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Original Article

Effects of four different enteral feeding methods on tumor Necrosis Factor-α (TNF-α) and high sensitive C-Reactive Protein (hs-CRP) in critically Ill Patients: double blinded, randomized controlled trial

Seyed Mohammad Hosein Mousavi Jazayeri[1], Alireza Ostadrahimi[1], Abdolrasoul Safaiyan[2], Shahryar Hashemzadeh[3], Firouz Salehpour[4]

[1]Nutrition Research Center, Faculty of Nutrition, Tabriz University of Medical Sciences, Tabriz, Iran - E-mail: ostadrahimi@tbzmed.ac.ir; [2]Road Traffic Injury Research Center, Department of Bio-statistics and Epidemiology, Tabriz University of Medical Sciences, Tabriz, Iran; [3]Department of General and Thoracic Surgery, Tabriz University of Medical Sciences, Tabriz, Iran; [4]Department of Neurosurgery, Tabriz University of Medical Sciences, Tabriz, Iran

Summary. *Background:* Despite advances on nutrition in Intensive Care Unit (ICU), effects of different nutritional treatments and methods on inflammatory markers are still controversial in critically ill patients. This study was designed to examine the effects of four different methods of enteral feeding on serum levels of tumor necrosis factor-α (TNF-α) and high sensitive C-reactive protein (hs-CRP) in surgical ICU patients. *Methods:* In a double blinded, randomized controlled trial, 25critically ill patients were recruited. They randomly divided to four groups regarding enteral feeding: early closed (EC), delayed closed (DC), early opened (EO) and delayed opened (DO). Blood samples were obtained to measure TNF-α and hs-CRP on day 1st, 3rd, 5th and 7th by using ELISA method. *Results:* Monitoring of TNF-α and hs-CRP revealed a significant elevation of these inflammatory factors at 3rd day of ICU admission (P< 0.001) and a significant decrease on 5th and 7thdays (P<0.001) in all groups. The inflammatory factors were controlled in early closed (EC)group more efficiently than other groups. *Conclusion:* Early closed (EC) enteral feeding can efficiently reduce both TNF-α and hs-CRP in ICU patients more than other methods of enteral feeding. Early initiation of closed enteral feeding has to be considered in critically ill patients.

Key words: enteral feedings, albumin, nutritional intake

Introduction

Nutrition in the Intensive Care Unit (ICU) encounters a variety of challenges such as: general condition, severity of illness and specific needs (1). Critically ill patients have high nutritional requirements and can become malnourished quickly (2). Some reports indicate that malnutrition occurs in up to 40% of the cases (3). Malnutrition is associated with delayed recovery, higher rates of morbidity and mortality, prolonged hospital stay and both increased healthcare costs and a higher early re-admission rate, due to a clear image of the process of catabolic stress and its relation to nutrition in surgical patients (4). Tumor necrosis factor-α (TNF-α) is one of the best described proinflammatory cytokines and has a key role in regulation of inflammation and rises in trauma patients (5-7). It is not only a potent stimulator of the activation of many cell types such as macrophages/monocytes and NK cells but also can induce cell survival or cell death by apoptosis (8). Raised TNF-α level subsequent to trauma is damaging to the body (9). High-sensitivity C-Reactive protein

(hs-CRP) is another marker of systemic inflammation (10), which is a negative acute phase responder in patients with in-hospital cardiovascular events after coronary artery bypass grafting (11) and patients with congestive heart failure (12). There are few studies regarding hs-CRP in ICU patients, but none of these studies have evaluated effects of different enteral nutrition treatments or methods(13-15). Although the expert committee of European Society for Clinical Nutrition and Metabolism (ESPEN) recommended that haemodynamically stable critically ill patients should be fed early (within 24 hours of admission) using an appropriate amount of feed, there are no data showing improvement in relevant outcome parameters using early enteral feeding in critically ill patients (16). Canadian Clinical Practice Guidelines reported there are inadequate study results to make a recommendation on the prescription of enteral nutrition via open or closed systems in ICU patients(17). So, better understanding regarding controlling inflammation in ICU patients could provide better targeted care and help prevent malnutrition, mortality as well as morbidity. The purpose of this trial was to determine the effects of closed vs. open treatments and early vs. delayed methods of enteral nutrition on TNF-α and hs-CRP in surgical ICU patients.

