Original Article

The prognostic significance of the timing of total enteral feeding in traumatic brain injury

Sivashanmugam Dhandapani, Manju Dhandapani[1], Meena Agarwal[1], Alka M. Chutani[2], Vivekanandhan Subbiah[3], Bhawani S. Sharma, Ashok K. Mahapatra

Departments of Neurosurgery, [1]Neuronursing, [2]Dietetics, and [3]Neuro-biochemistry, All India Institute of Medical Sciences, New Delhi, India

E-mail: *Sivashanmugam Dhandapani - ssdhandu@gmail.com; Manju Dhandapani - manjuseban@gmail.com; Meena Agarwal - ssdhandu@rediffmail.com; Alka M. Chutani - manjuseban@yahoo.co.in; Vivekanandhan Subbiah - svivek_aiims@yahoo.com; Bhawani S. Sharma - drsharmabs@yahoo.com; Ashok K. Mahapatra - akmahapatra_22000@yahoo.com
*Corresponding author

Abstract

Background: To study the effect of timing of total enteral feeding on various nutritional parameters and neurological outcome in patients with severe traumatic brain injury (TBI).

Methods: One hundred and fourteen patients, in the age group of 20–60 years, admitted within 24 h of TBI with Glasgow Coma Scale (GCS) 4–8 were enrolled for the study. Nineteen patients who had expired before the attainment of total enteral feeding were excluded from the analysis. Total enteral feeding was attained before 3 days, 4–7 days, and after 7 days in 12, 52, and 31 patients, respectively, depending on gastric tolerance. They were prospectively assessed for various markers of nutrition and outcome was assessed at 3 and 6 months.

Results: Prospective assessment of 67 hospitalized patients at 3 weeks revealed significant differences in anthropometric measurements, total protein, albumin levels, clinical features of malnutrition, and mortality among the three groups. 80% of those fed before 3 days had favorable outcome at 3 months compared to 43% among those fed later. The odds ratio (OR) was 5.29 (95% CI 1.03–27.03) and P value was 0.04. The difference between those fed before 3 days and 4–7 days was not significant at 6 months even though patients fed before 7 days had still significantly higher favorable outcome compared to those fed after 7 days (OR 7.69, P = 0.002). Multivariate analysis for unfavorable outcome showed significance of P = 0.03 for feeding after 3 days and P = 0.01 for feeding after 7 days.

Conclusions: In severe TBI, unfavorable outcome was significantly associated with attainment of total enteral feeding after 3 days and more so after 7 days following injury.

Key Words: Enteral feeding, malnutrition, outcome, traumatic brain injury

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INTRODUCTION

Traumatic brain injury (TBI) is the most common cause of death and disability in young people.[12] Numerous studies have consistently demonstrated the increased energy expenditure and increased nitrogen excretion

following TBI.[5,7,9,11,25] Therefore, adequate nutritional support in TBI is essential to provide the optimal milieu for neurological and systemic recovery. Despite various studies in TBI, "what, when, and how' of nutritional replacement remains elusive. In 1983, Rapp *et al*. demonstrated lower mortality with early parenteral nutrition compared with enteral feeding in patients of TBI.[19] Other studies later showed that early nutritional replacement was associated with improved outcome irrespective of enteral or parenteral route.[1,24] The American Association of Neurological Surgeons' (AANS) guidelines recommended full nutritional replacement to be instituted by the seventh day.[2] No evidence exists regarding whether early feeding prior to 7 days improves the outcome.[2] Moreover, the effects of the timing of total enteral feeding on various anthropometric, biochemical, clinical markers of malnutrition and the neurological outcome as a result thereof have not been studied. This is a non-randomized, prospective, comparative study performed to determine the differences in various parameters mentioned above among patients who had total enteral feeding before 3 days, 4–7 days, and after 7 days following TBI.

MATERIALS AND METHODS

Patient selection
Adult patients within 24 h of TBI, admitted with Glasgow Coma Scale (GCS) 4–8, to the Department of Neurosurgery, AIIMS, New Delhi, from June to December 2005, were enrolled for the study. Patients with age more than 60 years, GCS 3, diabetes mellitus, renal dysfunction, serious systemic injury, and bilateral non-reactive pupils had been excluded.

Study design
Standard care given to study patients consisted of ventilation, seizure prophylaxis with Phenytoin, antibiotic prophylaxis with Cefotaxime or Ceftriaxone and Netilmycin (for 3 days), and gastric ulcer prophylaxis with Ranitidine. Mannitol was given to patients with computerized tomography (CT) having evidence of mass effect (for 5 days). Frusemide was added to patients with midline shift (for 3 days). Fluid and electrolyte homeostasis was maintained. Decision regarding surgical decompression was taken according to the mass effect noted in CT and was individualized to each patient.

