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Comparison of Indirect Calorimetry versus Standard Weight-Based Formula in Ischemic Stroke Patients

Surya K. Dube[1] Hirok Roy[1] Bhagya R. Jena[1] Girija P. Rath[1] Nitasha Mishra[2] Kameshwar Prasad[3]

[1] Department of Neuroanaesthesiology and Critical Care, All India Institute of Medical Sciences, New Delhi, India
[2] Department of Anaesthesiology and Critical Care, All India Institute of Medical Sciences, Bhubaneswar, Odisha, India
[3] Department of Neurology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence Surya K. Dube, MD, DM, Department of Neuroanaesthesiology and Critical Care, All India Institute of Medical Sciences, New Delhi 110029, India (e-mail: surya.dube@aiims.edu).

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Abstract

Background Studies performed to calculate metabolic rate in stroke patients have conflicting results. The indirect calorimetry is the gold standard in measuring resting energy expenditure. We compared the intensive care unit (ICU) mortality and outcome in stroke patients receiving enteral nutrition based on energy requirement calculated by either indirect calorimetry or standard weight-based formula.

Methods Twenty ischemic stroke patients of older than 40 years requiring greater than 2 days of mechanical ventilation were prospectively enrolled. Demographic data, Glasgow Coma Scale (GCS), Canadian Neurological Scale, and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were obtained. Patients were randomized to receive enteral nutrition based on energy requirement calculated either by indirect calorimeter (group REE_{IC}) or by standard weight-based measurements (group REE_{ST}). Daily ventilatory parameters, Sequential Organ Failure Assessment (SOFA) score, and blood parameters were noted. The ICU mortality/duration of stay/complication and duration of hospital stay were compared. Patient outcome at discharge was assessed using modified Rankin scale (MRS).

Results Baseline characteristics were comparable. There were no ICU deaths in group REE_{IC}. Patients in group REE_{IC} had significantly ($p < 0.01$) more resting energy requirement and less maximum negative energy balance than those in group REE_{ST}. The SOFA score at days 5, 7, and 9 and the total leukocyte count (TLC) at day 5 were higher in group REE_{ST}. The duration of mechanical ventilation, ICU stay/complications, duration of hospital stay, and MRS at discharge were comparable.

Conclusion Ischemic stroke patients receiving indirect calorimetry–guided enteral nutrition had lesser incidence of organ failure but similar ICU stay and mortality and neurological outcome as compared with those receiving standard weight-based enteral nutrition.

Keywords
- indirect
- calorimetry
- ischemic
- stroke
- nutrition
- outcome

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Introduction

Stroke remains one of the important causes of mortality and morbidity worldwide. Malnutrition is quite common in stroke patients and nearly 20% of the patients with acute stroke are malnourished.[1] Like any other critically ill patients, nutritional supplementation is important for stroke patients and initiation of early enteral feeding is desirable in these patients. However, nutritional requirement in stroke patients is a complex phenomenon. Most of the previous studies performed to calculate metabolic rates in stroke patients have conflicting results.[2–5] Energy requirements in critically ill and ventilated patients can be calculated by indirect calorimetry (IC) or predictive equations.[6] IC remains the gold standard in measuring the resting energy expenditure (REE).[7] Many studies have pointed out poor correlation between energy measured by predictive equations and those by IC.[2–5]

Very few have studied the role of IC in assessing the outcome in stroke patients.[3,4] We hypothesized that stroke patients receiving enteral nutrition based on energy requirement calculated by IC might recover faster with fewer systemic complications and lesser intensive care unit (ICU) stay as compared with those receiving nutrition according to a standard weight-based formula. So, the primary aim of the study was to determine whether nutritional support guided by repeated REE measurements as measured through IC improved the ICU survival of stroke patients, as compared with single, initial weight-based measurements. In addition to this, we assessed the length of mechanical ventilation, duration of ICU and hospital stay, infectious complications, and neurological outcomes between the two groups of patients.