Material and Methods

This double blinded, prospective, randomized clinical trial was conducted in surgical ICU, Emam Reza Hospital of Tabriz University of Medical Science (TUMS), Tabriz, Iran. The study received ethical approval from the ethics committee of TUMS (Code No.: 92205) and written informed consent was obtained from patients or their relatives. Over 8 months, all patients admitted to the ICU were screened for study eligibility and randomly assigned to one of two treatment groups (open vs. closed enteral feeding) and one of two methods (early vs. delayed). Computer-generated random numbers were utilized for randomization. Study patients were respectively followed-up until they had completed a follow-up of 7 days. Inclusion criteria were: age of 18 – 65 years, those predicted to be kept in the ICU for more than 72 hours, APACHE II score (18)on admission of over 20, amenability to enteral feeding, no obstruction in the gastrointestinal (GI) tract, no GI bleeding, normal kidney function and enteral nutrition tolerance. Exclusion criteria were: patients who did not fulfill the follow-up period, who received anti-inflammatory drugs or corticosteroids before admission, GI bleeding or enteral feeding intolerance during study period, hemodynamically unstable patients, immunosuppressed patients, patients with chronic organ failure, patients with previous organ transplantation, pregnant women, those who received massive blood transfusion, post-cardiopulmonary resuscitation status and unknown outcome or losses of patient follow up due to transfer to other hospitals. A total of 25 patients were included in the study and divided into four groups. The first group received continuous early closed enteral feeding (EC) for 24-48 hours after admission to the ICU, second group received continuous delayed closed enteral feeding(DC) for 48 hours after admission to the ICU, third group received continuous early open enteral feeding (EO) for 24-48 hours after admission in ICU and fourth group received continuous delayed open enteral feeding(DO) for 48 hours after admission in ICU. As categorized by others (19), closed enteral feeding consisted of industrialized, sterile and liquid enteral formulas packed in bags ready to be administered. Open enteral feeding was characterized by being produced in a restricted and specific area in which powder industrialized nutrients are mixed. All subjects had received enteral nutrition by means of a modern continuous enteral feeding pump(20) consonant with the level of accuracy and features required in current markets (21). Early enteral nutrition was defined as set out in guidelines (22, 23). Serum TNF-α and hs-CRP was monitored on admission, 3rd, 5th and 7th day of ICU stay.

Blood sampling

Blood samples were collected in glass tubes and serum was extracted by centrifuger at 1,600 g for 15 minutes. Then, samples were frozen at refrigerator -70.

TNF-α determination

Serum level of TNF-α was measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit(AviBion Human TNF-α ELISA kit, Orgenium Laboratories Business Unit, Finland) guided by the manufacturer's instructions.

High-sensitive C Reactive Protein determination

Serum hs-CRP concentration was determined based on immunoenzymometric assay (Monobind Inc., Accu- Bind ELISA kit, hs-CRP: 3125-300, USA).

Statistical methods

The influential variables were adjusted between two treatments (Open and Closed) and each method (Early and Delayed) on the 1st day. Normality was evaluated by Q-Q test and then Mauchly's W test was checked for identity covariance matrix, and finally repeated measure with control covariates test was used by Minitab Software version 17. We used sidak as post-hoc. The results include four P-values for comparing multi and uni variates. The first was $P\text{-value}_{time}$ for comparing variations in four times of intervention, the second was $P\text{-value}_{treatment}$ for comparing the Open and Closed groups, the third was $P\text{-value}_{Method}$ for comparing the Early and Delayed groups and the third was $P\text{-value}_{Gender}$ for controlling gender as confounding variables. The level of significance was set at 0.05 and all results were expressed as Mean±SEM (standard error of mean).

Results and Discussion

According to Table 1, gender had no confounding effects on TNF-α (p=0.662) and hs-CRP (p=0.795). For controlling unknown effects between TNF-α and hs-CRP, multivariate test confirmed that there was a current statistically significant difference between treatments (open and closed systems) ($P\text{-value}_{Treatment}$=< 0.001) in each method (Early and Delayed) ($P\text{-value}_{Method}$< 0.001) in four times of intervention ($P\text{-value}_{Time}$< 0.001), and TNF-α and hs-CRP had a similar statistical significance, separately (P_{Time}< 0.001, $P_{Treatment}$< 0.001, $P\text{-value}_{Method}$< 0.001). For TNF-α, the Sidak test showed that there were significant differences between methods (P<0.001) except the first day in closed treatment. However, there were only significant differences regarding methods of enteral feeding on the 7th day in open treatment (P<0.001). For hs-CRP, the Sidak test showed that there was no significance difference between both the 1st and 7th days (P<0.001)