Enteral feeding was initiated either through nasogastric tube or orally as early as possible depending upon patients' consciousness, planned extubation, and gastric ileus. One liter of nasogastric tube feed consisted of 750 ml milk, 1 egg, 30 g sugar, 30 ml coconut oil, 30 g corn flour, and 15 g Trophox® nutritional supplement (http://www.raptakos.com/prodnew_trophox.htm). The ingredients in 1 l of the final mixture were around 1330 kcal energy, 45 g protein, 90 g fat, 100 g carbohydrate, 1.5 g calcium, 5.5 mg iron,

270 mg magnesium, 1 g phosphorus, 1.6 g potassium, 0.5 g sodium, 3.5 mg zinc, 0.5 mg copper, 50 μg selenium, 18 mg vitamin C, 1 mg vitamin B1, 2 mg vitamin B2, 4 mg niacin, 2.5 mg pantothenic acid, 1 mg vitamin B6, 120 μg folate, 150 mg choline, 3.5 μg vitamin B12, 1700 IU vitamin A, 0.7 mg vitamin E, 40 IU vitamin D, 0.3 μg vitamin K, 60 g saturated fatty acids (FA), 17.5 g monounsaturated FA (MUFA), 3.2 g polyunsaturated FA (PUFA), 0.03 g docosahexaenoic acid DHA, 330 mg cholesterol, 7.8 g branched-chain amino acid (BCAA) (3.6 g Leu, 2.2 g Val, 2 g Ile), 2.7 g Lys, 1.8 g Thr, 1.7 g Phe, 1 g Met, 0.8 g His, 0.5 g Trp, 5 g Glu, 3.2 g Pro, 3.2 g Asp, 2.3 g Ser, 1.7 g Tyr, 1.4 g Arg, and 1 g Gly.

The volume of feed was increased gradually according to the gastric tolerance (as per the residual feed on aspirate) and the day of attainment of total enteral feeding was noted. The total enteral feeding was considered to have been attained when patients received at least 50 kcal/kg/d and 2 g/kg protein (16% protein calories). No patient had received parenteral hyperalimentation or albumin supplements. Age, post-resuscitation admission GCS, associated systemic injury, surgical decompression, day of attainment of total enteral feeding, weekly anthropometric and biochemical parameters till 3 weeks, and clinical features of malnutrition at 3 weeks were noted in a pre-planned prospective database and were followed up.

Anthropometric measurements[8,14,15]
Every week since admission, non-stretchable inch tape and McGay caliper were used to measure mid-arm circumference (MAC) and triceps skin fold thickness (TSF), respectively, of hospitalized patients, over the midpoint of the nondominant arm between the acromion and olecranon processes, with the forearm flexed at 90°, and the mean of three measurements was recorded. Mid-arm muscle circumference (MAMC) was calculated from MAC and TSF using the formula: MAMC (cm) = MAC (cm) − [3.14 × TSF (cm)]. MAMC and TSF are indicators of somatic protein and fat reserves, respectively.

Biochemical assessment[13,14,17,22]
Serum total protein indicates overall nutritional status, whereas serum albumin and urine creatinine are biochemical markers of visceral protein anabolism and somatic protein reserve, respectively. Percent creatinine excretion in comparison to expected value (men 23 mg/kg, women 18 mg/kg) is an estimate of chronic protein status. Serum albumin and total protein levels were tested by bromcresol green dye binding method and biuret method, respectively, using Beckman Synchron CX5 Delta Clinical System (GMI Inc., MN, USA). Urine creatinine levels were tested by Jaffe's colorimetric method, using Hitachi 717 auto-analyzer (GMI Inc.).

Outcome
The primary outcome was Glasgow Outcome Scale

(GOS)[16] assessed at 3 and 6 months following injury, either directly or over telephone. Good recovery or moderate disability was considered as favorable outcome, and severe disability, persistent vegetative state, or death was considered as unfavorable outcome. The secondary outcomes assessed were changes in anthropometric values, biochemical markers, and clinical features of malnutrition and mortality at 3 weeks.

