PO Box 2345, Beijing 100023, China
Fax: +86-10-85381893
E-mail: wjg@wjgnet.com www.wjgnet.com

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Protective effect of early enteral feeding on postburn impairment of liver function and its mechanism in rats

Zhu L, Yang ZC, Li A and **Cheng DC**

Subject headings early enteral feeding; liver; postburn impa irments

Abstract

AIM To study the protective effect of early enteral feeding (EEF) on the postburn impairment of liver function and its mechanism.

METHODS Wistar rats with 30% of total body surface area (TBSA) full-thickness burn were employed. The effects of EEF on the postburn changes of gastric intramucosal pH, endotoxin levels in portal vein, water contents of hepatic tissue, blood concentrations of tumor necrosis factor (TNF-α), plasma activities of alanine aminotransferase (ALT) and asparate amin otransferase (AST), as well as the blood contents of total (TB) and direct bilirubin (DB), total protein (TP) and albumin (ALB) were serially determined within 48h postburn.

RESULTS EEF could significantly improve gastric mucosalacidos is, reduce portal vein endotoxin level and water content of hepatic tissue, as w ell as plasma concentrations of TNF-α at all timepoints after seve re burns ($P<0.01$); postburn elevation of the plasma activities of ALT, AST and the contents of TB, DB were effectively prevented, whereas the plasma conce ntrations of TP and ALB were markedly increased 24 h and 48 h posturn in EEF group compared with that of the burn without EEF group ($P<0.01$).

CONCLUSION EEF has significant beneficial effects on the impro vement of hepatic function in rats after severe burn, and is probably related with an increase in splanchnic blood flow, reduction of the absorption of gut-origin endotoxin and the consequent release of inflammatory mediators.

Li Zhu[1], Zhong Cheng Yang[1], Ao Li[1] and De Chang Cheng[2]
[1]Institute of Burn Research, Southwest Hospital, Third Military Medical University, Chongqing 400038, China
[2]Critical Care Department, Peking Union Medical College Hospital (PUMCH), Chinese Academy of Medical science (CAMS), Beijing 100730, China
Dr. Li Zhu, male, born on 1958-02-03 in Nanyang City, Henan Province, Han nationality, graduated from Third Military Medical University as a doctor-d egree postgraduate in 1996 and now working in PUMCH as a postdoctoral research fellow, majoring in Traumatic Surgery and Critical Care Medicine, having 17 paper s published.
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Correspondence to: Dr. Li Zhu, Institute of Burn Research, Southwest Hospital, Third Military Medical University, Chongqing 400038, China
Tel. +86-10-65233768, +86-10-65142049
Email. zhuli58@263.net
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INTRODUCTION

Acute impairement of hepatic function is one of the most common serious complica tions after severe burns with an extremely high incidence[1,2]; however, its prevention and treatment have not yet been effectively improved so far. In recent years, abundant researches have suggested that the posttrauma translocation of gut-origin endotoxin may lead to remote organ injury, and is also the major contributor to the hepatic dysfunction[3-5]. Meanwhile, it has become increasingly apparent that early enteral feeding (EEF) in various pathological conditions may produce multiple beneficial effects, including the stimulation of splanchnic and hepatic circulation, maintenance of gut mucosal integrity, prevention of intramucosal acidosis and permeability disturbances, and alleviation of the translocation of gut-origin bacteria and endotxin[6-10]. We therefore presume that EEF might be possible to improve hepatic function in severe burns, which up to now has been seldom documented. Thus, the present study is designed to verify this hypothesis, and in an attempt to seek ways to improve further the treatment of severely injured patients. This is no doubt of both theoretical and practical importance.

MATERIALS AND METHODS

Animals

Healthy adult wistar rats of either sex, weighing 220 g±30 g, were employed in the study. They were housed in individual metabolic cages in a temperature conditioned room (22 ℃-24 ℃) with a 12 h light-dark cycle, allowed access to standard rat chow (provided by Experimental Animal Center, Third Military Medical University) and water adlibium, and acclimatized to the surro undings for 7 days prior to the experiments.

Operative procedure

All animals were weighed and anesthetized with 1%

pentobarbital sodium (30 mg/kg, ip). After laparotomy, a polyeth ylene catheter (1.5 mm in diameter) for enteral feeding was inserted into duodenum on the anterior wall 1.5 cm from pylorus via a puncture hole made by a metal needle. The catheter was appropriately fixed, tunneled under the skin and exited through the nape skin. Animals were housed and fed as described above after operation.