Table 1. Mean±SE of TNF-α and hs-CRP between treatments and methods in different times

Treatments	**Open**		**Closed**			**Time**	**Treatments**	**Methods**	**Gender**
Methods	**Early (n=6)**	**Delayed (n=6)**	**Early (n=7)**	**Delayed (n=6)**					
TNF-α (pg/mL)	1st day	67.60±3.41	65.85±2.47	68.24±3.17	68.13±3.55	<0.001	<0.001	<0.001	0.595
	3rd day	182.56±7.94	225.43±10.04	170.60±4.68	211.71±5.99				
	5th day	160.38±8.89	202.36±12.22	148.44±3.69	179.18±2.05				
	7th day	129.96±9.10	184.55±7.63	118.42±4.34	151.25±3.67				
hs-CRP (μg/ml)	1st day	3.17±0.16	3.12±0.03	3.20±0.10	3.07±0.052	<0.001	0.001	<0.001	0.662
	3rd day	3.46±0.12	3.77±0.03	3.35±0.08	3.51±0.02				
	5th day	3.57±0.10	3.68±0.07	3.33±0.07	3.42±0.04				
	7th day	2.84±0.08	3.38±0.04	3.03±0.08	3.29±0.05				
Multivariate test	<0.001	<0.001	<0.001	0.795					

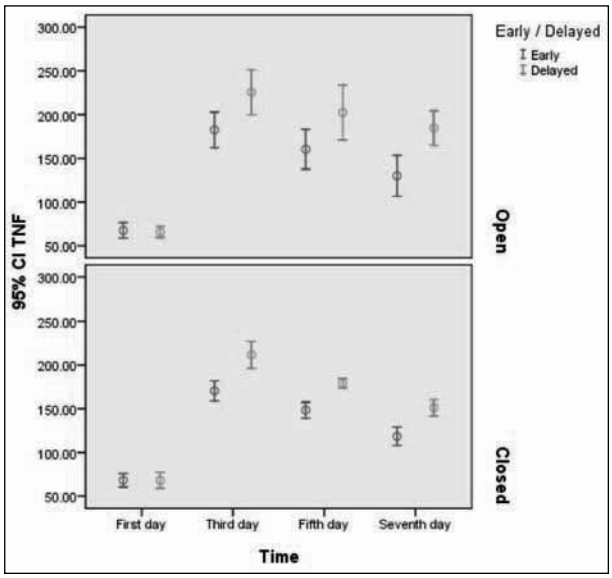

Figure 1. 95% CI of TNF-α (pg/mL)between treatments (Open and Closed) and methods (Early and Delayed) in deferent times

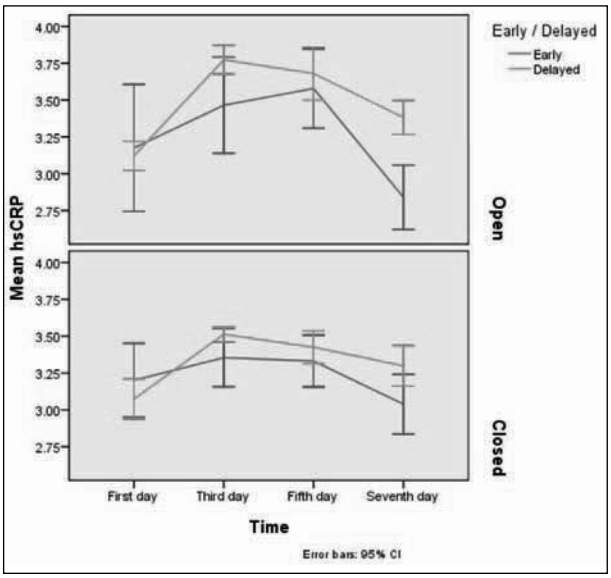

Figure 2. 95% CI of hs-CRP (μg/ml) between treatments (Open and Closed) and methods (Early and Delayed) in deferent times.