Statistical analysis

SPSS software (version 10, SPSS Inc., Chicago, IL, USA) was used for the statistical analyses. Continuous variables in two groups were compared by using independent-samples *t*-test. Continuous variables in more than two groups were compared by using one-way analysis of variance (ANOVA). Proportions were compared by using chi-square tests or Fisher's exact test, wherever appropriate. Subgroup analyses were done using Breslow-Day test of homogeneity of odds ratios (ORs). Multivariate analysis was conducted with logistic regression, adjusting for age, admission GCS, associated minor systemic injury, surgical intervention, and the day of attainment of total enteral feeding. Two-sided significance tests were used throughout, and the significance level was kept at $P \leq 0.05$.

RESULTS

From June to December 2005, 114 patients who fulfilled the eligibility criteria were enrolled for the study. Nineteen patients, who had expired before the attainment of total enteral feeding, were excluded from all analyses. Total enteral feeding was attained earlier than 3 days, 4–7 days, and later than 7 days in 12, 52, and 31 patients, respectively, depending on gastric tolerance. Out of these 95 patients, who were taken up for the analysis, 67 hospitalized patients were prospectively assessed weekly till 21 days for various secondary outcome parameters; the other 19 were discharged and 9 patients expired before 21 days. Primary outcome assessment was done at 3 and 6 months in 68 and 53 patients, respectively, either directly or over telephone.

The baseline characteristics of patients grouped according to the day of attainment of total enteral feeding are as shown in Table 1. Patients with poor GCS and those who underwent surgical decompression had significant delay in total enteral feeding, due to the associated gastric atony. Age and systemic injury did not significantly influence the day of attainment of total enteral feeding.

The anthropometric, biochemical, and clinical markers of malnutrition from admission till 3 weeks in different groups are as shown in Table 2 and Figures 1–4. There was deterioration in nutritional status as assessed using various parameters in all patients of TBI, which was proportionate to the delay in attainment of total enteral feeding. As shown in Figures 1–4, the groups showed significant fall in MAC, MAMC, and serum albumin values. As shown in Figure 3, serum total protein levels in those fed earlier than 7 days showed mild increase, whereas the levels in those fed later remained almost the same.

The percent fall in MAC and MAMC values was significantly greater in those fed 4–7 days (12 and 8%, respectively) and even more among those fed later than 7 days (17 and 15%, respectively) ($P = 0.001$). The fall in
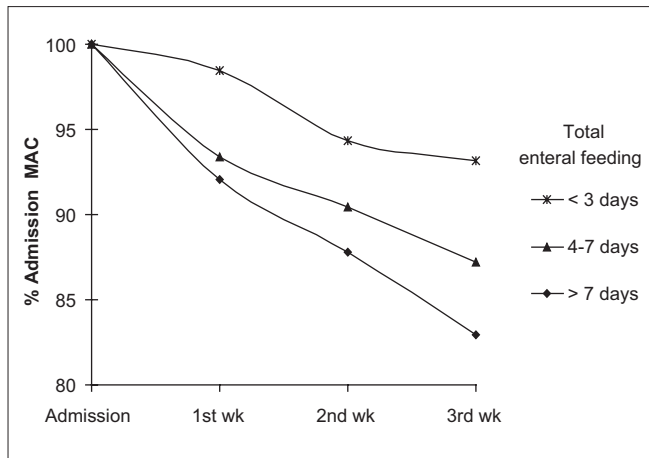
Table 1: Baseline characteristics

Baseline characteristics	Groups: Total enteral feeding			P value
	≤3 days (A)	4–7 days (B)	>7 days (C)	
Number	12	52	31	
Mean age (±SD)	31.7 (6.5)	34.4 (±11.7)	37.2 (±13.9)	0.36
GCS 4, 5	2	13	16	0.02
6, 7, 8	10	39	15	
Surgical decompression	3	32	22	0.02
Associated systemic injury	2	11	11	0.27

GCS: Glasgow Coma Scale

Table 2: Effect on various parameters

Parameter at 3 weeks	Total enteral feeding			P value
	≤3 days (A)	4–7 days (B)	>7 days (C)	
Mean % fall MAC (±SD)	8.1 (±5.7)	11.9 (±5.4)	17.3 (±7.1)	0.001
Mean %fall MAMC (±SD)	4.9 (±6.1)	7.7 (6.6)	15 (±7.5)	<0.001
Mean %fall TSF (±SD)	33.5 (±11.4)	35.6 (17.9)	39.4 (±22.3)	0.67
Mean serum total protein in g/dl (±SD)	7.3 (±1.8)	6.6 (±0.8)	5.9 (±0.8)	0.002
Mean serum albumin in g/dl (±SD)	3.3 (±0.5)	3.1 (±0.4)	2.8 (±0.4)	0.005
Mean 24-h urine creatinine in g/d (±SD)	1.1 (±0.2)	1.0 (±0.3)	0.9 (±0.2)	0.12
Mean % creatinine excretion (±SD)	78.7 (± 18)	73.5 (±22)	65.3 (±14)	0.15
Clinical features of malnutrition (%)	4/ 7 (57%)	23/ 34 (68%)	24/ 26 (92%)	0.04
Mortality (%)	2/ 12 (17%)	8/ 52 (15%)	15/ 31 (48%)	0.003

