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• BASIC RESEARCH •

Improvements of postburn renal function by early enteral feeding and their possible mechanisms in rats

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Abstract

AIM: To investigate the protective effects of early enteral feeding (EEF) on postburn impairments of renal function and their possible mechanisms.

METHODS: Wistar rats with 30 % of total body surface area (TBSA) full-thickness burn were adopted as the experimental model. The effects of EEF on the postburn changes of gastric intramucosal pH (pHi), endotoxin levels in portal vein, water contents of renal tissue, and blood concentrations of tumor necrosis factor (TNF-α), urea nitrogen (BUN), creatinine (Cr), as well as the changes of clearance of creatinine (CCr) were dynamically observed within 48 h postburn.

RESULTS: EEF could significantly improve gastric mucosal acidosis, reduce portal vein endotoxin levels and water contents of renal tissue, as well as blood concentrations of TNF-α after severe burns ($P<0.01$). The postburn elevations of BUN and BCr were not found to be recovered by EEF. However, the CCr in EEF group was greatly increased by 4.67-fold compared with that of the non-feeding burned control (16.43±2.90 *vs*. 3.52±0.79, $P<0.01$).

CONCLUSION: EEF has beneficial effects on the improvement of renal function in severely burned rats, which may be related to its increase of splanchnic blood flow, decrease of the translocation of gut-origin endotoxin and the release of inflammatory mediators.

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INTRODUCTION

Acute renal failure (ARF) is one of the well-known complications after severe burns with an extremely high incidence of death[1-4]. In most circumstances, it manifests as a part of multiorgan dysfunction syndrome[5, 6] and the kidney-oriented supportive therapy so far has not achieved satisfactory results[6, 7]. In recent years, abundant researches have suggested that the translocation of gut-origin endotoxin in certain pathological conditions may lead to remote organ injury[8, 9], which may also be the major contributor to renal dysfunction[10-13]. Meanwhile, it has become increasingly apparent that early enteral feeding (EEF) in various groups of patients could produce multiple beneficial effects, including increase of blood flow to the splanchnic organs, maintenance of gut mucosal integrity, prevention of intramucosal acidosis and permeability disturbances, and alleviation of the translocation of gut-origin bacteria and endotxin[14-19]. We therefore presume that EEF might be possible to improve renal function injured by severe burns, which up to now has been seldom documented. Thus, the present study was designed to demonstrate this hypothesis, in attempt to seek ways to improve the treatment of severely injured patients, which would be no doubt of both theoretical and practical importance.

MATERIALS AND METHODS

Animals

Healthy adult Wistar rats of both sexes, weighing 220±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 circle, allowed access to standard rat chow (provided by experimental animal center, Third Military Medical University) and water ad libium, and acclimatized to the surroundings for 7 days prior to the experiments.

Operative procedure

All animals were weighed and anesthetized with 1 % pentobarbitale sodium (30 mg/kg, ip). After laparotomy, a polyethylene catheter (1.5 mm in diameter) was inserted into duodenum on the anterior wall 1.5 cm from pylorus via a puncture hole made by a metal needle for enteral feeding. The catheter was appropriately fixed, tunneled under the skin and exited through the nape skin. The 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 a feeding tube were anesthetized, having their dorsal hair shaved and 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, shaved, resuscitated but not burned.

Feeding and experimental protocol

Nutrient feeding liquid was prepared as one with a caloric of 2.1 KJ/ml before use by mixing nutritional powder (ENSURE, USA) with an appropriate amount of warm boiled water. According to different feeding regimens, the animals were randomly divided into three groups: (1) EEF group. Enteral

feeding was initiated 1 h postburn in burned animals via a feeding tube with a total caloric of 202 KJ· Kg^{-1}· 24 h^{-1}. The feeding nutrient liquid required for 24 hours was administered evenly at 6 time points. (2) Burn group. The animals were treated exactly the same as EEF group, except that the nutrient feeding liquid was substituted for the same 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, nutrition liquid and water ad libium. Time points for different measurements and assays in all groups were made at 3, 6, 12, 24 and 48 h postburn, except for the determination of renal tissue water content, which was performed at 12 h after thermal injury. 24-hr urine was collected for the detection of urea nitrogen and creatinine that were used to calculate CCr. For plasma assays, rats were sacrificed by decapitation at each time point and heparinised blood was collected in a separator tube spun at 3 000 g for 10 min, decanted and frozen at -20 ℃ until analysis.