and also the 3rd and 5th days (P<0.001). However, the 1st and 7th days were significantly different from the 3rd and 5th days (P<0.001). In this study, a statistically significant increment of TNF-α was observed in all study groups during the 3rd day of examination but this increment statistically was lower in groups using early forms of enteral nutrition (EC_{1th}: 68.24±3.17 pg/mL; EC_{3rd}: 170.60±4.68 pg/mL; EO_{1th}: 67.60±3.41 pg/mL; EO_{3rd}: 182.56±7.94 pg/mL) compare to delayed forms (DC_{1th}: 68.13±3.55 pg/mL; DC_{3rd}: 225.43±10.04 pg/mL; DO_{1th}: 65.85±2.47 pg/mL; DO_{3rd}: 225.43±10.04 pg/mL). During the 5th and 7th days of the study TNF-α statistically reduced and this decrement was more efficient in groups with early enteral nutrition (EC_{5th}: 148.44±3.69 pg/mL; EC_{7th}: 118.42±4.34 pg/mL; EO_{5th}: 160.38±8.89 pg/mL; EO_{7th}: 129.96±9.10 pg/mL) than groups with delayed forms (DC_{5th}: 179.18±2.05 pg/mL; DC_{7th}: 151.25±3.67 pg/mL; DO_{5th}: 202.36±12.22 pg/mL; DO_{7th}: 184.55±7.63 pg/mL). Hs-CRP like TNF-α firstly increased and then decreased during the study period and the inflammatory factor was controlled efficiently in early forms of EN. 7th determinations of hs-CRP in comparison with first ones were significantly lower in early forms of EN (EC_{1th}:3.20±0.10 μg/ml; EC_{7th}: 3.03±0.08 μg/ml; EO_{1th}: 3.17±0.16 μg/ml; EO_{7th}: 2.84±0.08 μg/ml) than delayed forms (DC_{1th}: 3.07±0.052 μg/ml; DC_{7th}: 3.29±0.05 μg/ml; DO_{1th}: 3.12±0.03 μg/ml; DO_{7th}: 3.38±0.04 μg/ml).

The present study seems to be, to the best of our knowledge, the first study to test effects of enteral nutrition on serum levels of both TNF-α and hs-CRP among traumatically ill patients in surgical ICU, simultaneously. Statistical analysis of the study data showed that EC and EO enteral nutrition efficiently control the inflammatory factors, TNF-α and hs-CRP, better than delayed closed and delayed open enteral nutrition. Increased levels of TNF-α and TNFRs have been reported to be correlated with the severity of injury in the early post-injury period (24). In this study, peak plasma concentrations of TNF-α and hs-CRP were detected on the 3rd day after ICU admission; these results are inconsistent with other studies (24-26). The data further suggest that the trauma-induced elevation in TNF-α and hs-CRP levels decreased in early enteral nutrition (whether administered by open or closed systems) more than delayed enteral feeding. Marik et al. revealed statistically significant reductions in infection caused morbidity with early compared to delayed enteral feeding (27). Artinian et al.

showed that early enteral feeding was associated with a significant reduction of ICU and hospital mortality (28). Canadian Clinical Practice Guidelines stated that early vs. delayed nutrient intake is associated with a trend towards a reduction in mortality and infectious complications but not ICU or hospital length of stay in critically ill patients(17). American Society for Parenteral and Enteral Nutrition (ASPEN)guidelines also reported that feeding should be initiated within the 24-48 hours after admission in critically ill patients (29) but ESPEN guidelines recommended such protocol just for haemodynamically stable ICU patients (30). However, Khalid et al. showed that early enteral nutrition may be associated with reduced hospital and ICU mortality in patients with unstable hemodynamic condition (31). Marik PE et al (32) pointed out that early enteral feeding should be considered the standard of care, and also as an indicator of the quality of care delivered in ICUs. The study results also showed early closed enteral feeding had controlled the hs-CRP and TNF-α better than early open feeding system. Mickschl et al. (33) and Wagner et al. (34) revealed greater incidence of contamination for the open system formulas than the closed system. So, contamination may have a key explanatory role in the above-mentioned study result. On the other hand a randomized control trial on levels of hs-CRP in ICU suggested that the microbial content of formula have critical effects on the inflammatory markers (15).

Conclusion

The study results showed that early closed enteral nutrition can more efficiently reduce both TNF-α and hs-CRP in traumatic ICU patients than other feeding methods. Thus, it may be concluded that early closed enteral feeding is more effective than delayed enteral nutrition. Early initiation of enteral nutrition should be considered whether using liquid or powder formulas.

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Correspondence:
Prof Dr. Alireza Ostadrahimi,
Nutrition Research Center, Faculty of Nutrition,
Tabriz University of Medical Sciences, Tabriz. Iran.
E-mail: ostadrahimi@tbzmed.ac.ir