Burn injury and resuscitation

After a recovery period of 24 h, the animals inserted with feeding tube were anesthetized, dorsal hair shaved and then placed in a wooden template designed to expose 30% of the total body surface area (TBSA), and then immersed in water at 92 ℃ for 20 seconds, which resulted in a clearly demarcated full-thickness burn. One hour after burn injury, the animals were resuscitated with 10 mL of warm 0.9% NaCl (normal saline solution, 37 ℃) given by intraperitoneal injection. Control animals were similarly anesthetized and shaved but not burned.

Feeding and experimental protocol

Nutrient liquid for feeding was prepared before use as one with a caloric value of 2.1 KJ/mL by mixing nutritional powder (ENSURE, USA) with appropriate amount of warm boiled water. According to different feeding regimens, animals were randomly divided in to three groups: ① EEF group. Enteral feeding was initiated 1h postburn in burn ed animals via feeding tube with a total calorie of 202 $KJ \cdot Kg^{-1} \cdot 24\ h^{-1}$; the nutrient liquid required for 24 hours was administered evenly at 6 timepoints. ② Burn group. The animals were treated exactly the same as EEF group, except that the nutrient liquid was substituted by equal amount of saline. ③ Control group . Only the feeding tube was inserted, whereas no tube feeding and burn were conducted. The animals in this group were allowed access to standard rat chow, nutrient liquid and water ad libium. Timepoints for different measurements and assays in all groups were made at the 3rd, 6th, 12th, 24th and 48th hpostburn, except for the determination of liver tissue water content, which was performed at the 12th after thermal injury. For plasma assays, rats were sacrificed by decapitation at each timepoint and heparinised blood was collected in separate tubes, spun at 3 000 g for 10 min, and the plasma frozen at -20 ℃ until analysis.

Measurements

The gastric intramucosal pH (pHi) was determined with an indirect method as previously described[11] with minor modificat ion. Briefly, animals were anesthetized and given cimetidine (15 mg) intraperit oneally 1h prior to each timepoint, and then a polyethylene catheter was inserted into gastric lumen through pylorus via a puncture hole on the anterior wall of duodenum made by a metal needle after a midline laparotomy. An amount of 2.5 mL normal saline was injected into gastric lumen though the catheter and aspirated out to get rid of intragastric residues, and then 1.5 mL normal saline was injected and retained in the gastric lumen. After an equilibration interval of 60 min, 1 mL of saline solution were aspirated and Pco_2 determined using the blood gas analyzer. A simultaneously obtained arterial blood sample was used for determining the $[HCO_3^-]$. pHi was then calculated as:

$$pHi=6.1+\log([HCO_3^-]/[Pco_2\times 0.03])$$

The multifunction-biochemical analyzer Beckman Synchron CX-7 was used for performing performing liver function tests. The plasma activities of alanine aminotr ansferase (ALT), asparate aminotransferase (AST), as well as the blood contents of total (TB) and direct bilirubin (DB), total protein (TP) and albumin (ALB) were determined at each timepoint.

Portal plasma endotoxin levels were assayed with the limulus-amoebocyte-lysate test (LAL)[12]. In brief, plasma samples were diluted tenfold with pyrogen-free water and heated to 75 ℃ for 5 min to inactivate the plasma inhibitor. The samples were incubated with LAL at 37 ℃ for 33 min. The chromogenic substrate was added and the samples incubated for another 3 min. Acetic acid stopped the reaction. The optical density was read at 545 nm and endotoxin concentration was expressed as Eu/mL.

Radioimmunoassay of TNF-α levels in systemic circulation was conducted according to the instructions with kits from Dong Ya Research Institute of Immuno-technology.

Liver tissue water contents were determined with a method as reported in a previous study[13] with minor modification. Eight Liver tissue samples for each group were harvested at 12 h postburn, weighed, put in oven at 90 ℃ for 24 h, and then weighed again. The liver tissue water contents were calculated as:

Liver tissue water contents=(wet weight-dry weight/wet weight)×100%

Statistical analysis

Data were expressed as mean±standard error of the mean. Experimental results were analyzed by analysis of variance and *t* tests for multiple comparisons. Statistical significance was determined at $P<0.05$.

