Prospective Controlled Trial to Compare Immune-Enhancing and Regular Enteral Diets to Reduce Septic Complication in Major Burn Patients

Watcharade Iamsirisaengthong MD*,
Kusuma Chinaroonchai MD*, Chomchak Chuntrasakul MD*,
Somphon Roeksomtawin MD*, Pornprom Muangman MD*

** Division of Trauma Surgery, Department of Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Background: *Many studies reported the benefit of glutamine and arginine rich enteral diet or immune-enhancing enteral diet in reduction of the septic complication in trauma patients. However most of the studied subjects were trauma, not burn patients. Many physiologic changes after injury in burn patients quite alike other types of trauma patients, so that many but not all changes in trauma patients can be applied to burn patients. In addition, septic complication in burn patients had some differences in pathophysiology when compared to general trauma patients such as the consequence burn wound infection as a wound complication or the respiratory tract malfunction sequelae from inhalation injury, etc.*
Objective: *To demonstrate the benefit of immune-enhancing enteral diet in reduction of septic complication in major burn patients.*
Material and Method: *A prospective randomized controlled trial was conducted in 20 major burn patients.*
Results: *No statistically significant difference in septic complications ($p = 0.370$) and mortality rate ($p \geq 0.05$) between both groups was observed. However, immune-enhancing diet group showed advantage in increasing in bodyweight ($p = 0.010$), albumin level ($p = 0.005$) and transferrin level ($p < 0.001$).*
Conclusion: *Immune-enhancing diet may demonstrated trend of decreasing in septic complications and the significance in maintaining body weight and increasing in albumin and transferrin level in major burn patients.*

Keywords: *Glutamine, Arginine, Enteral diet, Septic complication, Burn*

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The enteral route for nutrition support was proved for its superiority over the parenteral one in many aspects, e.g. much like physiologic route, lower cost and complications[1,2]. ASPEN[3] and ESPEN[4] suggest that enteral nutrition should be the first standard option if the patient does not have any contraindication.

Nowadays, there are many specialized enteral diet formulas with additional protein known as immune-enhancing enteral diets. These diets could reduce septic complications especially in severely ill patients such as surgical critically ill patients in intensive care unit (ICU), severe traumatic patients[5-8]. However, none of previous studies has been focused on these benefits in major burn patients.

Correspondence to:
Muangman P, Division of Trauma Surgery, Department of Surgery, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok 107100, Thailand.
Phone: +66-2-4197728
E-mail: pmuangman@yahoo.com

The hormonal responses after severe stress such as severe infection or critical injury are increased in releasing of glucagon, cortisol and cathecolamines that will stimulate proteolysis. Hyperproteolytic response after severe injury causes muscular protein breakdown to be used as other source of energy in stress condition[9,10]. Using muscular protein as body fuel results in decrease of lean body mass (LBM). 30% LBM loss relates to severe septic complication and 40% LBM loss can cause dead[11].

Glutamine, an amino acid that is the precursor in nucleic acid production, is the main energy source for many cells, especially the cells that have high mitotic ability such as enterocytes. Glutamine make enterocytes function normally in nutritional purposes (absorption and excretion) and work effectively as natural immunity to prevent human body from numerous enteral bacteria from penetrating and entering into bloodstream as known as bacterial translocation which might cause gastrointestinal (GI) tract sepsis

that can end up with multiorgan failure problem at last[9]. The important role of glutamine in metabolic pathway make it be conditionally essential amino acid for human body in crisis period[12].

The other conditionally essential amino acid in stress response mechanism is arginine[13,14]. It plays important roles in cell growth, proliferation and differentiation of lymphocytes and synthesis of collagen in wound healing process. It is a unique biosynthetic substrate for production of nitric oxide (NO), a potent vasodilator. Arginine-NO synthesis pathway facilitates bactericidal action of immune function response[15].