MAC: Mid-arm circumference, MAMC: Mid-arm muscle circumference

Figure 1: Timing of total enteral feeding versus mid-arm circumference
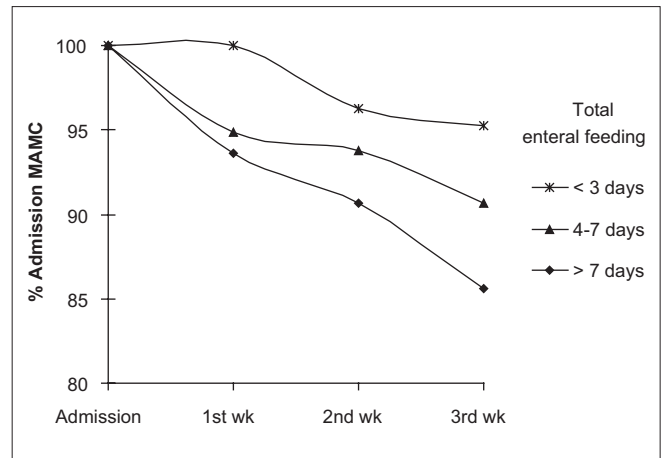

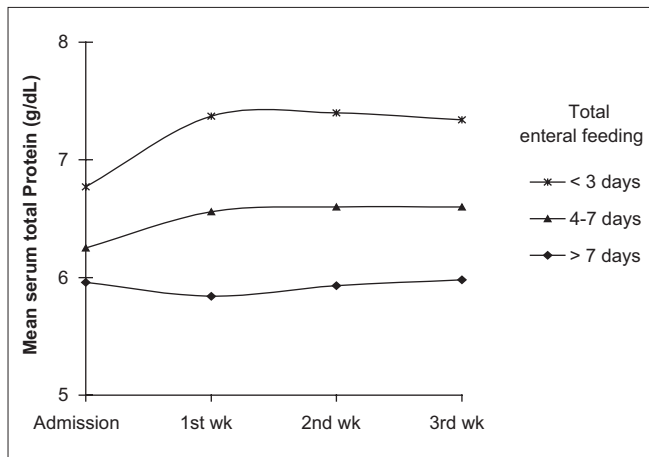**Figure 2: Timing of total enteral feeding versus mid-arm muscle circumference**

Figure 3: Timing of total enteral feeding versus serum total protein
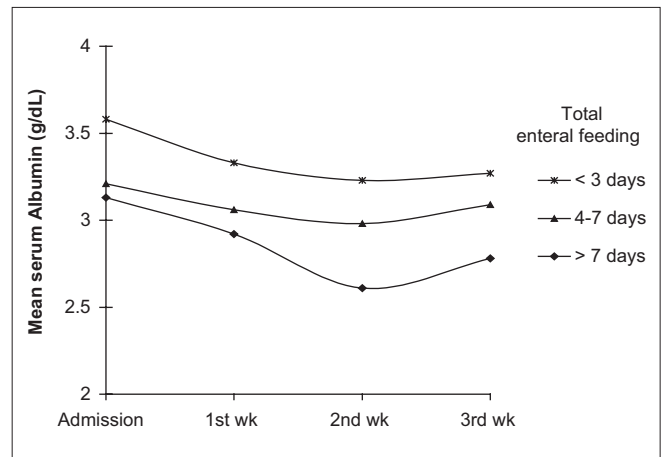

Figure 4: Timing of total enteral feeding versus serum albumin

Table 3: Primary outcome

Glasgow Outcome Score		Groups: Total enteral feeding			P value
		≤3 days (A)	4–7 days (B)	>7 days (C)	
3 months	Number	10	30	28	0.001
	Favorable (4, 5)	8	19	6	
	Unfavorable (1, 2, 3)	2	11	22	
6 months	Number	8	24	21	0.009
	Favorable (4, 5)	5	13	3	
	Unfavorable (1, 2, 3)	3	11	18	

A versus B and C: P = 0.04 at 3 months and 0.24 at 6 months, A and B versus C: P < 0.001 at 3 months, P = 0.002 at 6 months

TSF values, though similar, was not significant. The total protein (mean values: 7.3, 6.6, and 5.9 g/dl) and albumin levels (mean values: 3.3, 3.1, and 2.8 g/d) showed significant differences proportionate to the delay in attainment of total enteral feeding ($P \leq 0.005$). Urinary creatinine and percent creatinine excretion had similar falling values which were not statistically significant.