Methodology

After obtaining institutional ethics committee approval, 20 patients (10 patients in each group) older than 40 years with ischemic stroke and likely to require more than 2 days of mechanical ventilation were enrolled for the study. The study is registered in the clinical trial registry of India (Regd. No. CTRI- 2019/05/018979). Pregnant patients, patients on dialysis or having congestive heart failure or hepatic dysfunction, those having chest drain or leaks in the endotracheal tube, or those requiring fraction of inspired oxygen (FIO_2) > 0.6 were excluded from the study. On admission demographic data, APACHE II score, Glasgow Coma Scale (GCS) score, and Sequential Organ Failure Assessment (SOFA) severity index were recorded. For calculation of SOFA score, central nervous system (GCS), cardiovascular system (mean arterial pressure), respiratory system (PaO_2/FiO_2 ratio), coagulation abnormality (platelet count), hepatic system (bilirubin levels), and renal system (creatinine level) were assessed. Each of the six variables was given a score ranging from 0 to 4 and the final score ranges from 0 to 24. On admission, the location(s) of stroke in the brain was/were noted and severity was assessed using the Canadian Neurological Scale (CNS).[8] Baseline investigations like hemogram and electrolytes including serum sodium, potassium, renal function tests, serum albumin, and blood sugar were recorded. Enteral feed using a nasogastric tube (NGT) was started in all stroke patients unless there was a definitive contraindication for the same or any surgical intervention was planned. All the patients weaned off from mechanical ventilation were shifted to a high-dependency unit (HDU) from the ICU.

The patients were randomized into two groups based on REE, that is, **group I (REE_{IC}):** nutritional supplementation based on energy requirements calculated by the indirect calorimeter and **group II (REE_{ST}):** nutritional supplementation according to weight-based measurements (European Society for Clinical Nutrition and Metabolism [ESPEN] guidelines, i.e., 25 kcal/kg/d). In group REE_{IC}, REE was measured using an indirect calorimeter (Deltatrac metabolic monitor, Datex, Helsinki, Finland) connected to a ventilator. Measurements were made over 30 to 40 minutes under resting condition in nonfasted state. The device was calibrated for gas and pressure before each measurement according to the manufacturer's recommendations. All measurements were performed by a single individual who has experience using the technique, thus limiting operator-dependent errors. Energy obtained from non-nutritional sources (glucose and glucose saline infusions used for drug dilution and lipids delivered with drugs like propofol) were not considered while deciding energy supplementation in the study. However, those were considered while calculating total energy intake and daily energy balance. Daily energy balance was calculated as the difference between energy delivery and energy target. Supplemental parenteral nutrition was given to bridge the energy gap. Blood sugar was maintained between 120 and 150 mg/dL in all patients using intravenous insulin infusion when required. Episodes of hypoglycemia (blood sugar levels <60 mg/dL) were treated with an infusion of dextrose solution.

The study continued till patients were managed in the ICU. Daily hemograms, serum electrolytes, serum urea, creatinine, and serum albumin were estimated in all patients. The length of mechanical ventilation, duration of ICU and hospital stay, ICU mortality, and complications were noted. Patient outcomes at discharge were assessed using modified Rankin scale (MRS). We included all eligible patients within an 18-month interval and formal sample size calculation was not done in our study. The statistical analysis was performed using STATA14.0 (College Stations, Texas, United States). Qualitative data were presented as frequency/number (%) and quantitative data were expressed as mean ± standard deviation (SD)/median (range). The difference in proportions was compared using the chi-squared test/Fisher's exact test. The difference in means/medians was compared using Student's *t*-test or Wilcoxon's rank-sum test. A *p*-value of less than 0.05 was considered statistically significant.

