015). In contrast, other studies have suggested better short-term outcomes in patients receiving low caloric intake (Arabi et al., 2010; Krishnan et al., 2003). "Besides this, the findings of the study by Zusman et al. (2016) suggested that both underfeeding and overfeeding appear to be harmful to critically ill patients (Zusman et al., 2016). Therefore, determination of energy requirements has vital importance as prescribed targets are used to guide nutrition delivery (Stapel et al., 2018; Tatucu-Babet, Ridley, and Tierney, 2016). However, accurately determining energy needs in critically ill patients is difficult because the effects that disease, injury, and stress have on REE are often varied and unpredictable"(Espinoza et al., 2016; Singer and Singer 2016; De Waele et al., 2019). "In clinical practice, PEs that estimate EE are the most commonly used method due to their ease of application; however, these equations have repeatedly proven inaccurate (Tatucu-Babet, Ridley, and Tierney 2016; Waele et al., 2016; Zusman et al., 2018). Importantly, these equations are not generally validated in those with higher nutritional risk, and its inaccuracies increase in obese, elderly, most severely unwell, and more malnourished populations (Reeves and Capra, 2003; Tatucu-Babet et al., 2016) and can lead to underfeeding or overfeeding (Ladd et al., 2018). Therefore, to feed critically ill patients adequately, an exact estimate of caloric goals is required, which is ideally performed using IC (Zusman et al., 2016; Gonzalez-granda et al., 2018; Oshima et al., 2019).

IC is currently the gold standard for measuring REE in critically ill patients (Gonzalez-granda et al., 2018; McClave et al., 2003; Oshima et al., 2017; Sioson et al., 2017). IC is a non-invasive method that precisely measures REE by measuring the volume of O2 (VO2) consumed, and the volume of CO2 (VCO2) produced and then, by using the Weir equation, REE calculates as follows (Espinoza et al., 2016; Das Gupta et al., 2017; Haugen and Li, 2007; Oshima et al., 2017; Stapel et al., 2018):

REE (kcal/day) = [(3.9 x VO2) + (1.1 x VCO2) – 61] x 1440.

Both the European (ESPEN) and American (ASPEN/SCCM) clinical practice guidelines recommend the use of IC to measure EE (McClave, et al. 2016; Singer et al. 2019). However, despite recent technological advancement in metabolic carts, these recommendations have poorly implemented in practice to date (Lev, and Singer 2010; Oshima et al. 2017) and many ICU clinicians still apply weight-based formulas to calculate EE (Singer and Singer 2016; De Waele et al. 2019). whereas the use of IC to guide nutrition therapy is limited yet, and its impact on clinical outcomes is not entirely proven. This narrative review aims summarize the recent findings on IC guided nutrition therapy and its impact on clinical outcomes in critically ill patients and provide recommendations for clinical practice.

MATERIALS AND METHODS

The literature search was conducted in electronic databases, i.e., PubMed and Google Scholars." All randomized Studies included in this narrative review were conducted on critically ill patients who were adults (≥18 years old), mechanically ventilated, admitted to ICU, with more than 48 hr stay in the ICU.

In all included studies, IC was used to guide nutrition therapy in the intervention group and compared to a standard care group where a predictive equation was used to estimate energy requirement in adult critically ill patients. For understanding the impact of IC on clinical outcomes, "studies must report the percentages of energy received and at least one of the relevant clinical outcomes such as mortality, infectious complications, length of ICU, and hospital stay or duration of mechanical ventilation as primary or secondary outcomes. Non-randomized studies and Studies in non-critically ill patients who were not incubated were excluded."

Effects of indirect calorimetry-guided nutrition therapy on clinical outcomes

Despite the guidelines recommendations, for indirect calorimeter has been given little attention in the clinical practice. To date, only five randomized controlled trials have investigated the impact of IC-guided nutrition therapy on clinical outcomes and compared to energy delivery using weight base equations. Generally, all studies have shown conflicting results regarding the impact of IC on clinical outcomes in critically ill patients. However, some benefits of IC were shown in 2 trials.

