Immunonutrition and Cytokine Response in Patients with Head Injury

Jiraporn Khorana MD*, Kittipan Rerkasem MD, PhD*,
Chatchawann Apichartpiyakul PhD**, Choompone Sakonwasun MD**,
Wanarak Watcharasakslip MD*, Tanat Waniyapong MD*,
Thanya Norasethtada MD*, Kaweesak Jittawatanarak MD*

** Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*
*** Department of Microbiology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*

Background: *To investigate whether short-term postoperative immunonutrients feeding can modulate the level of cytokines in patients with head injury compared to standard enteral tube feeding formula.*
Material and Method: *A randomized double-blind study was carried out on 40 moderate to severe head injury patients. They were randomized to have continuous nasogastric tube feeding within 24 hours after surgery of either the immunonutrient containing enteral formula (group A) or the standard enteral formula (group B). The level of interleukin-6 (IL-6) and 10 (IL-10) were measured on day 1 (before feeding), and subsequently on day 3 and day 5.*
Results: *Twenty patients were randomly selected in each group, who had similar severity levels of injury. Compared to the level of IL-6 on day 1, the level of IL-6 was markedly reduced on day 3 in group A ($p = 0.002$), whereas such reduction in group B was not statistically significant.*
Conclusion: *Short term postoperative immunonutrient feeding can reduce cytokine level, indicating that systemic inflammatory response syndrome might be modulated by such feeding.*

Keywords: *Craniocerebral trauma, Cytokines, Enteral nutrition, Food, Formulated*

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Head injury is a common type of trauma. Statistical data show that Thailand was ranked sixth in the world for road fatalities with more than 10,000 deaths per year because of head trauma(1). Head injury carries a high risk of post-operative morbidity and mortality(2). Extracranial infection due to immune dysfunction seems to partially explain this(3). It is hypothesized that both the activation of microglial cells and the accumulations of T-cells after crossing the blood brain barrier indicate production of pro-inflammatory mediator in the brain after injury(3). The leakage of pro-inflammatory mediators into the circulation causes immune dysfunctions such as systemic inflammatory response syndrome (SIRS) and compensatory anti-inflammatory response syndrome (CARS). These two immune responses tend to be responsible for organ dysfunction and increased susceptibility to infections respectively(4).

Interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrotic factor are the important cytokines in SIRS, whereas interleukin-10 (IL-10) is the essential cytokine in CARS(5,6). Clinicians tried to counteract these immune dysfunctions with immunonutrition (immune enhancing nutrition). Recent studies have reported that some nutritional substances such as omega-3 fatty acids, arginine, and glutamine have immunological benefits beyond their metabolic nutritional value(7). As it is indicated that the use of omega-3 fatty acids in status of volunteers resulted in less potent inflammatory prostanoids than in the control group(8,9). Arginine and glutamine have traditionally been known as nonessential amino acids, but laboratory and clinical data suggest that they may be

Correspondence to: Rerkasem K, Department of Surgery, Faculty of Medicine, Chiang Mai University, Chiang Mai 50200, Thailand. Phone: 053-945-532, Fax: 053-946-139, E-mail: krerkase@mail.med.cmu.ac.th

semiessential during critical illness such as infection and injury[10]. Moreover, glutamine is utilized at a high rate by lymphocytes and macrophages as oxidative fuel, and their proliferation depend upon glutamine concentration[11,12]. Arginine has a useful effect on cellular immunity, resulting in increase thymic size and enhanced lymphocyte proliferation[13]. Arginine seems to be essential in the regulation of the cellular immune response and the inflammatory process during critical illness[14]. Subsequently, these immuno-nutrient components have been used in various combinations in an attempt to modulate immune function in malnourished critically ill patients[15].