Result

A total of 32 patients were enrolled in this study, of which 12 were excluded (►**Fig. 1**). The demographic parameters and

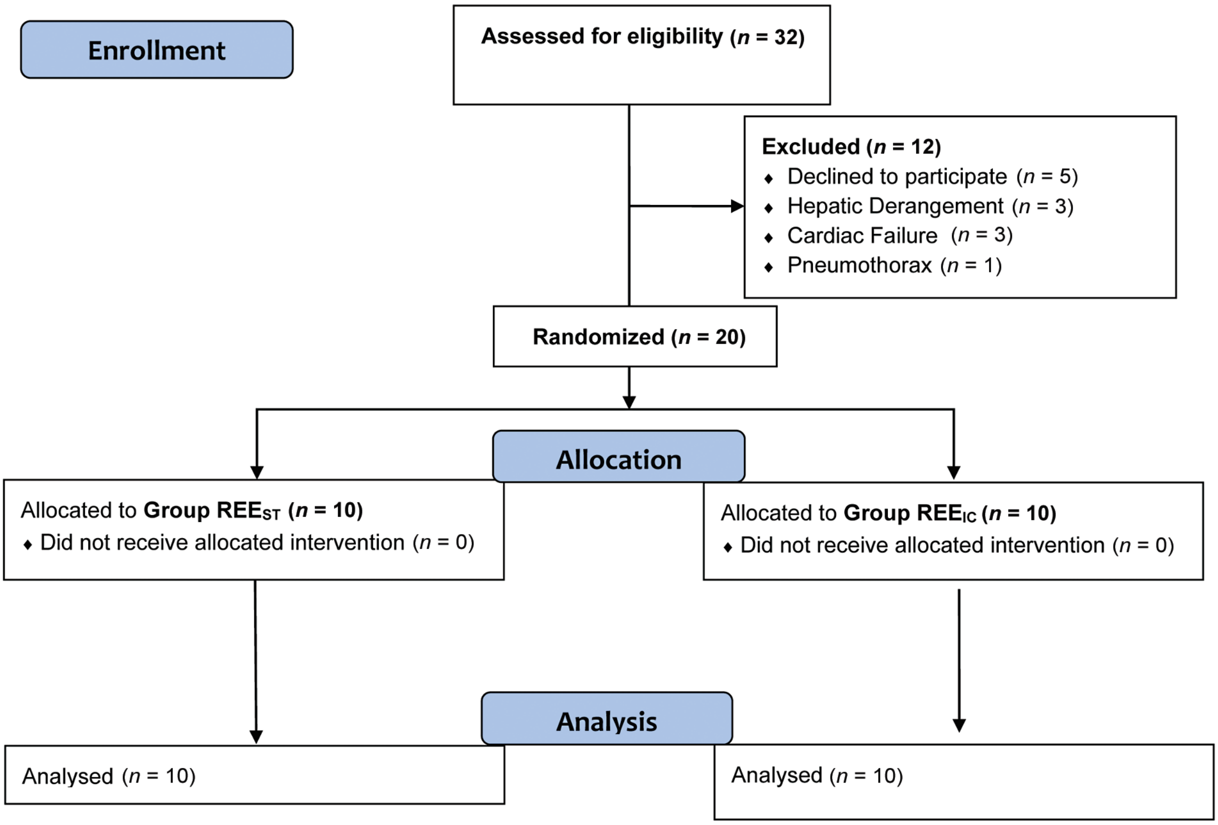

Fig. 1 Consort flow diagram of the study.

baseline characteristics of the patients are summarized in ►**Table 1**. Both groups were comparable in terms of demographic characteristics, APACHE II score, GCS, CNS, vascular territory of the stroke, and the treatment received.

Nutrition-related data of the patients are summarized in ►**Table 2**. Mean REE was significantly higher in group REE_{IC} ($1,647 \pm 47$ vs. $1,355 \pm 47$; $p < 0.001$), but the mean total energy delivered was similar between the two groups.