Measurements

The gastric intramucosal pH was determined with an indirect method as previously described[20] with minor modifications. Briefly, the animals were anesthetized and injected cimetidine (15 mg) intraperitoneally 1 h prior to each time point, 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. A 2.5-ml of normal saline was injected into gastric lumen though the catheter and removed in order to get rid of intragastric residues, then 1.5-ml of normal saline was injected and retained in the gastric lumen. After an equilibration interval of 60 min, 1 ml of saline solution was aspirated and PCO_2 was determined using the blood gas analyzer. A simultaneously obtained arterial blood sample was used to determine 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 employed to detect urea nitrogen and creatinine in both blood and urine.

Portal plasma endotoxin levels were assayed with the limulus-amoebocyte-lysate test (LAL)[21]. Briefly, plasma samples were diluted tenfold with pyrogen-free water and heated to 75 ℃ for 5 min to overcome assay inhibition by plasma. The samples were incubated with LAL for 33 min at 37 ℃. Then the chromogenic substrate was added and the samples was incubated for another 3 min. After the reaction was stopped with acetic acid, sample optical density was read at 545 nm and the endotoxin concentration was finally 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 Immunotechnology.

Renal tissue water contents were determined with a method as reported in a previous study[22] with minor modifications. Eight renal tissue samples for each group were harvested at 12 h postburn, weighed and put in an oven at 90 ℃ for 24 h, then weighed again. The renal tissue water contents were calculated as: Renal tissue water contents=(wet weight - dry weight / wet weight)×100 %

Statistical analysis

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

RESULTS

BUN and BCr in both EEF and Burn groups were significantly increased postburn with the peak value at 6 h. Though gradually decreased thereafter, they were still significantly higher than those of the control at 24 and 48 h time points ($P<0.01$). The beneficial effects of EEF on the renal function manifested as the improvement of CCr, in which a 4.67-fold increase was observed in EEF group as compared with burn group and the CCr value in EEF group tended to be close to that in the control (Table 1).

Gastric mucosal acidosis was significantly improved in EEF group as indicated by the elevation of gastric pHi at most of the postburn time points, however, gastric pHi in burn group was sustained in lower levels until 48 h postburn (Table 2).

Table 3 displays the changes in portal endotoxin levels after severe burns. Three hours postburn, endotoxin concentration was significantly increased in burn group and peaked at 6 h, another increase appeared at 24 h and persisted until 48 h postburn. However, the portal endotoxin levels in animals that received EEF markedly decreased at almost all time points as compared with that of the burn group.

The data for plasma TNF-α levels are shown in Table 4. In accordance with other observations, EEF could also significantly reduce TNF-α levels in systemic circulation at most postburn time points as compared with that of burnt animals.

Table 1 Effects of EEF on postburn changes of BUN, BCr and CCr ($\bar{x}\pm s$)