RESULTS

Postburn EEF has beneficial effects on the hepatic functions as demonstrated by the significantly reduced plasma activities of ALT, AST and the blood contents of TB and DB, whereas the plasma

concentrations of TP and ALB were markedly increased 24 h and 48 h posturn in the EEF group compared with that of the burn group without EEF as shown in Tables 1 and 2.

Gastric mucosal acidosis was significantly improved in EEF group animals as indicated by the elevation of gastric pHi at most of the postburn timepoints, however, gastric pHi in the burn group sustained in lower levels until 48 h postburn (Table 3).

Table 4 displays the changes in portal endotoxin levels after severe burns. Three hours postburn, endotoxin concentration significantly increased in the burn group and reached a peak in 6 h; another increase appeared after 24 h and persisted until 48 h postburn. However, the portal endotoxin levels in animals that received EEF markedly decreased at nearly all timepoints postburn compared with that of the burn group.

The data for plasma TNF-α levels are shown in Table 5. In accordance with other observations, EEF could also significantly reduce TNF-α levels in the systemic circulation at most postburn timepoints as compared with that of burn animals.

The hepatic tissue water contents in the three experimental groups were 71.17 % ± 0.60 %, 73.01 % ± 0.52 % and 70.18 % ± 0.52 % respectively. Evidently, the liver tissue water content in the EEF group was significantly lower than that in the burn group without EEF 12 h postburn (P<0.01).

Table 1 The effects of EEF on the postburn changes of plasma ALT, AST activities and TB, DB contents ($\bar{x}$±s)

Group (samples)	Postburn hours				
	3	6	12	24	48
EEF (40)					
ALT (mmol·s^{-1}/L)	1.21±0.07^{b,d}	1.54±0.14^{b,d}	1.75±0.17^{b,d}	1.39±0.09^{b,d}	1.09±0.09^{b,d}
AST (mmol·s^{-1}/L)	8.58±0.64^{b,d}	11.47±0.81^{b,d}	14.30±1.04^{b,d}	9.75±0.80^{b,d}	7.24±0.65^{b,d}
TB (mmol/L)	16.85±2.01^{a,d}	14.97±2.36^{d}	12.90±2.01^{a,d}	10.82±1.71^{b,d}	6.59±1.61^{b}
DB (mmol/L)	7.72±1.90^{d}	4.68±1.46^{b,d}	2.42±0.78^{b}	1.72±0.36^{b}	1.74±1.09^{b}
Burn (40)					
ALT (mmol·s^{-1}/L)	2.06±0.13^{d}	2.90±0.19^{d}	3.19±0.23^{d}	2.99±0.17^{d}	2.21±0.14^{d}
AST (mmol·s^{-1}/L)	12.20±0.77^{d}	18.77±0.84^{d}	23.13±1.14^{d}	16.18±0.94^{d}	12.56±1.00^{d}
TB (mmol/L)	19.26±2.97^{d}	16.98±2.11^{d}	15.08±2.37^{d}	18.32±2.69^{d}	10.82±1.97^{d}
DB (mmol/L)	8.26±2.17^{d}	9.77±2.02^{d}	5.50±1.32^{d}	7.10±1.43^{d}	3.54±0.94^{d}
Control (40)					
ALT (mmol·s^{-1}/L)	0.61±0.09	0.57±0.07	0.63±0.08	0.58±0.07	0.64±0.10
AST (mmol·s^{-1}/L)	1.55±0.10	1.64±0.09	1.60±0.10	1.71±0.11	1.58±0.10
TB (mmol/L)	5.63±1.41	6.04±1.27	5.81±1.62	6.17±1.02	5.76±1.38
DB (mmol/L)	1.62±0.56	1.46±0.39	1.55±0.42	1.73±0.41	1.53±0.47

^{a}P<0.05, ^{b}P<0.01 *vs* burn group; ^{d}P<0.01 *vs* control.