Table 1 Baseline characteristics of the two groups of patients[a]

Parameter	Group REE_{ST} ($n = 10$)	Group REE_{IC} ($n = 10$)	*p* value
Age (y)	62.1 (15.05)	51.2 (5.94)	0.13
Weight (kg)	54.4 (3.38)	53.71 (8.01)	0.79
Male:female[b]	8 (80):2 (20)	7 (70):3 (30)	0.83
APACHE II score	22 (5.01)	21.8 (5.15)	0.93
SOFA score	9.8 (3.3)	9.2 (2.5)	0.65
GCS	8.1 (2.07)	8.3 (1.49)	0.80
Canadian Neurological Scale	2.8 (1)	3.05 (0.7)	0.53
Diagnosis[b]			
Middle cerebral artery	4 (40)	4 (40)	0.67
Anterior cerebral artery	4 (4)	2 (2)	
Posterior cerebral artery	2 (20)	4 (40)	
Treatment[b]			
Surgery	4 (40)	4 (40)	0.76
Conservative medical therapy alone	6 (60)	5 (50)	
Neuroradiological intervention	0	1 (10)	

Abbreviations: GCS, Glasgow Coma Scale; SOFA, Sequential Organ Failure Assessment.
[a]Data shown as mean ± (standard deviation), unless specified.
[b]Data shown as number (percentage).

Table 2 Nutritional data of the patients

Parameter	Group REE_{ST} ($n = 10$) Mean (SD)	Group REE_{IC} ($n = 10$) Mean (SD)	p value
REE (kcal/d)	1,355 (83)	1,647 (47)	< 0.001
Mean energy delivered (kcal/d)	1,431 (436)	1,734 (239)	0.15
Daily energy balance (kcal/d)	−38 (103)	88 (239)	0.53
Cumulative energy balance (kcal/d)	703 (1,435)	869 (1,017)	0.83
Maximum negative energy balance (kcal)	−303 (156)	−139 (55)	< 0.001
Mean protein delivered/d (g/kg/d)	2.0 ± 0.18	2.1 ± 0.19	0.35

Abbreviation: REE, resting energy expenditure; SD, standard deviation.

Table 3 Clinical course of the patients[a]

Parameter	Group REE_{ST} ($n = 10$)	Group REE_{IC} ($n = 10$)	p-value
Duration of intensive care unit (ICU) stay	8.9 (2.3)	9.4 (1.8)	0.59
Duration of mechanical ventilation	8.1 (1.9)	8.4 (1.8)	0.72
Need for tracheostomy	3 (30)	3 (30)	0.87
Complication[b]			
Ventilator-associated pneumonia (VAP)	3 (30)	3 (30)	0.89
Other infections	2 (20)	2 (20)	
Cardiac complication	2 (20)	0	
Modified Rankin scale score	3.3 (1.6)	2.6 (1)	0.25
Duration of hospital stay[c]	13.5 (5–60)	17 (9–91)	0.74

[a]Data shown as mean ± (standard deviation) unless specified.
[b]Data shown as number (percentage).
[c]Data shown as median (range).

There was no difference in average daily and cumulative energy balance between the two groups. However, group REE_{ST} had a significantly more negative energy balance (-303 ± 156 vs. -139 ± 55; $p < 0.001$) as compared with group REE_{IC}.

The ICU course of all the patients is summarized in ►**Table 3**. Both the groups had a similar duration of ICU say, mechanical ventilation, and requirement of tracheostomy. The incidence of ventilator-associated pneumonia (VAP) and other infectious complications was similar between the groups. Two patients in group REE_{ST} and none in the group REE_{IC} had cardiac complications (arrhythmia/symptomatic bradycardia). The total leukocyte count (TLC) at day 5 was higher and significantly lower at day 9 in group REE_{ST} (►**Fig. 2A**). The rest of the parameters (►**Figs. 2–4**) were comparable between the two groups. Group REE_{ST} had significantly higher SOFA scores on days 5, 7, and 9 (►**Fig. 5**). There was no difference in the mean MRS on discharge and the median hospital stay between the two groups. Two patients in group REE_{ST} died during treatment in the ICU. The causes of death were cardiac arrhythmia in one and multi-organ failure in the other.

