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Effect of enteral nutrition with eicosapentaenoic and gamma-linolenic acids for preventing pressure ulcers in patients after neurosurgery

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SUMMARY

Background & aims: To explore the effect of enteral diets enriched with eicosapentaenoic acid (EPA) and gamma-linolenic acid (GLA) in the prevention of pressure ulcer formation and improving the outcomes of post-neurosurgical patients.
Methods: The prospective, randomized, controlled study was conducted in the department of neurosurgery of university-affiliated hospital. A total of 19 patients who have undergone neurosurgery for serious neurological conditions, were randomly assigned to two groups; one with a diet enriched with EPA・GLA, another with an isonitrogenous and isocaloric control diet, delivered for a minimum of 4 days and monitored for 14 days.
Results: Only a single new pressure ulcer was observed on day 7 in the EPA・GLA enriched diet group, showing apparently lower incidence of pressure ulcer compared to the control group, in which 2 lesions on day 4, 3 lesions on day 7 and 4 lesions on day 14 were observed. Those who received the study diet experienced significantly improved outcomes due to reduced incidence of new pressure ulcers.
Conclusions: Enteral diets enriched with EPA・GLA contributed to preventing pressure ulcers in patients after neurosurgery. The beneficial effect of the EPA・GLA diets was associated with a lower occurrence of new pressure ulcers in the clinical nutrition management of neurosurgical outcomes.

Key words：eicosapentaenoic acid, gamma-linolenic acid, enteral nutrition, pressure ulcer, decubitus

1. Introduction

Fatty acids are used not only as a source of energy and as a component of cell membranes, but also as physiologically active substances having anti-inflammatory effects within living organisms.[1] Fatty acids are classified by the presence or absence of a double bond (i.e. saturated or unsaturated) and by the length of chain (carbon number). Unlike mono-unsaturated fatty acids which have one double bond, polyunsaturated fatty acids which have two or more double bonds, need to be ingested as essential fatty acids, since they are not biosynthetically prepared in the human body. Polyunsaturated fatty acids are roughly

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divided into the categories n-3 and n-6, depending on whether a double bond appears on the third carbon atom or the sixth respectively, counting from the end where the methyl group is located. The former transforms from alpha-linolenic acid to eicosapentaenoic acid (EPA), and the latter transforms from linoleic acid to gamma-linolenic acid (GLA) and arachidonic acid.[2, 3]

EPA and GLA respectively have an anti-inflammatory effect, inhibiting the production of inflammatory eicosanoid.[4~6] Furthermore, EPA is known to reduce inflammatory mediators by competing with arachidonic acid.[7~10] In addition, GLA is reported to have a role in promoting the production of prostaglandin E_1 and improving blood flow.[11, 12]

In many cases of severely impaired consciousness, patients have to go through neurosurgery under general anesthesia for several hours, and are at risk of pressure ulcers due to long-term bed rest during pre-, intra- and post-operative duration, which limits changes in position. If pressure ulcers could be prevented by feeding an enteral diet enriched with EPA and GLA, which is highly likely to reduce symptoms such as inflammation, diminished blood flow and malnutrition leading to the occurrence of pressure ulcers, it can be supposed that this diet might make a great contribution to the improvement of many aspects of nursing-care and reduction of the costs. Because it could alleviate the burden placed on patients, reduce the burden placed on nursing and care staff, and in addition decrease the burden of medical expenses. In this study, therefore, we explored the effect of enteral nutrition enriched with these polyunsaturated fatty acids to prevent the occurrence of pressure ulcers in order to establish a method of proper nutritional management for perioperative duration.

2. Materials and methods

2.1. Subjects

The inclusion criteria were as follows;

1) Patients who have severely impaired consciousness after neurosurgery at a level of 8 or less on the Glasgow Coma Scale (GCS)[13] **(Table 1)**.
2) Patients who are required to undergo bed rest for 4 days or more after neurosurgery.
3) Patients suited to post-operative enteral diets.
4) Both male and female patients whose ages were 20 or more years.
5) Patients for whom written informed consent could be obtained from the patient themselves or their legal guardians.