The presence of clinical features of malnutrition (edema, skeletal prominence, or cheilosis) at 3 weeks was significantly associated with total enteral feeding after 7 days with OR 6.2 (95% CI 1.3–30.2) and *P* value 0.01. Feeding after 7 days also showed significant association with mortality at 3 weeks with OR 4.5 (95% CI 1.7–11.8) and *P* value 0.001.

Primary outcome

The GOS at 3 and 6 months in various groups are shown in Table 3. The overall difference was statistically significant with *P* values of 0.001 and 0.009, respectively. Eighty percent of those fed earlier than 3 days had favorable outcome at 3 months compared to 43% among those fed later. The OR was 5.29 (95% CI 1.03–27.03) and *P* value was 0.04. In the subgroup analysis, total feeding earlier than 3 days had significant influence

on favorable outcome, especially in patients with GCS >5 and those managed conservatively ($P = 0.02$). The difference between those fed earlier than 3 days and 4–7 days was not significant at 6 months even though patients fed earlier than 7 days had still significantly higher favorable outcome compared to those fed after 7 days following injury (OR 7.69, $P = 0.002$).

Multivariate analysis

Logistic regression analysis was performed adjusting for age, admission GCS, associated minor systemic injury, surgical intervention, and timing of total enteral feeding. As shown in Figure 5, age more than 40 years, and total enteral feeding after 3 and 7 days emerged as independent risk factors for unfavorable outcome at 6 months with P values 0.02, 0.03, and 0.01, respectively. Other variables were not found to be significant.

DISCUSSION

Nutritional demand in patients with severe TBI is increased due to hypermetabolism and increased protein catabolism.[5,7,11,25] This hypermetabolic response in TBI has been found to be due to increased release of cytokines, catecholamines, and cortisol.[11,20] Inadequate or delayed caloric replacement has been found to be associated with increased morbidity and mortality, possibly due to various complications related to poor nutritional status, like infection, sepsis, poor wound healing, and vital organ dysfunction.[11,23] Therefore, the goal of nutritional management is to oppose the hypercatabolism associated with injury and inflammation, to provide nutrients to sustain visceral protein levels and immunological competence, and to provide materials for healing of injured tissue.[11,23] With the evidence that neurons are capable of regenerating, it becomes even more crucial to provide an environment conducive for repair.[4]

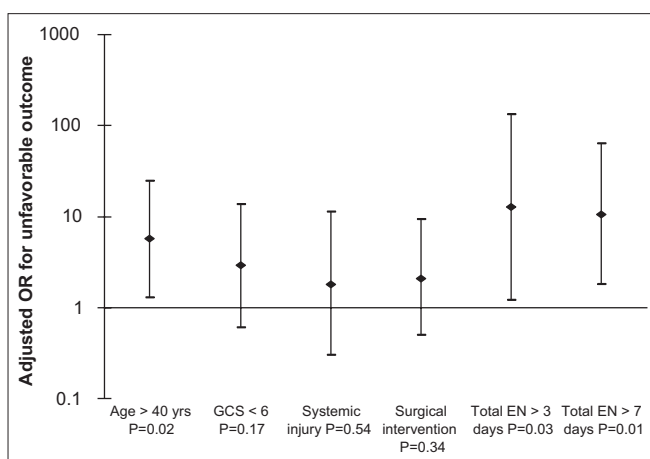Nutritional support can be provided by both enteral and parenteral routes, depending on the medical circumstances.