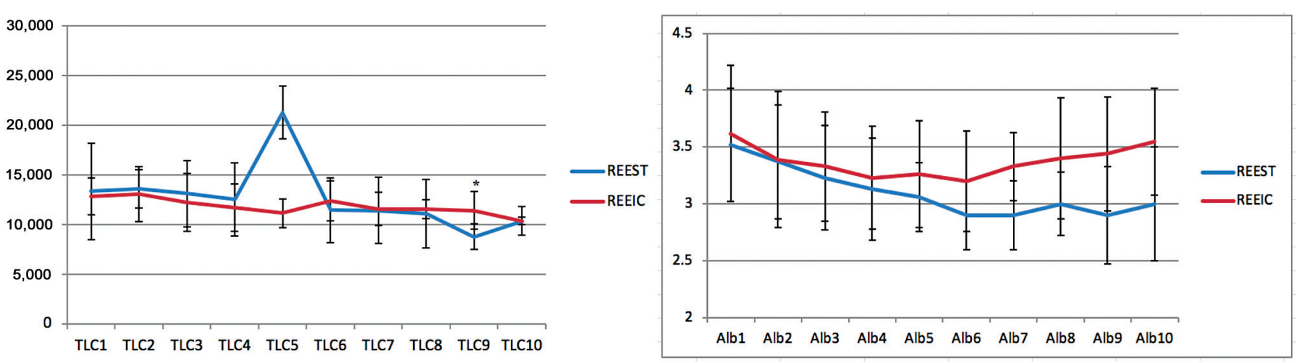

Fig. 2 Trend of (A) total leucocyte count (TLC) and (B) serum albumin concentration. The TLC was significantly higher on day 5 in group REE_{ST}, whereas serum albumin levels were comparable between the groups.

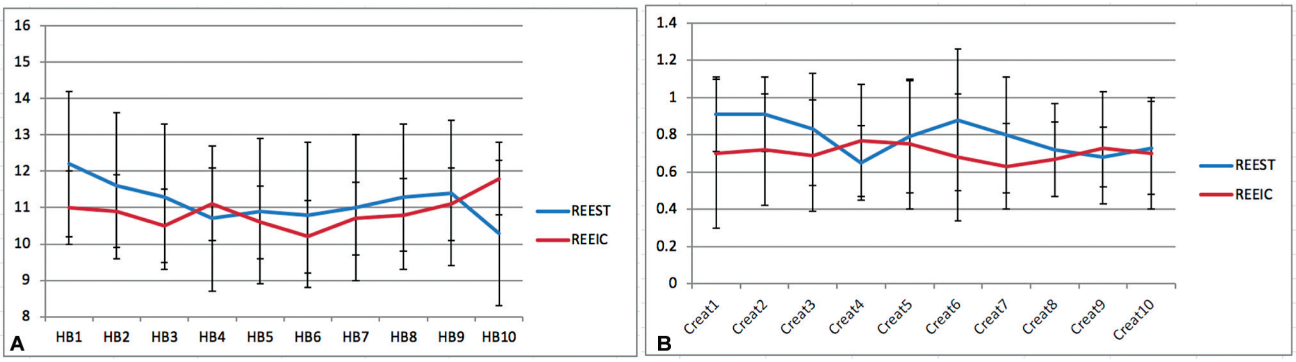

Fig. 3 Trend of (A) hemoglobin and (B) serum creatinine concentrations. There was no difference between the groups considering these parameters.