In Thailand, there were multiple enteral diet formulas but there was a few immune enhancing enteral formulas. Neomune® is one of immune enhancing enteral formulas that contain both glutamine and arginine, and is well known and widely used by surgeons, internists and intensivists. But there is still unclear in septic complication reduction advantage especially in major burn patients. The objective is to study the septic complication of immune enhancing formula that composed of glutamine and arginine in major burn patients compared with standard formula.

Material and Method

This study was prospective randomized controlled trial. The patients with 20% or more than 20% of TBSA burn, age 18-60 years who were admitted to burn unit at Siriraj Hospital from December 2009 to December 2010 were enrolled. Diabetic patients, patients with HIV infection and patient with past history of malignancy were excluded from the subject enrollment. All of them never received enteral nutrition before admitted and no additional parenteral nutrition was administered.

The study was approved by ethic committee of Siriraj Hospital, Mahidol University. Patients were randomized based on computer program and divided into two groups, immune enhancing group and controlled group. Immune-enhancing group received Neomune® which composed of 25% protein. Controlled group received blenderized diet that composed of 17% of protein. Energy calculation in both groups was the same and calculated by using the equation as total energy requirement = Harris-benedict equation x stress factor x activity factor. The patients got initial resuscitation at emergency room then they were admitted to burn unit to reevaluate clinical response and continue resuscitation. After the clinical was stable, enteral nutrition was given to patient correspond to the assignment.

The primary objective of the study was to compare number of septic complication event between each group. Septic complication event defined as one or more of the following.

- Pneumonia: Fever >38°C with clinical dyspnea and sputum culture (C/S) found organism $>10^5$ colony forming unit/milliliters (CFU/mL).

- Urinary tract infection: Fever >38°C with urine C/S found organism $>10^5$ CFU/mL.

- Catheter related sepsis: Fever >38°C with tip of catheter C/S found organism $>10^5$ CFU/mL.

-Wound infection: Diagnosis by 2 burn surgeons with swab C/S found organism > 10^5 CFU/mL

The secondary objective was to collect the clinical data of each patient including length of hospital stay, wound healing, mortality rate and nutritional parameters of each patient compose of body weight gained, level of albumin, prealbumin and transferrin.

Statistical analysis

The continuous data are showed as means $\pm$ standard error of the mean. All variables were tested for statistical significance using Fisher's exact test, T-test and ANCOVA (analysis of variance). Two-sided *p*-value was calculated to evaluate demographic and nutritional parameters while one-sided *p*-value was calculated to evaluate length of hospital stay, wound healing and mortality rate. The *p*-value <0.05 was considered statistically significant. All statistical analysis was performed using SPSS version 13.

Table 1. Patient selection criterias

Patient selection criterias	
Inclusion criteria	Exclusion criteria
- Age 18-60 year	- Immunocompromised host (DM, HIV infection)
- ≥20% TBSA burn injury	- Previous history of malignancy
- No previous enteral nutrition treatment	
- No additional parental nutrition treatment	

Results

No significant difference in gender, age, size of burn injury and size of deep burn injury was observed between both groups (Table 2). Immune-enhancing group tended to have lower septic complications compared to controlled group, but there was no significant difference (40% vs. 70%, $p = 0.37$). There was no significant difference between both groups in mortality rate (10% vs. 10%), length of hospital stay (35.4 vs. 40.4 days) and wound healing time (32.3 vs. 38.3 days) (Table 3).

Immune-enhancing group had higher weight gain (60.6 vs. 54.8 kgs.), albumin level (3.4 vs. 2.6 g/dL) and transferring level (257.8 vs. 218.0 mg/dL) compared to controlled group significantly. But there is no significant difference of prealbumin level (0.314 vs. 0.284 g/dL) between both groups (Table 4).