Group	Samples	Postbun hours (h)				
		3	6	12	24	48
EEF	40					
BUN (mmol/L)		10.30±0.67[a d]	17.67±1.52[b d]	13.73±1.43[d]	8.73±2.10[d]	7.50±1.16[d]
BCr (mmol /L)		53.77±3.20[d]	89.60±6.54[b d]	55.44±3.57[d]	46.95±2.66[d]	42.90±2.23[d]
CCr (ml/h/100g)					16.43± 2.90 [b]	
Burn	40					
BUN (mmol/L)		11.76±1.72[d]	15.42±1.74[d]	13.48±1.56[d]	9.27±1.75[d]	7.68±1.63[d]
BCr (mmol /L)		51.80±2.83[d]	71.23±2.63[d]	57.70±4.93[d]	44.75±1.69[d]	41.76±1.26[d]
CCr (ml/h/100g)					3.52 ±0.79[d]	
Control	40					
BUN (mmol/L)		4.67±0.85	4.49±0.58	4.74±0.80	4.31±0.69	4.52±0.93
BCr (mmol /L)		37.43±3.64	37.67±3.26	37.28±4.42	36.94±3.71	37.69±3. 47
CCr (ml/h/100g)					19.45±2.21	

[a]$P<0.05$, [b]$P<0.01$ *vs* Burn group; [c]$P<0.05$, [d]$P<0.01$ *vs* Control.

Table 2 Effects of EEF on postburn changes of gastric intramucosal pH ($\bar{x}\pm s$)

Group	Samples	Postbun hours (h)				
		3	6	12	24	48
EEF	50	7.119±0.078[ab]	6.943±0.089[ab]	7.074±0.037[ab]	7.285±0.098[a]	7.257±0.077[ab]
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	7.343±0.045	7.306±0.069	7.348±0.074

[a]$P<0.01$ *vs* Burn group; [b]$P<0.01$ *vs* Control.

Table 3 Effects of EEF on postburn changes of portal endotoxin level (Eu / ml, $\bar{x}\pm s$)

Group	Samples	Postbun hours (h)				
		3	6	12	24	48
EEF	40	0.683±0.072[ab]	0.797±0.085[ab]	0.542±0.078[ab]	0.725±0.061[ab]	0.461±0.049[ab]
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

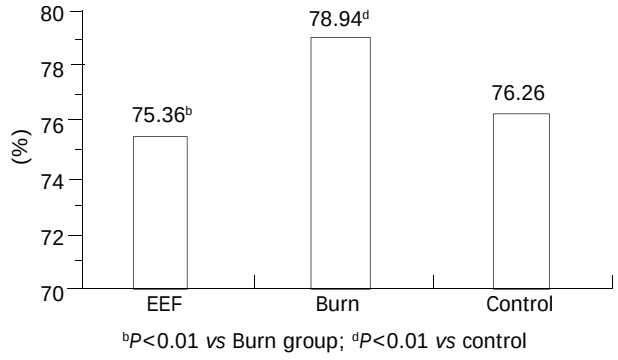
[a]$P<0.01$ *vs* Burn group; [b]$P<0.01$ *vs* Control.

Table 4 Effects of EEF on postburn changes of plasma TNF-a level (ng / ml, $\bar{x}\pm s$)

Group	Samples	Postbun hours (h)				
		3	6	12	24	48
EEF	40	1.48±0.38[ab]	2.57±0.45[ab]	2.36±0.47[ab]	1.92±0.26[ab]	1.68±0.45[ab]
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	0.85±0.10

[a]$P<0.01$ *vs* Burn group; [b]$P<0.01$ *vs* Control.

For EEF, burn and control groups of animals, the renal tissue water contents reached 75.36±0.99 %, 78.94±1.56 % and 76.26±1.25 % respectively (Figure 1). It was evident that a significant decrease of renal tissue water content was seen in EEF group compared with that in burn group at 12 h postburn ($P<0.01$).



[b]$P<0.01$ *vs* Burn group; [d]$P<0.01$ *vs* control

Figure 1 Effects of EEF on water content of renal tissue 12 h postburn.

DISCUSSION

Nutritional support plays an important role in the management of critically ill patients to prevent and treat multiple organ dysfunction syndrome (MODS)[23]. Numerous clinical and animal studies have demonstrated that early enteral feeding could preserve the gut barrier function, diminish hypermetabolic response, maintain caloric intake, reduce the chance of gut origin infection and significantly shorten hospital stay following injury[14-19]. Unfortunately, the protective effects of EEF on the splanchnic function after severe traumas were relatively neglected in most of these investigations.