Table 2 The effects of EEF on the postburn changes of plasma total p rotein and albumin levels (c/g·L^{-1}, $\bar{x}$±s)

Group (samples)	Postburn hours				
	3	6	12	24	48
EEF (40)					
Total protein	43.10±2.31^{d}	42.49±3.00^{d}	47.61±4.39^{c}	58.33±2.93^{b}	62.36±4.18^{b,d}
Albumin	19.32±1.34^{d}	19.49±1.63^{a,d}	22.76±2.19^{d}	25.70±2.40^{b}	26.77±1.25^{b}
Burn (40)					
Total protein	43.54±2.51^{d}	44.79±2.03^{d}	44.80±3.63^{d}	48.84±4.30^{d}	52.77±1.45
Albumin	19.78±2.11^{d}	20.99±1.23^{d}	21.54±1.72^{d}	21.84±1.84^{c}	22.50±0.83^{d}
Control (40)					
Total protein	53.67±2.43	57.41±1.83	52.55±2.62	55.76±3.18	53.92±2.88
Albumin	25.38±1.62	25.72±1.38	26.08±1.72	24.46±1.33	25.64±1.43

^{a}P<0.05, ^{b}P<0.01 *vs* burn group; ^{c}P<0.05, ^{d}P<0.01 *vs* control.

Table 3 The effects of EEF on the postburn changes of gastric intram ucosal pH ($\bar{x}$±s)

Group	Samples	Postburn hours				
		3	6	12	24	48
EEF	50	7.119±0.078^{a,b}	6.943±0.089^{a,b}	7.074±0.037^{a,b}	7.285±0.098^{a}	7.257±0.077^{a,b}
Burn	50	7.017±0.037^{b}	6.826±0.049^{b}	6.802±0.080^{b}	6.949±0.082^{b}	7.074±0.041^{b}
Control	50	7.321±0.054	7.296±0.067	7.296±0.067	7.306±0.069	7.348±0.074

^{a}P<0.01 *vs* burn group; ^{b}P<0.01 *vs* control.

Table 4 The effects of EEF on the postburn changes of portal endotox in level (Eu/mL, $\bar{x}\pm s$)

Group	Samples	Postburn hours				
		3	6	12	24	48
EEF	40	0.683±0.072[a,b]	0.797±0.085[a,b]	0.542±0.078[a,b]	0.725±0.061[a,b]	0.461±0.049[a,b]
Burn	40	1.394±0.126[b]	1.518±0.173[b]	1.124±0.133[b]	1.627±0.215[b]	1.168±0.188[b]
Control	40	0.206±0.032	0.195±0.043	0.189±0.049	0.204±0.037	0.215±0.051

[a]$P<0.01$ *vs* burn group; [b]$P<0.01$ *vs* control.

Table 5 The effects of EEF on the postburn changes of plasma TNF-α level (ng/mL, $\bar{x}\pm s$)

Group	Samples	Postburn hours				
		3	6	12	24	48
EEF	40	1.48±0.38[a,b]	2.57±0.45[a,b]	2.36±0.47[a,b]	1.92±0.26[a,b]	1.68±0.45[a,b]
Burn	40	1.92±0.19[b]	4.49±0.47[b]	3.51±0.45[b]	4.07±0.71[b]	3.24±0.61[b]
Control	40	0.83±0.08	0.78±0.11	0.83±0.12	0.81±0.09	0.81±0.09

[a]$P<0.01$ *vs* burn group; [b]$P<0.01$ *vs* control.