The exclusion criteria were as follows;

1) Pregnant or breast-feeding female patients.
2) Patients under 20 years of age.
3) Patients with low life expectancy (less than 28 days due to chronic or terminal diseases such as unmanaged cancers).
4) Patients with uncontrolled diabetes.
5) Patients unsuitable for enteral nutrition.
6) Patients with acute nephritis, nephrosis, renal failure, hepatic disorder or similar conditions requiring strict restriction of proteins and electrolytes.
7) Patients unsuitable for enteral nutrition due to ileus or absence of residual function of intestinal tract.
8) Patients with moderate to severe neutropenia (WBC count <1000 cells/mm^3).
9) Patients with hyperlipidemia (TG>500 mg/dl, T-Cho>300 mg/dl).
10) Patients showing obvious gastrointestinal bleeding.
11) Patients with uncontrolled diarrhea.
12) Patients with congenital disorders of amino acid

Table 1
Glasgow Coma Scale (GCS)

Parameters	Scales
Best eye response (4-point scale)	1. No eye opening 2. Eye opening to pain 3. Eye opening to verbal command 4. Eyes open spontaneously
Best verbal response (5-point scale)	1. No verbal response 2. Incomprehensible sounds 3. Inappropriate words 4. Confused 5. Orientated
Best motor response (6-point scale)	1. No motor response 2. Extension to pain 3. Flexion to pain 4. Withdrawal from pain 5. Localising pain 6. Obeys Commands

The GCS is scored between 3 and 15, 3 being the worst, and 15 the best. It is composed of three parameters: best eye response (E), best verbal response (V), best motor response (M), as given above.

Note that the phrase 'GCS of 11' is essentially meaningless, and it is important to break the figure down into its components, such as E3V3M5 = GCS 11. A GCS of 13 or higher correlates with a mild brain injury, 9 to 12 is a moderate injury and 8 or less a severe brain injury.

metabolism.

13) Patients with heart failure associated with nausea, vomiting and diarrhea.
14) Patients with an allergy to the ingredients contained in the enteral diets used.
15) Patients who had participated in other clinical trials within the previous 30 days of the registration to this study.
16) Patients taking steroids.
17) Patients judged unsuitable for this study by the researchers for reasons not covered above.

2.2. Study design

The study was conducted as a prospective randomized controlled trial. Patients showing critically impaired consciousness with GCS scores of 8 or less for whom four or more days of post-operative bed rest had been prescribed were randomly allocated into two groups: one to be given the enteral diet enriched with EPA・GLA, and the other to be fed with an isonitrogenous and isocaloric control diet. All patients were evaluated regarding the incidence frequency of pressure ulcers based on DESIGN-R[14] **(Fig. 1)**. As for treatments and nursing-care other than nutritional care,

DESIGN-R assessment of progression towards healing

Chart number:
Name of patient:

					Date	/	/	/	/	/	/
Depth: this shoud be measured at the deepest point of the wound. If the wound becomes shallower, the decreased depth should be reflected in the assessment											
d	**0**	No particular skin lesion and no redness	**D**	**3**	Lesion extends into the subcutanecous tissue						
	1	Persistent redness		**4**	Lesion extends to muscle, tendon and bone						
	2	Lesion extends into dermis		**5**	Lesion extends into the articular or body cavity						
				U	It is impossible to measure the depth						
Exudate:amount											
e	**0**	None	**E**	**6**	Heavy: requires dressing change more than twice a day						
	1	Slight: dose not require daily dressing change									
	3	Moderate: requires daily dressing change									
Size: the area of a skin injury(length×width). Longest measurement in the wound is length; width is longest measurement perpendicular to that axis											
s	**0**	None	**S**	**15**	100 cm² or lager						
	3	Smaller than 4 cm²									
	6	4 cm² or lager, but smaller than 16 cm²									
	8	16 cm² or lager, but smaller than 36 cm²									
	9	36 cm² or lager, but smaller than 64 cm²									
	12	64 cm² or lager, but smaller than 100 cm²									
Inflammation/Infection:											
i	**0**	None	**I**	**3**	Clear signs of local infection (eg, inflammation, pus and foul smell)						
	1	Signs of inflammation (fever, redness, swelling, and pain around the wound)		**9**	Systemic impact, such as fever						
Granulation tissue: percentage of healthy granulation											
g	**0**	Granulation cannot be assessed because the wound is healed or too shallow	**G**	**4**	Healthy granulation tissue occupies 10% or more, but less than 50%						
	1	Healthy granulation tissue occupies 90% or more		**5**	Healthy granulation tissue occupies less than 10%						
	3	Healthy granulation tissue occupies 50% or more, but less than 90%		**6**	No healthy granulation tissuse exists						
Necrotic tissue: when necrotic and non-necrotic tissues are mixed, the dominating condition should be used for assessment											
n	**0**	None	**N**	**3**	Soft necrotic tissue exists						
				6	Hard and thick necrotic tissue is attached to the wound						
Pocket: the area obtained by subtracting the uleer from the entire affected area, including the pocket											
p	**0**	None	**P**	**6**	Smaller than 4 cm²						
				9	4 cm² or larger, but smaller than 16 cm²						
				12	16 cm² or larger, but smaller than 36 cm²						
				24	36 cm² or larger						
Region [sacrum, ischium, trochanter, calcanum, heel, other region]					Total						