Chuntrasakul et al[16] conducted a randomized controlled trial (RCT) in 36 patients with severe trauma or burn patients and gave two different types of nutritional supplementations, i.e. Neomune (Thai Otsuka Company, Bangkok, Thailand) versus Traumacal (Mead Johnson) from post-operative day 2 to day 10. These two nutritional supplements have a high protein content, but Neomune also contains arginine, glutamine, and omega-3 fatty acids. They aimed to evaluate the metabolic and immune effect of these nutritional supplementations. They found that patients in the Neomune group had a higher level of total plasma protein compared to the control group (6.52 and 5.59 g/dl)[16]. The ICU stay was shorter in the Neomune than in the Traumacal group (3.41 and 7.83 days). In addition, the respirator days were also fewer in the Neomune than in the Traumacal group (2.71 and 7.39 days). They found that patients in the Neomune group had a higher level of plasma albumin, shorter intensive care unit stays, and fewer respirator days, compared to the control group[16]. Briassoulis et al carried out a RCT to compare the nutritional and inflammatory changes in children with severe head injury fed by a regular or an immune-enhancing diet. They found immune enhancing formula can decrease interleukin-8 and gastric colonization of bacteria[17]. Heyland et al reported a systematic review on the effect of immunonutrition on the outcome in critically ill patients[18]. They found that immunonutrition was associated with lower infectious complications. This is markedly lower in surgical patients than other critically ill patients[18]. Recently another systematic review reported further on effect of immunonutrition on the outcome in the subtype of critical ill patients[19]. They found that immuno-modurating diets supplemented with omega-3 fatty acids improved the outcome of medical ICU patients (with SIRS/sepsis). On the other hand, immuno-modurating diets supplemented with arginine with/without additional glutamine or FO do not appear to offer an advantage over standard enteral formulas in ICU, trauma, and burn patients. Arguments also raised against arginine supplementation in septic patients are mainly pointed at stimulating nitric oxide (NO) production, with concerns about toxicity of increased NO [20]. This might cause hemodynamic instability with refractory hypotension and increased mortality. This effect appears to be transient, when supplied as a bolus but seems without hemodynamic side effects when supplied continuously[20].

However, recent knowledge on the role of immunonutrition in influencing the cytokine response and the outcome of adult patients with head injury has not clearly been established. The objectives of the present study were to analyze the effect of an immune-enhancing diet on the cytokine change in patients with head injury (Neomune compared with standard formula).

Material and Method

A double blind randomized controlled trial in patients with head trauma comparing two high protein enteral formulas, namely Neomune and standard formula was conducted. These two formulas contain similar nutritional components, and Neomune contains immunonutrients (Table 1). Since this is the first study for such an issue, the sample size could not properly be determined. Therefore, the authors carried out a pilot study of 40 patients, which included 20 for each arms.

Subjects

Forty patients with moderate to severe head injury in Maharaj Nakorn Chiang Mai Hospital during 2006-2007 were enrolled in the present study following research ethics committee approval (012/2549). Informed consent was obtained from the patients or their relatives. The inclusion criteria were: a) age between 15-75 years, b) admission within 48 hours after traumatic event, c) Glasgow Coma Scale range between 5-10[21,22], and d) requiring neurosurgical operation and post-operative enteral nutrition. The exclusion criteria included: a) history of diabetes mellitus b) condition of hyperglycemia after operation requiring insulin treatment c) history of hepatic or renal diseases, d) history of significant abdominal injury and need for exploratory laparotomy, e) history of significant chest injury and need for thoracotomy, f) history of significant fracture and need for operative fixation, and g) history of hypotension following surgery.

Feeding protocol

Within 24 hours after neurosurgical operation, patients were randomized to receive either Neomune (Thai Otsuka company) (group A), or or high protein formula (modified Panenteral-Thai Otsuka company) (group B). Neomune is an enteral feeding supplemented with arginine, glutamine, and omega-3 fatty acids. The high protein formula was modified from the Panenteral (Thai Otsuka company) and contained protein 30 g/L to increase protein content similar to the Neomune (Table 1). The randomization was done on 1:1 basis just before the planned initiation of enteral feeding. Randomization was carried out by block randomization technique. Six blocks of four were used to generate a random sequence, which was concealed in an opaque envelop. Randomization with prepared formula masking was assigned from the manufacturer. These two products were similar in both color and taste. Neither participants nor researchers, including surgeons, recognized the type of supplement. All feeding were delivered through a nasogastric tube, initiated in the first 24 hours after the operation. The hourly amount was calculated according to the following protocol. Feeding was carried out by infusion pump. The goals for enteral feeding were increased during the first three days 50%, 80%, and eventually 100% of the predicted basal metabolic rate (PBMR). The authors continued feeding until nasogastric tube feeding was no longer needed. PBMR was estimated by the simplified formula based on age and weight using the Harris Benedict equation[23,24]. Moreover, the value was multiplied by stress-related correction factors (1.5) to estimate the corresponding predicted energy expenditure.