DISCUSSION

Nutritional support plays an important role in the management of critically ill patients for preventing and treating multiple organ failure[14]. However, the concept of the administration of enteral nutrition very early after injury is relatively new[8]. More than a decade ago, Moore *et al*[15] reported that immediate postoperative feeding by needle catheter jejunostomy was safe and feasible; and that early nutritional support could decrease the incidence of septic complications in the severely injured patient. In a subsequent study, Mochizuki *et al*[16] showed that immediate enteral feeding in burned guinea pigs was associated with a decrease in the hypermetabolic state. They demonstrated that early enteral feeding could suppress the expected rise in glucagon, cortisol and norepinephrine after major burn injury, compared with delayed enteral feeding. Since then results of a number of clinical and animal studies were reported, showing that very early enteral feeding could preserve the gut barrier function, diminish hypermetabolic response, maintain caloric intake, reduce infective complications and significantly shorten hospital stay following injury[6,7,16-18]. Unfortunately, most of these studies paid more attention merely to its trophic and metabolic effects, whereas the other benefits such as its role played in the protection of splanchnic functions were greatly neglected. In the present study, we showed that postburn EEF could result in a lowe ring of plasma ALT, AST activities and TB, DB contents, as well as a rapid restoration of plasma TP and ALB level that have significantly decreased after severe burns. These clearly meant that early enteral feeding could effectively improve hepatic dysfunction caused by burn injury. A previous study showed that circula ting levels of bile acids could be a sensitive and specific indicator of liver function, an elevation of serum bile acid levels indicating a deterioration in liver function[19]. In a rat model of hemorrhagic shock, Zaloga *et al*[19] found enteral administration of a peptide-based diet early after hemorrhagic shock, could significantly prevent the elevation of circulating bile acid levels, whereas a 3.6 times of serum bile acid level above baseline was no ted in animals with same amount of enteral saline therapy. In a similar rat model, Bortenschlager *et al*[20] also observed that enteral nutrient s significantly decreased liver injury. After hemorrhagic shock, AST in saline controls and enterally fed animals increased from 246 U/L±17 U/L to 1605 U/L±593 U/L and from 283 U/L±39 U/L to 551 U/L±94 U/L respectively; ALT increased from 60 U/L±4 U/L to 726 U/L±355 U/L in controls and 61 U/L±6 U/L to 161 U/L±38 U/L in enterally fed animals. These results further indicated that EEF could protect animals from liver injury in various forms of injury.

The mechanisms of EEF in improving postburn liver function so far have not been fully clarified yet. It has been noted that in severe trauma including burns, the loss of a large amount of body fluids and the release of stress hormones cause a sharp reduction of blood flow to many organs, especially the gastrointestinal tract. Reduced intestinal blood flow then leads to translocation of bacteria an d/or their toxic products through the gut mucosa. Subsequent bacteria and/or toxin-induced persistent and excessive release of cytokines (i.e. tumor necrosis factor, interleukins) from hepatic macrophages and complement activation may initiate progressive multiple organ failure and even cause death[21-23]. In acc ordance with this theory, many studies suggested that the hepatic ischemia and endotoxemia occurred in various pathological conditions and were the major contributors to liver dysfunction[3-5,24]. However, Zaloga[25] also proposed that deprivation of exogenous nutrients for a certain period of time, via a mechanism of substrate lack and tissue antioxidant system depletion, could also compromise organ function.

Postprandial gut hyperemia is a local vascular response to the presence of foodstuff in the lumen, an important physiological phenomenon for food digestion and absorption. Even though in some

pathological conditions, this phenomenon still exists. In burned guinea pigs, Inoue *et al*[26] using radiolabeled microspheres demonstrated that during initial 24 h of enteral feeding, blood flow to the jejunum and cecum was higher in the fed group than in the control. Purcell *et al*[27,28] studied oleic-acid-induced lung injury in dogs mechanically ventilated with positive end-expiratory pressure (PEEP) which limited hepatic blood flow and oxygen delivery, and found that in such dog receiving EEF there were a significant increase in hepatic blood flow and oxygen delivery, witha highest increase in portal blood flow. In a dog model of splanchnic ischemia induced with endotoxin, Eleftheriadis *et al*[29,30] reported that after early enteral feeding, portal vein, hepatic and superior mesenteric artery blood flow; hepatic and intestinal microcirculation; hepatic tissue PO_2 and energy charge; and intestinal intramucosal pH, which were all reduced in the early septic condition, were significantly increased. In present study, we showed that postburn EEF could effectively restore reduced gastric intramucosal pH, decrease endotoxin concentrations in portal vein and TNF-α levels in systemic circulation, and alleviate liver tissue edema, as compared with saline feeding burn controls. All above indicate that in addition to provide nutrients, posttrauma EEF exerts its protective effect on liver function most likely via a mechanism of postprandial hyperemia to improve gut blood flow and splanchnic ischemic status, and to maintain gut mucosal integrity, which may block the vicious circle of mutual activation between the translocation of gut origin bacteria with their toxic products and the release of inflammatory mediators[31], thereby reducing hypoxic and inflammatory tissue damage.

The fact that EEF may improve postburn hepatic function is of both theoretically and practically importance. Although the results from animal study can not be a pplied directly to humans, the data from this study might provide valuable clues to the further improvement of prevention and treatment of post-tramatic multiple organ dysfunction syndrome. Now, EEF should not be considered merely as a sim ble nutritional support. Further investigations are needed to demonstrate whether or not the results from this animal experiment can apply to clinical settings.

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