In a previous study, Roberts and his associates[24] observed that acute impairment of renal function inflicted by rhabdomyolysis was improved with EEF. Through 72 h dynamic observation, they found both BUN and BCr in EEF rats decreased by 65.7 % and 60 % respectively and the mortality reduced by 43 % compared with that of the animals fed with water. In contrast, in present animal model of severely thermal injury, BUN and BCr in both EEF and burn groups were significantly elevated, and no effect of EEF on the postburn changes of these variables was noted. We conjecture the phenomenon might be attributed to the more severity of the injury, difference in feeding components and blood condensation postburn. It has been reported that CCr could correlate well with the inulin clearance and exhibit renal function more accurately in the presence of acute renal failure[25]. In a animal study on renal dysfunction caused by ischemia, Mouser and his colleagues[25] demonstrated that the percentage of CCr increment in enterally fed animals was 2.5-fold higher than that in animals fed intravenously, whereas no significant changes of BUN and BCr were observed, showing that the improvement of renal function would not be always in accordance with BUN and BCr changes. In the present study, CCr in EEF animals increased by 4.67-fold compared with that in burn group, indicating that EEF could exert protective effects on the postburn renal impairment, and that aborative

attention should be paid to the selection of proper variables to perform such investigations.

The mechanisms of EEF to improve posttrauma renal function so far have not been clarified yet. It was once considered that the enhanced feeding of certain nutrients such as proteins or amino acids might increase the glomerular filtration rate (GFR). However, Mouser *et al*.[25] have shown that even with the same kind of nutrients, CCr in intravenously fed animals with renal ischemia was significantly lower than that in enterally fed animals, suggesting that the enteric factors beyond nutrients play a role in the improvement of impaired renal function. In fact, in severe traumas including burn, loss of large amount body fluids and release of stress hormones caused a sharp reduce of blood flow to many organs, especially the gastrointestinal tract and the kidney. Reduced intestinal blood flow then led to translocation of bacteria and/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) and complement activation initiated progressive multiple organ failure and even caused death[26, 27]. In accordance with this theory, numerous studies have proposed that the renal ischemia and endotoxemia occurred in various pathological conditions be the major contributors to the renal dysfunction[10-13, 28-30].

Postprandial gut hyperemia is a locally mediated 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*[31] using radiolabeled microspheres demonstrated that blood flow to the jejunum and cecum was higher in the diet group than in the control during initial 24 h of enteral feeding. In a dog model of splanchnic ischemia induced with endotoxin, Eleftheriadis *et al*.[32] reported that portal vein, hepatic and superior mesenteric artery blood flow, hepatic and intestinal microcirculation, hepatic tissue PO_2 and energy charge, and intestinal intramucosal pH were significantly increased after early enteral feeding, which were all reduced in the early septic condition. In the 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, as well as alleviate renal tissue edema compared with burn controls. All the above indicate that in addition to provision of nutritional substrates, posttrauma EEF is most likely via a mechanism of postprandial hyperemia, to improve gut low flow and splanchnic ischemic status, to maintain gut mucosal integrity, and to block the vicious circle of mutual activation between the translocation of gut origin bacteria and their toxic products, and the release of inflammatory mediators[33], thereby reducing hypoxic and inflammatory tissue damage. However, detailed mechanisms are needed to be further studied.

The facts that EEF could improve postburn renal function are of both theoretical and practical importance. The present study revealed that EEF should not be taken merely as a method or a route for nutritional support. Its clinical value has exceeded the range of nutrition and is not limited to the locally enteric benefits as well. Although the results from the animal study can not be extrapolated directly to humans, a better understanding of the postburn EEF might lead to new ways for the further improvement in prevention and treatment of MODS posttrauma.

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