Firstly, Saffle study in 1990 compared the effectiveness of IC guided enteral nutrition to enteral nutrition guided by Curreri formula in burn patients. This study found no differences in-hospital mortality, hospital LOS between the group that received IC-guided enteral nutrition and the group that received enteral nutrition guided by Curreri formula (RR 1.33, 95% CI 0.24, 7.26, p=0.74*; Saffle, Larson, and Sullivan 1990). On the other hand, Singer et al. (2011), in the pilot TICACOS study, randomized 112 patients to IC guided enteral nutrition (study group) and enteral nutrition determined by a weight-based formula (control group). Supplemental PN was used to achieve the energy targets in the study group when necessary." The mean target EE between IC and SC groups was (1976 versus 1838kcal), mean energy delivered was higher in the IC-guided group compare to SC group (2086 vs 1480kcal, respectively). "The study found a trend toward reduced hospital mortality in-hospital mortality in patients that received IC guided enteral nutrition compared to patients that received enteral nutrition determined by a weight-based formula (32.3% in study group vs 47.7% in the control group, p = 0.058)." However, the number of mechanical ventilation days (16.1 ± 14.7 vs 10.5 ± 8.3 days, $p = 0.03$) and length of ICU Stay (17.2 ± 14.6 vs 11.7 ± 8.4 days, $p = 0.04$) were significantly increased in the intervention group compared to the control group. No differences were observed in ICU mortality between both groups (Lev et al. 2011). Furthermore, recently, Landes et al. (2016), randomized 27 patients to the physician-directed control group and to the IC-directed study group the results of this study showed that delivery of nutrition in both groups was suboptimal, with all patients receiving only 82.0 ±15.4 % of caloric requirements and there were no differences between groups regarding outcome (duration mechanical ventilation, healing of pressure sores) (Landes et al. 2016).. In another more recent published and slightly larger trail (EAT-ICU) assigned 203 patients to receive either IC-guided nutritional support or a simple weight-based equation. They found no difference in mortality, duration of ICU., infectious complications, and quality of life at six months (Lange et al. 2017). Similarly, in another pilot study (ONCA Study) by Gonzalez-granda et al. (2018), 40 mechanically ventilated patients were randomized into a group in which their energy requirements were determined by IC (IC group) and a group in which energy needs were calculated with a weight-based formula as standard care (SC group). The finding of this study showed that the IC group achieved 98% of their energy goal, whereas the SC group reached only 79% of the energy target." No statistically significant differences were observed between groups in the primary outcome of change in bioelectrical impedance phase angle (related to nutritional status and prognosis). Besides, a shorter length of ICU stay was observed in the IC group than in the SC group (13±8 vs 24±20 days, $P < 0.05$). In contrast, a non-significant increase in-hospital mortality was reported in the IC group while no differences in ICU mortality, hospital LOS, and duration of MV were observed between the two groups (Gonzalez-granda et al. 2018).

Table 1: Randomized control trials on IC guided nutritional therapy

First Author, Year Country	Saffle, 1990 (Anon)	Singer et al., 2011 (Israel)	Landes et al., 2016 (United State)	Allingstrup et al., 2017, (Denmark)	Gonzalez-Granda et al., 2018, (Germany)
Study Design No of hospital	Prospective single-center RCT	Prospective single-center RCT	Prospective single-center RCT	Prospective single-center RCT	Prospective single-center RCT
ICU., population	49 burned patients	130 MV patients General-ICU	27 long term MV patients	203 MV patients Medical ICU	40 MV patients Medical ICU
Age, years (mean±SD)	IC: 29.2±1.9 SC: 36.8± 1.9	IC: 59±18 SC:62±17	IC:72±7 SC: 74±10	IC:62±16 SC:65±17	IC: 57±16 SC: 56±14
BMI (kg/m²) (mean±SD)	NR	IC: 27.8±6.3 SC: 27.4±7.3	IC: 25.3±6.4 SC: 25.7±7.5	IC: 22.7±4.5 SC: 22±3.8	IC:27.8±6.2 SC:25.0±4.3
APACHE II Score	NR	IC:22.1±7.4 SC:22.4±6.8	IC: 34.7±12.0 SC: 38.7±13.4	NR	IC: 27.1±7.0 SC: 28.9±8.3
SOFA	NR	IC: 6.4±2.9 SC: 6.6±3.5	NR	IC: 8(6-11)* SC: 8(5-10)	IC: 12.1±3.3 SC: 11.4±3.0
Mean energy requirement (kcal/day)	IC: 2764±97.7 SC: 3913±96.7	IC: 1976±468 SC: 1838±468	IC: 1976.2±481.1 SC:2067.33±340.8	IC: 2069(1816-2380) SC: 1887(1674-2244)	NR
Mean energy delivered (kcal/day)	IC:3530±134.1 SC:3490±132.1	IC: 2086±460 SC: 1480±356	IC: 86.5%±12% SC: 77%±18%	IC: 1877(1567-2254) SC: 1061(745-1470)	IC:98%±8% IC:98%±8%
Hospital Mortality N(%)	IC: 3(11.6) SC: 2(8.7)	**IC**: 21(32) SC: 31(48)	NR	NR	**IC**: 5(25) SC: 3(15)
Mortality (ICU) (%)	NR	**IC**: 16(25) SC: 17(26)	NR	NR	**IC**: 3(15) SC: 3(15)
LOS (ICU), Days (mean±SD)	NR	**IC**:17±15 SC: 12±8	IC: 49±22 SC: 46±31	IC:7(5-22) SC:7(4-11)	**IC**:13±8 SC:24±20
Duration of MV, Days (mean±SD)	NR	**IC**: 16±15 SC: 11±8	NR	NR	**IC**:9±8 SC:10±5
LOS (Hospital) (days),(mean±SD	IC: 48.8±4.5 SC: 48.5±5.2	IC: 34±23 SC: 32±27		IC:30(12-53) SC:34(14-53)	**IC**:31±24 SC:40±23