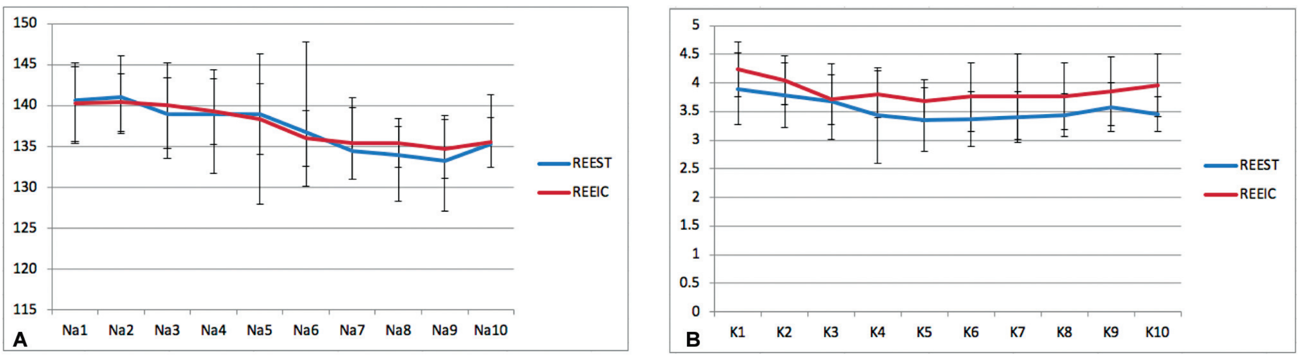

Fig. 4 Trend of (A) serum sodium and (B) potassium concentrations. Both the electrolyte levels were comparable between the groups.

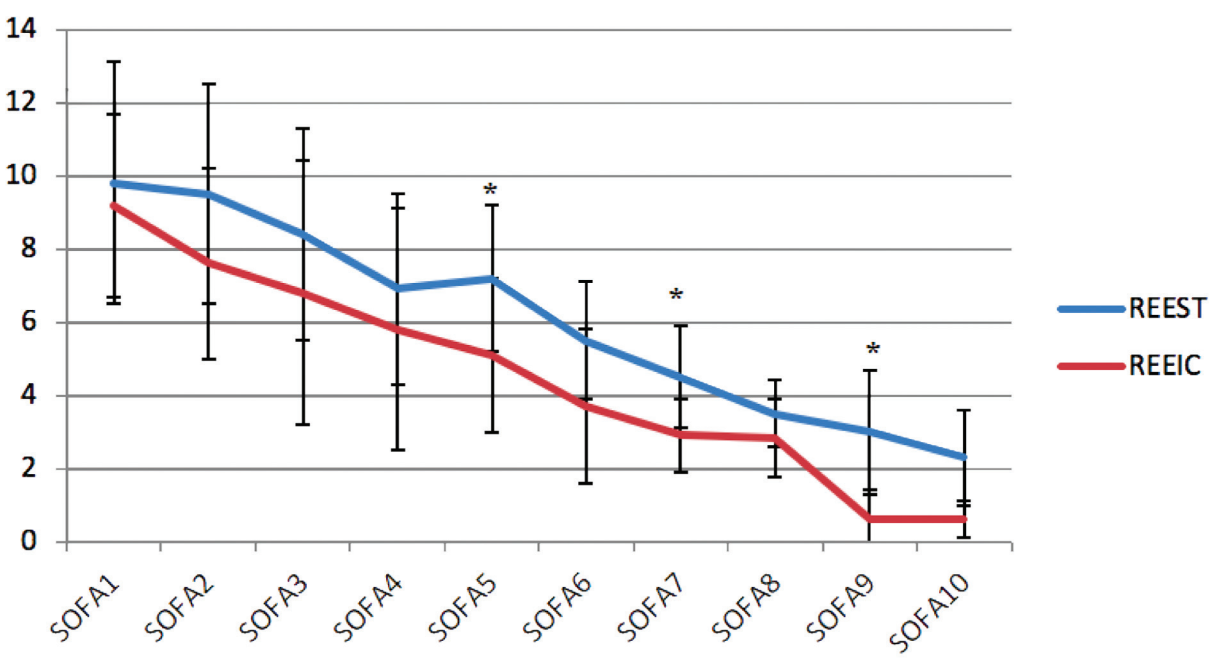

Fig. 5 Trend of Sequential Organ Failure Assessment (SOFA) scores. The SOFA scores were significantly higher on days 5, 7, and 9 in group REE_{ST} indicating a greater degree of organ dysfunction in that group.