Patients were fed by continuous drip. During the study period, those with transient diarrhea were initially treated by decreased infusion rate and, if it persisted, by temporary discontinuation of feeding for 4 hours. Temporary elective discontinuation of feeding was allowed for planned removal of nasogastric tube. Failure was defined as the inability to follow the protocol because of persistent gastrointestinal complications or permanent discontinuation of nasogastric feeding for any reason.

Data collection

Data collection included history taking, physical examination, and laboratory measurement. Venous blood samples were taken from all patients to measure the immediate (before feeding)(Day 1), 48-hour postoperative (PO) (Day 3) and 96-hour PO(Day 5) concentrations of interleukin-6 (IL-6) and interleukin-10 (IL-10). The primary end point of the present study was the level of cytokine change before and after operation. The secondary end point was the complication rate postoperation i.e. chest infection, wound infection, urinary tract infection, gastrointestinal bleeding, and death.

Cytokine and infection indices

The concentrations of IL-6 and IL-10 were measured by using commercially available ELISA kits according to the instructions of the manufacturer

Table 1. The composition of formula

Formula	Neomune formula	Standard formula (modified Panenteral formula)
Classification	Immuno-enriched, lactose-free normal caloric, high nitrogen	Whole protein formula, MCT enriched lactose free
Protein (g/L)	62.5	56.1
Fat (g/L)	28	44
Carbohydrate (g/L)	125	94
NPC:N	75:1	86:1
Protein source (%)	Casein 70% Arginine 20% Glutamine 10%	Casein 100%
Fat source (%)	Corn oil 30% MCT 50% Fish oil 20%	Soy bean oil 52% MCT 48%

NPC = non protein calorie, n = nitrogen, MCT = medium chain triglyceride

(R&D Systems Inc., Minneapolis, USA). Inter- and intra-assay coefficients of variation were less than 10%. Nosocomial infections were required to be established. Cytokine and infection indices were compared between the two groups.

Statistical analysis

Normally distributed data is expressed as mean ± SEM, whereas abnormally distributed data are given as median and range. Student's t-test was used to compare continuous data such as cytokine levels between groups. Similarly, the paired t-test was used to compare cytokine level between day 1, day 3, and day 5 after operation. Pearson's Chi-Squared or Fisher's Exact test as appropriate for category data as analytical methods. Statistical significance was pre-determined at $p < 0.05$.

Results

There were 40 consecutive patients in the present study: 20 patients in group A and 20 patients in group B. More men (80%) than women (20%) were enrolled in the study population. The mean age was 40.9 years (range 16-75). Most patients were transferred from another hospital (92.7%), and the rest were from the emergency unit (7.3%). Sixty five percent of the patients were injured from motorcycle accidents. The mean length of intensive care stay after operation was 9.5 ± 5.0 days and the mean length of mechanical ventilator was 4.9 ± 2.0 days. No patient died. There was no statistically significant difference between the two groups in terms of baseline clinical study (Table 2). All patients were operated on within 24 hours after accidents, so all patients received the initial enteral nutrition within the first 48 hours.

The level of IL-6 and IL-10 were significantly reduced between before and after feeding in Group A compared to those in Group B (Table 3, 4) especially during day 1 to day 3 after operation. Postoperative complications seem to be lower in Group A than in Group B, but these findings were not statistically significant (Table 5). The mean duration of retained nasogastric tube in group A and group B was 5.4 and 16.8 days (p = 0.31) and the mean duration of stay in the intensive care unit was 9.6 and 9.3 days respectively (p = 0.85).