Figure 5: Logistic regression for unfavorable outcome

The advantage of enteral nutrition is that it is more physiological, has fewer complications, is less expensive, and is associated with rapid normalization of nutritional status, improved immune function, decreased likelihood of gut absorption disturbances, reduced incidence of sepsis, and reduced length of hospital stay.[1,10,21] In addition to providing adequate nutrition, enteral feeding may help blunt the stress response by decreasing the intestinal permeability to toxins and bacterial translocation.[10]

In a prospective, randomized controlled trial (RCT), Rapp et al. (1983) reported a significantly higher 18-day mortality rate (8/18) in enterally fed patients as compared to early total parenteral nutrition (TPN) (0/20).[19] In a subsequent RCT, Young et al. (1987) found significantly higher percentage of favorable outcome at 3 months with early TPN (44%), as compared to patients who were fed enterally (18%).[26] But there was no difference in outcome at 6 months and 1 year.[26] Borzotta et al. (1994) noted both early jejunal feeding and early TPN to be equally effective in meeting nutritional goals and found them to have similar infection rates, while the cost of patient care was much higher in TPN group.[1]

Yanagawa et al., in a meta-analysis (2002), noted that early feeding (either enteral or parenteral) was associated with a trend toward better outcome in terms of survival and disability.[24] As TPN was mostly initiated early in comparison to enteral feeding, better outcome found in TPN[19,26] might be just due to the early nutritional replacement and not necessarily dependent on the route of nutritional administration. Only few studies are available to assess the effect of early versus late enteral feeding on the outcome in patients with severe head injury. Minard et al. (2000) noted that there was no difference in length of stay, infectious complications, or mortality among patients given early (initiated within 72 h) versus delayed (initiated once gastric ileus had resolved) feeding.[18] Suchner et al. (1996) concluded in 34 patients that early enteral nutrition following emergency craniotomy was associated with accelerated normalization of nutritional status and improved substrate tolerance, as there was significantly increased visceral protein synthesis.[21] All these studies had taken attainment of total feeding by 7 days as early nutritional replacement. No study till now has demonstrated whether early feeding prior to 7 days improves the outcome.

In the present study, nutritional status of patients during hospital stay was assessed weekly from admission till 21 days and the outcome was assessed at 3 and 6 months. Patients with GCS score 3 were not included due to the very high mortality as per literature and observation.[3,6] Patients with systemic diseases such as diabetes mellitus or renal dysfunction, and serious multi-system injury that may possibly influence either the assessment of

nutritional status or outcome were also excluded. The present study shows favorable outcome to be associated with early attainment of total enteral feeding preferably before 3 days and not later than 7 days.

The study also shows significant influence of the timing of total enteral feeding on anthropometric measurements such as MAC and MAMC which are indirect estimates of somatic protein reserves.[8,14] TSF did not show significant difference possibly due to its relative insensitivity to acute changes in nutritional status.[22] There were also significant differences noticeable among the three groups in serum protein and albumin levels. These indicate that protein catabolism is more detrimental than increased energy expenditure in influencing neurological outcome in patients with TBI. The mild increase in total protein levels noted in those fed earlier than 7 days may be due to early nutritional replacement added on to the increase in acute phase reactants.[22]

The unfavorable outcome in patients who had delayed enteral feeding also implies the possible necessity of parenteral nutritional replacement if gastric atony prevents enteral feeding more than 7 days. The basis for improved neurological recovery and survival rate in the early total enteral feeding group may be because of improved nutrition maintained during the initial phase of injury preventing the effects of hypermetabolism and increased protein catabolism. The antioxidant minerals and vitamins in the enteral feed might have reduced lipid peroxidation caused by free radicals accumulated due to low cellular adenosine triphosphate (ATP). Further RCTs are needed to confirm the improved outcome seen among those who received total enteral feeding earlier than 3 days following injury.

Different nutrition formulations in patients with TBI have not yielded much except for the effect of high protein content (15% nitrogen calories).[2] We have considered attainment of total enteral feeding in our study, when patients receive at least 50 kcal/kg/d with 16% protein calories. Among the nutritional supplements, zinc addition has been found in a pilot study to have lower mortality trend.[27]

The Institute of Medicine (IOM) committee report found the majority of clinical guidelines for TBI not to specifically address optimal nutritional support for TBI.[9] They also made recommendations for research on continuing the development of animal models and the identification of biomarkers, and on promising areas of nutrition research. Though there are studies demonstrating benefits of selected nutritional interventions (BCAA, choline, creatine, magnesium, eicosapentaenoic acid EPA, DHA, vitamin D, and Zinc) in animal models of TBI and general critical care patients, there are no clinical trials that confirm similar beneficial effects in human TBI.[2,9]

CONCLUSIONS

In summary, among patients with severe TBI, delayed attainment of total enteral feeding was found to have significant association with anthropometric, biochemical, and clinical markers of nutritional depletion. Also, unfavorable neurological outcome was significantly associated with attainment of total enteral feeding after 3 days and more so after 7 days following injury.

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