Discussion

Nutrition is an important aspect of the management of critically ill stroke patients. The reported prevalence of malnutrition in poststroke patients ranges from 6.1 to 62%.[9] This wide variation can be attributed to the difference in preexisting comorbidity of the patients, type of stroke, and its complications as well as in the nutrition status assessment tools used in different studies. Such a high incidence of malnutrition may lead to increased chances of morbidly and mortality, infectious complications, and extended duration of ICU and hospital stay. Hence, nutritional supplementation in terms of early enteral nutrition is required while managing poststroke patients. However, the issue of nutrition in poststroke patients is a little bit complicated since the issue of the existence of a hypermetabolic state (that can lead to the onset of protein and caloric malnutrition) after stroke is still controversial.[2,4,10] It is an accepted fact that the prognosis of hemorrhagic stroke is comparatively less favorable than that of ischemic stroke. IC is considered the gold standard for energy requirement estimation in critically ill patients, and IC-based nutrition supplementation might be more useful for critically ill poststroke patients since it will also take into account the effects of fever and sedation. There are very few studies in the available literature that address the issue of nutrition in ischemic stroke patients using IC. So, we planned this study to compare the ICU mortality and patient outcome in ischemic stroke patients receiving nutritional supplementation based on IC versus the standard single weight-based formula.

In critically ill patients, an accurate estimation of energy expenditure is essential to avoid the consequences of inappropriate feeding. We found significantly higher mean REE in the indirect calorimeter group as compared with the standard treatment group ($1,647 \pm 47$ vs. $1,355 \pm 47$; $p < 0.001$) though the baseline weights and sex distribution of the patients in both the groups were comparable. This difference could be due to a more accurate calculation of REE by IC that better estimates the energy requirement based on the ongoing metabolic derangements in the early poststroke period. Elevated catabolism and metabolic rate are expected in the acute phase of stroke as a part of the acute phase response mediated through elevated catecholamines, cytokines, and counter-regulatory hormones.[11–14] Stroke severity, type, and size might influence the metabolic response following stroke. In a study by Finestone et al, the authors did not find any significant change in metabolic rate related to these variables, which they explained in terms of an inadequate number of observations for comparative evaluation.[2] In our study, the location and severity of stroke were similar in both groups, and due to insufficient data for a meaningful intergroup comparison, we cannot comment on the effects of these variables on metabolic rates in our patients. In a previous similar study on 11 patients using IC, the authors reported the mean REE to be $1,252 \pm 192$ kcal/d (24–72 hours after stroke) and $1,219 \pm 242$ kcal/d (10–14 days after stroke), which is lower than what we observed in group REE_{IC} (►**Table 2**). This could probably be because of increased stress response leading to increased catecholamine and other hormone levels, which, if been measured in our patients, would have explained this discrepancy better.

We assessed organ failure in our study using the SOFA score, which predicts mortality in critically ill patients based on derangement/dysfunction of six organ systems. It is a good indicator of prognosis as it categorizes mortality risk in ICU patients irrespective of the score at the time of admission.[15] Significantly higher SOFA scores on days 5, 7, and 9 and TLC on day 9 were another finding of our study (►**Figs. 2** and **3**). The difference cannot be attributable to the comparatively more unfavorable baseline clinical condition of the patients in group REE_{ST} since baseline APACHE II and initial SOFA score were comparable between the two groups (►**Table 1**, ►**Fig. 5**). However, this difference can be attributed to negative energy balance in group REE_{ST}. The maximum negative energy expenditure in group REE_{ST} was significantly more as compared with group REE_{IC} (-303 ± 156 vs. -139 ± 55; $p < 0.001$). Patients in group REE_{IC} received nutritional supplements based on a dynamic measurement performed daily, which possibly led to a more aggressive approach to achieve the set energy goal. In contrast, group REE_{ST} patients might have received suboptimal calorie intake since it was according to a fixed weight-based formula. Negative energy balance has been linked to an increased propensity of infection and mortality in critically ill patients in previous studies.[16–18] This explains a higher degree of organ dysfunction/infection of patients in group REE_{ST} in our study as evidenced by comparatively higher (but not significant) TLC on day 5, significantly more TLC on day 9, and higher cardiac complications (►**Fig. 5** and ►**Table 3**).