Discussion

Severe trauma is a life threatening condition among Thai youngsters, both directly and indirectly, via hypercatabolism, hypermetabolism, malnutrition, and immunologic dysfunction during subsequent clinical course[2]. Inflammatory and infectious episodes may complicate the clinical course and ultimately result in sepsis and multiple organs failure. It has been suggested that early immunomodulatory intervention strategy might reduce the early hyperinflammatory phase[25]. The present study showed that Neomune,

Table 2. Baseline clinical data

Clinical data	Group	
	A (n = 20)	B (n = 20)
Number of males/female	15/5	17/3
Mean age (yr)	40.2	41.6
Number of motorcycle accidents (%)	13 (65%)	13 (65%)
Diagnosis		
Epidural hematoma (%)	4 (20%)	4 (20%)
Subdural hematoma (%)	3 (15%)	8 (40%)
Intracerebral hematoma (%)	6 (30%)	1 (7.7%)
Median Glasgow Coma Scale	7	7
Type of operation		
Craniotomy (%)	5 (25%)	4 (20%)
Craniectomy (%)	3 (15%)	4 (20%)
Ventriculostomy (%)	10 (50%)	6 (30%)
Mean hemoglobin ± SEM (g/dl)	10.1 ± 0.50	10.0 ± 0.40
Total protein ± SEM (g/dl)	6.4 ± 0.17	6.0 ± 0.21
Albumin ± SEM (g/dl)	3.7 ± 0.11	3.6 ± 0.13
Cholesterol ± SEM (mg/dl)	157.5 ± 9.61	135.6 ± 7.15

Group A = Neomune formula group, Group B = Standard formula group, n = number, SEM = the standard error of the mean

Table 3. The mean of cytokine concentrations (piccogram/milliliter-pg/ml) during day 1, day 3 and day 5 between group A and group B

Interleukin (pg/ml)	Group A		Group B		p-value
	Mean	SEM	Mean	SEM	
IL-6					
Day 1	124.8	21.8	112.7	33.7	0.765
Day 3	67.4	12.0	96.5	26.2	0.322
Day 5	29.1	3.9	45.9	10.9	0.161
IL-10					
Day 1	24.9	6.1	19.3	5.0	0.489
Day 3	10.9	2.4	21.7	4.1	0.030
Day 5	6.0	2.7	15.4	3.7	0.091

SEM = standard error of mean, n = number

Table 4. The mean difference of cytokine concentrations (pg/ml) during period of time between group A and group B

Group	Mean difference	SEM	p-value
Group A			
IL-6 day 1-IL-6 day 3	57.4	15.8	0.002
IL-6 day 3-IL-6 day 5	19.4	10.9	0.109
IL-10 day 1-IL-10 day 3	14.0	4.7	0.008
IL-10 day 3-IL-10 day 5	3.6	3.0	0.259
Group B			
IL-6 day 1-IL-6 day 3	16.2	19.1	0.406
IL-6 day 3-IL-6 day 5	42.1	28.7	0.160
IL-10 day 1-IL-10 day 3	2.4	4.6	0.618
IL-10 day 3-IL-10 day 5	5.0	4.2	0.255

SEM = standard error of mean

Table 5. The perioperative complication rate in the two groups (percentage in parenthesis)

Complication	Group	
	A (n = 20)	B (n = 20)
Wound infection	0	0
Chest infection	7 (35%)	12 (60%)
Urinary tract infection	0	1 (5%)
Gastrointestinal bleeding	1 (5%)	0
Death	0	0

Group A = Neomune formula group, Group B = Standard formula group, n = number

an immunonutritional supplement containing arginine, glutamine, and fish oil, can reduce the level of IL-6 and IL-10 in the early postoperative period much more than those in the control group. Since IL-6 is considered a pro-inflammatory cytokine and IL-10 is an anti-inflammatory and inmmunosuppressive cytokine[5], these two immunonutritions seemed to reduce the chance of hyperinflammation and immunosuppressive event. Consequently, this may reduce the chance of SIRS and CARS[25], which will subsequently reduce the chance of organ dysfunction and sepsis respectively. This might partially explain why the rate of chest infection and the duration of retained nasogastric tube in Neommune group was tended to be less than those in the control group.

The present study also demonstrated the rate of chest infection in the Neomune group to be only half of that in the control group. Although the difference did not reach statistical significance, it still had a clinical importance. Since most chest infections following endotracheal tube must be treated in the intensive care unit, with respiratory support, and with a longer hospital stay, use many hospital care resource for treatment[26,27]. Perhaps the presented sample size was not enough to show the effect of immunonutrition on mortality, or some other hard endpoint (> 150 patients)[28] and more data from future researches on this issue are needed.