Discussion

From previous studies, immune-enhancing diet could reduce septic complications. Unfortunately there was no previous study that focus on major burn patients. In the current study, the authors focus only major burn patients, excluding patients with altered immune response (immunocompromised or previous history of malignancy). The results showed that immune-enhancing diet demonstrated trend of lowering septic complications compared to controlled group without the effect on the mortality rate, length of hospital stay and duration of complete wound healing. It might due to too small sample size, the results could not point out statistical significance. So further study with more sample size might be considered. However, immune-enhancing group showed benefit to maintain body weight, increase albumin and transferrin level that indicated better nutritional status. Most of major burn injury in many countries as well as Thailand causes from flame burn injury[16]. It may co-associated with inhalation injury that results in higher morbidity and mortality in the same burn size[17-19]. Infection is also

Table 2. Demographic data

	Immune group	Controlled group	*p*-value
Gender (male)	70%	80%	1.0
Age (year)	40±17.2	46.4±20.6	0.46
%TBSA Burn injury	40.6±12.5	44.3±19.6	0.62
%TBSA Deep burn injury	28.8±14.3	40.4±15.2	0.98

Table 3. Septic complication

	Immune group	Controlled group	*p*-value
Septic complication	40%	70%	0.37
Mortality rate	10%	10%	1.0
Length of stay (day)	35.4±15.2	40.4±15.2	0.47
Wound healing (day)	32.3±14.3	38.3±14.9	0.37

Table 4. Nutritional parameters

		Immune group	Controlled group	*p*-value
Body weight (kg)	Day 1	60.1±9.1	57.1±17.3	0.54
	At discharge (Day D/C)	60.6±9.0	54.8±10.1	0.01*
Albumin (g/dL)	Day 1	2.6±0.5	2.5±0.3	0.34
	Day D/C	3.4±0.6	2.6±0.2	0.005*
Prealbumin (g/dL)	Day 1	0.209±0.03	0.214±0.02	0.66
	Day D/C	0.314±0.05	0.284±0.06	0.17*
Transferrin (mg/dL)	Day 1	204.3±9.0	205.8±8.3	0.70
	Day D/C	257.8±26.3	218.0±11.3	<0.001*

*Using ANCOVA

the leading cause of dead in inhalation injury as in major burn injury. If some intervention such as immune-enhancing enteral diet can reduce septic complication in these group of patients, it may achieve the better outcome. The future study in this aspect should be conducted.

Conclusion

Immune-enhancing diet demonstrated trend of decreasing in septic complications and the significance in maintaining body weight and increasing in albumin and transferrin level in major burn patients. It is the preferred formula diet for early enteral feeding after severe burn injury.

What is already known on this topic?

Immune-enhancing diet was proved to be benefit in trauma patients by decreasing mortality rate and their complications such as infection etc.

What this study adds?

Immune-enhancing diet trended to be benefit in septic complication in major burn patients. This formula showed the significance in maintaining body weight and increasing in albumin and transferrin level in major burn patients that demonstrate the better nutritional status.

Potential conflicts of interest

None.

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การศึกษาไปข้างหน้าแบบสุ่มมีกลุ่มควบคุมเพื่อเปรียบเทียบการให้สารอาหารกระตุ้นภูมิคุ้มกันกับสารอาหารสูตรปกติเพื่อลดภาวะการติดเชื้อในผู้ป่วยที่บาดเจ็บจากน้ำร้อนลวกหรือไฟไหม้

วัชเรศร์ เอี่ยมศิริแสงทอง, กุสุมา ชินอรุณชัย, สมพล ฤกษ์สมถวิล, จอมจักร จันทรสกุล, พรพรหม เมืองแมน