Fig 1
The DESIGN-R evaluation sheet: An absolute evaluation tool for monitoring pressure ulcer wound healing

the hospital’s standard care protocols based on each patient's individual condition were adopted.

2.3. Administration

Administration started with the administration of enteral nutrition (300-400 Kcal/dose) via tube at low speed in the early post-operative stages (within 24 hours), gradually increasing the injection speed as appropriate by checking the tolerance so that the target energy intake quantity of standard body weight (in kg) x 30 Kcal/day could be achieved via enteral diet. The terminal end of the enteral feeding tube was inserted into the stomach. Although in principle the dose regimen was continuous enteral feeding, switching to intermittent feeding in conjunction with the monitoring of digestive system symptoms was also allowed. Feeding was continued for a minimum of four days, while monitoring continued for 14 days. The study was

Table 2
Baseline demographic and clinical characteristics of the two groups

Characteristic	Control diet (n=7)	EPA・GLA enriched diet (n=12)
Age	67.7±11.0	65.8±9.6
Gender Male	5	7
Female	2	5
Type of enteral feeding	Gastric 7	Gastric 12
Admission weight (Kg)	61.8±4.5	60.8±2.9
GCS	7.3±1.5	7.2±1.8
Serum albumin (g/l)	3.8±0.4	3.6±0.4

EPA: eicosapentaenoic acid, GLA: gamma-linolenic acid, GCS: Glasgow Coma Scale

completed when, after the resumption of oral feeding, the energy intake from enteral feeding dropped to 75% or less of the patient's total energy requirement. The use of transfusion was limited as much as possible for the correct evaluation of the enteral diets effects, and use of fat emulsion was contraindicated.

2.4. Number of patients

In total 19 patients were enrolled in this study, including 12 patients placed in the EPA・GLA enriched diet group and 9 patients in the control group. Ages ranged from 49 to 86 years of age, with the average age being 67.3 years of age. The ratio of male to female patients was 12:7. The breakdown of the patients by neurosurgical disease was as follows: 10 cases of subarachnoid hemorrhage (52.6%), 5 cases of intra-cerebral hemorrhage (26.3%), 2 cases of acute subdural hemorrhage (10.5%), 1 case of acute epidural hemorrhage (5.3%) and 1 case of cerebral thrombosis (5.3%).

2.5. Endpoints

1) Primary endpoint: Number of newly-developed pressure ulcers per day (counting ulcers with d1 or higher score according to assessment by DESIGN-R).

2) Secondary endpoints: Adverse events and laboratory abnormalities.