Abbreviations: IC, indirect calorimetry; SC, standard care; NR, not reported; MV, mechanical ventilation; LOS, length of stay; ICU, intensive care unit.

The recent data from RCTs have shown conflicting results regarding the benefit of using IC to guide nutrition therapy over PEs on clinical outcomes in critically ill patients. Singer at al. (2011) reported a non-significant reduction in-hospital mortality in the IC group while in the study by Gonzalez-granda et al. (2018) showed a non-significant increase in in-hospital mortality compared to a standard care group. Meanwhile, no differences in ICU mortality and hospital LOS were found between IC and SC groups in any study. Furthermore, TICACOS is the only study that revealed an increased in the mean duration of MV in IC versus PEs groups. Besides, similarly to other outcomes, mixed findings were reported for LOS-ICU. A significant reduction in LOS-ICU was shown by Gonzalez-Granda et al. (2018) while Singer at al. (2011) and Allingstrup et al. (2017) conversely found a significant increase in LOS-ICU. As well as compare to other studies, only Singer at al. (2011) investigated outcome related to infectious complications the study demonstrated a significant increase in infection rate with a trend for an increased incidence of VAP (ventilator-associated pneumonia) in the study group (27.7 vs 13.8%; p = 0.08). No studies investigated muscle wasting during ICU stay in critically ill patients.

In summary, due to the contradictory findings in these recent RCTs, the impact of IC guided nutrition therapy on clinical outcomes has not been fully observed. Although across all studies, the IC guided group achieved higher calorie intake compared to the SC group. Which indicates that energy delivery close to measured EE only can be achieved when IC is used, thereby minimizing negative energy balance and the risk of inadequate or excessive energy delivery. It could be a good reason for its routine use for measuring EE in nutrition therapy. On the other hand, with recent advances in technology, indirect calorimeters are now easier to operate, more portable, and affordable. Unfortunately, still, it is an underutilized tool among dietitians in critical care settings and conventionally is used in patients in whom altered EE is suspected, or the nutritional support based on PEs fails to respond. The routine implementation of this device in clinical practice will not be justified until further data is available to support the current guidelines recommendations.

Conclusion and Recommendation

The use of IC to direct nutritional care is limited, and its benefits are poorly appreciated in clinical practice because there is still a lack of conclusive data to show the clinical benefits of nutritional therapy guided by IC compare to PEs. In this regard, the results of existing RCTs had not resulted in greater clarity, as both benefits and harm have been demonstrated when IC guided nutrition therapy, which is not justifiable for its routine use in clinical care settings. Moreover, it also declared from the recent findings that IC could only effectively guide nutrition when the measured calorie administered, which needs an effective strategy to deliver the prescribed calories and optimize the advantages of nutritional support.

In most countries data regarding the impact of IC guided nutrition therapy on clinical outcomes is still lacking and is less commonly used in practice. It is suggested that respective institutions adopt IC and pay attention to the usage and implementation of this device in their routine feeding protocol to optimize nutrition therapy. This review will assist in developing a better understanding of the influences of IC on clinical outcomes in critically ill patients. Further research, specifically adequately powered multicenter RCTs, is also needed to investigate the impact of the IC guided nutrition therapy on important clinical outcomes such as LOS. LMV, infection complications, and mortality.

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