ภูมิหลัง: *จากผลของการศึกษาจากหลายงานวิจัยยืนยันถึงประโยชน์ในการช่วยลดอัตราการติดเชื้อในผู้ป่วยอุบัติเหตุที่ได้รับอาหารที่มีสารอาหารโปรตีน กรดอะมิโนกลูตามีนและอาร์จีนีนปริมาณสูง โดยการศึกษาข้างต้นทำการศึกษาในกลุ่มผู้ป่วยตัวอย่างที่เป็นผู้ป่วยอุบัติเหตุส่วนใหญ่ที่ไม่ใช่ผู้ป่วยแผลไหม้ ซึ่งการเปลี่ยนแปลงทางพยาธิสรีรวิทยาหลังการบาดเจ็บด้วยแผลไหม้ต่างจากการเปลี่ยนแปลงทางสรีรวิทยาหลังการบาดเจ็บด้วยอุบัติเหตุ ในหลาย ๆ ด้าน ดังนั้นพยาธิสรีรวิทยาที่ทำให้เกิดภาวะแทรกซ้อนที่นำไปสู่การติดเชื้อของผู้ป่วยแผลไหม้ ย่อมมีความแตกต่างจากพยาธิสรีรวิทยาที่ทำให้เกิดภาวะแทรกซ้อนที่นำไปสู่การติดเชื้อของผู้ป่วยอุบัติเหตุ อาทิเช่น ภาวะติดเชื้อที่แผลไหม้ หรือภาวะปอดอักเสบติดเชื้อที่เกิดภายหลังจากภาวะ สูดสำลักควัน (inhalation injury) ซึ่งเป็นภาวะที่พบเฉพาะในผู้ป่วยแผลไหม้เท่านั้น*

วัตถุประสงค์: *งานวิจัยเรื่องนี้มุ่งหวังศึกษาถึงประโยชน์ของการให้อาหารสูตรที่มีสารอาหารที่กระตุ้นภูมิคุ้มกัน (immune enhancing enteral diet) กับอัตราการเกิดภาวะติดเชื้อในผู้ป่วยแผลไหม้ที่มีการบาดเจ็บขนาดใหญ่ (major burn patient)*

วัสดุและวิธีการ: *งานวิจัยชนิดนี้เป็นงานวิจัยชนิด prospective randomized controlled trial ทำการศึกษาเทียบระหว่างผู้ป่วยแผลไหม้ขนาดใหญ่ 2 กลุ่มคือ กลุ่มทดลองที่ได้รับอาหารสูตรที่มีสารอาหารที่กระตุ้นภูมิคุ้มกัน กับกลุ่มควบคุมที่ได้รับอาหารสูตรปกติ*

ผลการศึกษา: *มีผู้ป่วยแผลไฟไหม้ขนาดใหญ่จำนวน 20 รายที่เข้าร่วมการวิจัยนี้ แม้ว่าผลการทดลองจะพบว่าการให้อาหารสูตรที่มีสารอาหารกระตุ้นภูมิคุ้มกันแก่ผู้ป่วยแผลไหม้ขนาดใหญ่จะไม่ช่วยลดอัตราการเกิดภาวะติดเชื้อ ($p = 0.370$) และอัตราการตาย ($p \geq 0.05$) แต่พบว่าอาหารสูตรนี้ช่วยเพิ่มน้ำหนักตัวของผู้ป่วย ($p = 0.010$) รักษาระดับอัลบูมิน ($p = 0.005$) และระดับทรานเฟอริน ($p < 0.001$) ในเลือดได้ ซึ่งอาจสามารถบ่งถึงภาวะโภชนาการที่ดีกว่าในกลุ่มทดลองที่ได้อาหารสูตรพิเศษ*

สรุป: *การให้อาหารสูตรที่มีสารอาหารที่ช่วยเสริมสร้างภูมิคุ้มกันมีแนวโน้มอาจช่วยลดอัตราการติดเชื้อในผู้ป่วยแผลไหม้ นอกจากนั้นยังพบว่าในผู้ป่วยแผลไหม้กลุ่มที่ได้รับอาหารสูตรเสริมสร้างภูมิคุ้มกันนี้สามารถเพิ่มน้ำหนักตัวของผู้ป่วย และรักษาระดับอัลบูมินและระดับทรานเฟอรินในเลือดได้ดีกว่าอย่างมีนัยสำคัญ*