2.6. Ethical considerations

Prior to the study, the approval was obtained from the Institutional Review Board of Juntendo University, Faculty of Health Science and Nursing (Approval Code: 22005) and the Ethical Review Board of Juntendo University Shizuoka Hospital (Approval Code: 22.302). The study was performed in conformity with “Ethical Guidelines for Clinical Research” compiled by the Ministry of Health, Labor and Welfare[15] and “Helsinki Declaration”.[16] In addition, it was made clear to patients or their legal guardians that the enteral diet to be used as a control was a fluid diet containing a wide variety of balanced nutritional ingredients necessary to post-operative recovery and in general use, and that it would not cause any significant problems for the control group. Then, written consent was obtained for voluntary enrollment in the study from each patient or

Table 3
Composition of the enteral diets

Nutrient	Control diet	EPA・GLA enriched diet
Protein		
% of total calories	18.0	16.7
g/l	45.0	62.5
Carbohydrate		
% of total calories	56.8	28.2
g/l	142.0	106.0
Lipids		
% of total calories	25.2	55.1
g/l	28.0	93.7
n-6:n-3	3:1	1.6:1
n-3 (g/l)	0.2	10.0
EPA (g/l)	0	5.1
GLA (g/l)	0	4.1
DHA (g/l)	0	2.2
Vitamins		
Vitamin E (IU/l)	6	320
Vitamin C(mg/l)	90	840
B-carotene (mg/l)	780	672
Vitamin A (IU/l)	1830	4710
Vitamin D (IU/l)	160	430
Vitamin K1 (μg/l)	63	40
Folic acid (μg/l)	200	420
Thiamine (mg/l)	1.0	3.2
Riboflavin (mg/l)	1.0	3.6
Vitamin B6 (mg/l)	1.0	4.3
Vitamin B12 (mg/l)	2.0	6.0
Niacin (mg/l)	13	29
Biotin (μg/l)	38	6.0
Panthothenic acid	5	13
Trace minerals		
Na (mg/l)	1850	1310
K (mg/l)	1300	1960
Cl (mg/l)	800	1690
Ca (mg/l)	650	1060
P (mg/l)	550	1000
Mg (mg/l)	260	320
Cu (mg/l)	0.7	2.2
Zn (mg/l)	7.0	18
Fe (mg/l)	8.0	20
Se (μg/l)	250	160
Osmolarity (mOsm/l)	380	384

EPA: eicosapentaenoic acid, GLA: gamma-linolenic acid, DHA: docosahexaenoic acid

Table 4
Pressure ulcer status in the control diet and EPA・GLA enriched diet groups

Pressure ulcer status	Baseline		Day 4		Day 7		Day 14	
	Control	EPA・GLA	Control	EPA・GLA	Control	EPA・GLA	Control	EPA・GLA
Pressure ulcer total number	0	0	2	0	3	1	4	0
DESIGN-R			d1:2		d1:3	d1:1	d1:3 d2:1	
Pressure ulcer total number	0	0	2	0	3	1	4	0
Worse					1		1	
No change			2		2		3	
Recover						1		

The control diet (control) and EPA・GLA enriched diet (EPA・GLA) groups included 7 and 12 patients, respectively.
EPA: eicosapentaenoic acid, GLA: gamma-linolenic acid

his/her legal guardian prior to the study initiation.

3. Results

The study was performed after obtaining informed consent from 19 patients **(Table 2)**. **Table 3** shows the detailed composition of the enteral diets that were used for the EPA・GLA enriched diet group of 12 patients and the control diet group of 7 patients, respectively. The EPA・GLA enriched enteral diet contained 5.1g/liter of EPA and 4.1g/liter of GLA, while the control diet contained neither EPA nor GLA. There were no changes in other contents and the target amount of energy to be given throughout the study duration. No surgical procedures were required for suppuration or other symptoms during the feeding period. In addition, there were no cases of discontinuation due to adverse events during the course of this study.

Regarding new occurrence of pressure ulcers, only a single lesion was observed on day 7 in the EPA・GLA enriched diet group, showing apparently lower incidence of pressure ulcer compared to the control group, in which 2 lesions on day 4, 3 lesions on day 7 and 4 lesions on day 14 were observed **(Table 4)**. This was considered to be the evidence for the preventive effect of EPA・GLA enriched diet on pressure ulcers. Investigation on changes in CRP, an inflammatory index, showed more significant suppression of inflammation in the EPA・GLA enriched diet group when compared to the control group (t-test, $p<0.05$) **(Fig. 2)**. Based on this, it was suggested that the development of new pressure ulcers was prevented by the suppression of inflammation.