Limitation

Although there are several cytokines indices such as IL-1, IL-6, IL-8, IL-10, and tumor necrosis factor which represented the cytokines of pro-inflammatory cytokine and anti-inflammatory cytokines, but the present study could only assay only IL-6 and IL-10 due to limitation of the authors' resource. The present study is underpowered for assessment of an effect on clinical outcomes.

Conclusion

The present study showed that short term immunonutritient feeding can reduce cytokine level, so SIRS and CARS might be controlled. Further study in a large sample size is needed to show the role of immunonutrition on clinical outcome.

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Author disclosure statement

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การศึกษาผลของอาหารสูตรเพิ่มภูมิคุ้มกันในผู้ป่วยบาดเจ็บทางสมอง

จิราภรณ์ โกรานา, กิตติพันธุ์ ฤกษ์เกษม, ชัชวาลย์ อภิชาตปิยกุล, ชุมพล สกลวสันต์, วนรักษ์ วัชรศักดิ์ศิลป์, ธนัฐ วานิยะพงศ์, ธัญญา นรเศรษฐ์ธาดา, กวีศักดิ์ จิตตวัฒนรัตน์

ภูมิหลัง: *ผลของอาหารสูตรเพิ่มภูมิคุ้มกันในผู้ป่วยบาดเจ็บทางสมองในผู้ใหญ่ยังไม่มีข้อมูล การศึกษานี้มีจุดประสงค์ว่า การให้สูตรอาหารเพิ่มภูมิคุ้มกันเปรียบเทียบกับสูตรอาหารทางสายยางที่ใช้ในปัจจุบันจะสามารถลดระดับ cytokine ในผู้ป่วยประเภทนี้ได้หรือไม่*

วัสดุและวิธีการ: *เป็นการศึกษาแบบสุ่มและปิดบังรหัส(double blind)ในผู้ป่วยที่บาดเจ็บทางสมองระดับปานกลางจนถึงรุนแรง มีผู้ป่วยอยู่ในการศึกษากลุ่มละ 20 คน ผู้ป่วยจะได้รับอาหารทางสายยางอยู่ 1 ใน 2 ประเภทภายใน 24 ชั่วโมงหลังจากผ่าตัดสมองคือประเภทแรก, สูตรอาหารเพิ่มภูมิคุ้มกัน (Neomune) (กลุ่ม ก) หรือ ประเภทที่ 2, สูตรอาหารที่ใช้เป็นมาตรฐานทั่วไป (modified Panenteral) (กลุ่ม ข) โดยในช่วงหลังผ่าตัดได้ทำการวัดระดับ interleukin-6 (IL-6) และ 10 (IL-10) วันก่อนให้อาหารและ ในวันที่ 3 และ 5 หลังจากเริ่มให้อาหาร*

ผลการศึกษา: *ผู้ป่วยทั้งสองกลุ่มไม่พบความแตกต่างกันทางระดับความรุนแรงของการบาดเจ็บ จากผลการตรวจระดับของ IL-6 พบว่าลดลงในทั้งสองกลุ่ม โดยที่กลุ่ม ก ที่ได้รับอาหารสูตรอาหารเพิ่มภูมิคุ้มกัน ระดับ IL-6 จะลดอย่างมีนัยสำคัญทางสถิติในวันที่ 3 เมื่อเทียบกับระดับ IL-6 ก่อนผ่าตัด (p = 0.002) ในขณะที่กลุ่ม ข ลดลง แต่ไม่มีนัยสำคัญทางสถิติ*

สรุป: *อาหารสูตรเพิ่มภูมิคุ้มกัน (Neomune) สามารถลดระดับ cytokine ได้ ซึ่งบ่งว่า กลุ่มอาการ systemic inflammatory response syndrome อาจจะสามารถควบคุมได้โดยสูตรอาหารประเภทนี้ ซึ่งต้องการการศึกษาในกลุ่มที่ใหญ่ขึ้นเพื่อยืนยันผลต่อไป*