The tight calorie control study (TICACOS) is a study similar to ours that has been conducted previously to determine whether nutritional support guided by repeated measurements of resting energy requirements using an indirect calorimeter improves the outcome of critically ill patients.[19] In the study, 130 critically ill patients were randomized to receive nutrition based on energy calculations either by IC or by standard 25 kcal/kg/d formula according to the ESPEN guidelines. Although there are subtle similarities between the two, the two studies are different. In the TICASOS study, the authors excluded patients with a severe neurological insult (severe head injury) since severe head injury patients are expected to have a longer length of stay as compared with other patients with various other pathology (medical illness, lung injury, postsurgical patients, etc.). So, the results of the TICASOS cannot be extrapolated to poststroke patients. In contrast, our study specifically included ischemic stroke patients. Second, in TICASOS study, the IC measurements were repeated at 48-hour intervals, but we performed the same every day, which arguably has given a more precise picture of the energy needs of patients. Finally, the IC group had a lesser mortality rate (32.3 vs. 47.7%; $p = 0.058$), significantly higher SOFA scores on day 3, and greater incidence of VAP, length of ventilation days, and length of ICU stay. However, the SOFA scores were higher on the fifth, seventh, and ninth day in our study and apart from that we did not find any difference between the two groups in terms of ICU/hospital stay, infectious complications, and neurological condition on discharge.

There are certain limitations in our study. Ours is an observational study with a small sample size, which might not have been optimal to ensure adequate power to detect statistical significance. Second, we studied ICU mortality instead of hospital stay in our patients. It can be argued that hospital mortality is a better endpoint than ICU mortality in critically ill patients since nutrition-related interventions are unlikely to have an impact on short-term variables like ICU mortality. But there is another way of looking at it. Any intervention will be more effective if it is done at a stage when it is required the most. There is evidence to support a positive correlation between the severity of injury and elevations of metabolic rate in different injuries.[20] As reported previously, cytokine levels are shown to be increased on day 4 and the increase in energy expenditure peaked approximately 10 days after the initial insult.[10,20] Metabolic stresses (mediated through cytokines and counter-regulatory hormones) are more evident in the acute phase of stroke.[2] Studies have shown the REE to be more in the early stages of stroke (1–3 days) as compared with late stages (10 days and more), indicating augmented energy requirement in early stages of stroke.[15] Moreover, the mean ICU duration in our patients was nearly 10 to 11 days (►**Table 3**). In our center, we shift the patients from the ICU to HDU after weaning from mechanical ventilation and ensuring a comparatively stable condition. So, our idea of restricting the study to comparison of the ICU mortality is not completely irrational. Third, we did not assess the level of metabolic stress in these patients (in terms of inflammatory markers/catecholamine levels), which could have provided more important information. Finally, we excluded a few categories of patients based on ineligibility for IC.

Conclusion

Stroke patients receiving IC-guided nutrition had similar ICU survival and neurological outcomes as compared with those receiving standard weight-based nutrition. Nutrition based on IC results in a lesser incidence of organ failure as compared with standard weight-based formula in stroke patients. Our study had limited number of patients, but larger prospective studies will provide more meaningful insight on the subject matter.

Disclosure(s)
Part of this study was presented at the 47th SNACC Annual Meeting, Phoenix, United States.

Acknowledgment
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Conflict of Interest
None declared.

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