There were no remarkable changes of body weight and BMI in either of the two groups. Although transferrin, retinol-binding protein and prealbumin, indexes of nutrition levels, showed a mild increase after starting the enteral diets in both groups, there was no significant difference between the two groups. The absence of significant difference in these nutritional indexes between the two groups made it clear that enteral diets enriched with EPA・GLA, which can control the inflammation, are more effective than other diets without EPA・GLA.

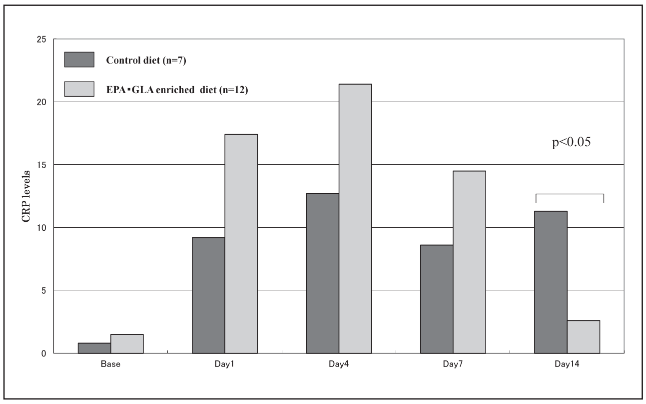

Fig 2

Improvement of CRP level of patients fed EPA・GLA enriched diet when compared to patients receiving control diet.
CRP: C-reactive protein, EPA: eicosapentaenoic acid, GLA: gamma-linolenic acid

4. Discussion

At present there is no accurate data on the incidence or frequency of pressure ulcers in patients after neurosurgical operation. Since many cases of patients with severely impaired consciousness for having neurosurgery are placed in the situation of general anesthesia for several hours, it is known that they are quite vulnerable to development of pressure ulcers. Therefore, it is important to swiftly take preventive measures for pressure ulcers. To date, although there have been some research reports regarding the prevention with nursing care or appropriate care for the ulcer pressure,[17] most of which recommend supplying energy, protein, vitamins and minerals as nutrition therapy based on the evidence. In the past, the widely prevailing attitude in the medical and nursing practice was that patients should lose weight to prevent pressure ulcers, since weight gain would lead to the elevation of compression force.[18] Recently, however, it was found that caloric restriction sufficient to cause weight loss actually increases the incidence of pressure ulcers. It has thus become essential to provide patients with nutritional care and appropriate administration of sufficient nutrition, targeting the prevention and treatment of pressure ulcers as the nutrition management.[19]

Regarding the prevention of pressure ulcers with nutritional therapy, the previous key studies showing the effects of nutritional therapy included the patients with fracture of the femur,[20] fracture of the pelvis[21] and various severe diseases.[22] All of those studies had positive outcomes of lower incidence of pressure ulcer in the study groups with nutrition-enriched diets than in the groups without such a diet. In addition, researchers of those reports on whether recovery from pressure ulcers would be promoted by implementing diets enriched with ascorbic acid,[23] protein[24] and zinc[25] only recognized the improvement of circulatory deficit and tissue repair. But Theilla et al. reported lower incidence of new pressure ulcer in the control group only when patients were given a dietary fluid that was specifically enriched with fatty acids but had equal levels of energy, protein, vitamins and minerals, and suggested that the suppression of inflammation by fatty acids might contribute to the lower incidence of new pressure ulcers.[26]

Further evidence confirming the anti-inflammatory effects of EPA・GLA-enriched enteral diets can be seen [27-30] when comparing the groups using EPA・GLA-enriched enteral diets with the other groups using nutrition diets of standard composition, in the patients with acute respiratory distress syndrome (ARDS), severe acute lung injury (ALI) and sepsis, it became clear that length of stay in ICU, length of artificial respiratory management, organ failure and also mortality rate were decreased in the groups using EPA・GLA-enriched enteral diets.

It has been believed that inflammation and low nutrition contribute to the formation of pressure ulcers.[31] The results of our study showed that EPA・GLA-enriched enteral diets suppressed inflammation and improved low nutrition and had an effect which prevented the formation of pressure ulcers. Pressure ulcers, once developed, will not only inflict suffering on patients themselves but also impose a heavy burden on nursing and care staff. Therefore, it is clear that there are high values in preventing pressure ulcers.

Recently the work of the NST (Nutrition Support Team) has been enhanced, and a framework of support systems for patients requiring tube feeding with enteral nutrition is being built by requesting the understanding of doctors and nurses so that optimal nutrition management can be provided, such as proper timing of the start of therapy, dosage adjustment, safe methods of administration to prevent aspiration pneumonia and management of the defecation. However, it is true that there are many cases where difficulty in feeding sufficiently due to lack of appetite, gastrointestinal symptoms and more, in some patients, causes poorer nutritional status than in their state prior to hospitalization. Particularly in post-neurosurgery patients there are many cases where it is difficult to simultaneously put into practice protocols to prevent pressure ulcers and follow manuals for nutrition management. On the other hand, pressure ulcers that develop despite nursing care given according to protocol, it is necessary to look for other options different from conventional care. Since our study clarified that a proper choice of enteral diet would contribute to the prevention of pressure ulcers in hospital wards and in further improvement of care, and make it possible to save hours of nursing care, we consider it easy to implement this nutritional management in medical and nursing areas of practical care.

5. Conclusions

Along with the recent remarkable improvements in nursing and care skills, it has been reported that the incidence of pressure ulcers in hospitals has decreased by utilization of nursing protocols for prevention of pressure ulcers and proper nursing and care products.

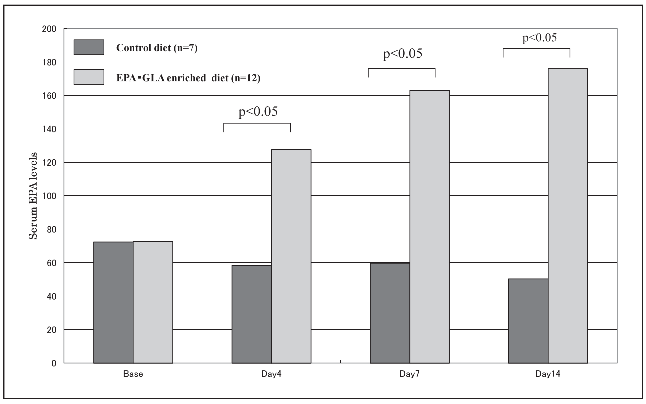

Fig 3
Serum EPA level of patients fed EPA・GLA enriched diet when compared to patients receiving control diet.EPA: eicosapentaenoic acid, GLA: gamma-linolenic acid

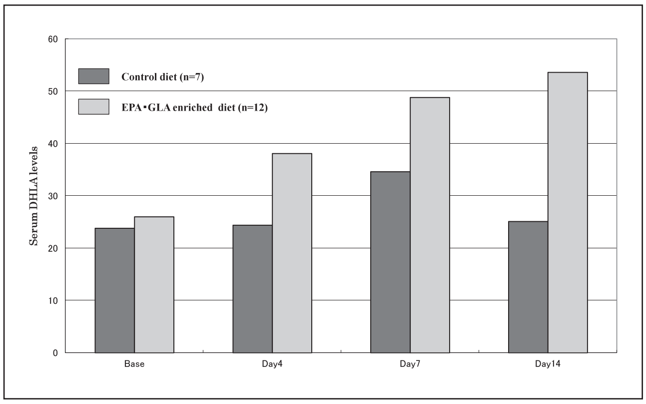

Fig 4
Serum DHLA level of patients fed EPA・GLA enriched diet when compared to patients receiving control diet.
DHLA: dihomo-gamma-linolenic acid, EPA: eicosapentaenoic acid, GLA: gamma-linolenic acid

We do, however, think that those pressure ulcers that develop in spite of proper nursing and care require an approach mediated by other factors than nursing and care, and that nutritional management should play its part. It was considered that nutritional management using EPA・GLA-enriched enteral diets could be a useful option for pressure ulcer prevention in patients who need long-term immobile bed rest in a supine position, as with post-neurosurgical patients.

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