EFFECTIVENESS AND SAFETY OF PARENTERAL NUTRITION IN CRITICALLY ILL PATIENTS WITH INTRACRANIAL HEMORRHAGE

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BACKGROUND The hypercatabolism syndrome may occur in critically ill patients after the intracranial hemorrhage. Mixed enteral and parenteral nutrition is used to provide nutrition support.

MATERIAL AND METHODS We observed 20 patients with intracranial hemorrhage and consciousness score up to 13 (the Glasgow Coma Scale) in the early postoperative period.

RESULTS Administration of parenteral mixture ("three-in-one") was followed by the progressive growth of transferrin concentration and did not lead to the significant increase of triglycerides concentration in the blood serum. We also noted that the parenteral nutrition lead to the increase of malonedialdehyde (MDA) in the blood serum above normal levels, but the total serum antioxidant activity was normal.

CONCLUSION The 3-component mixture that contains polyunsaturated fatty acids omega 6/omega 3 — 2.5:1 and olive oil, administered to critically ill patients after intracranial hemorrhage, improves protein metabolism indicators and sustains lipid peroxidation and antioxidant activity in the blood serum.

Keywords: intracranial hemorrhage, craniocerebral injury, parenteral nutrition.

ALV – artificial lung ventilation
AOS – antioxidant system
AVM – arteriovenous malformation
EN – enteral nutrition
EN-PN – enteral and parenteral nutrition
ICH – intracranial hemorrhage
LPO – lipid peroxidation
MDA – malondialdehyde
PaO_2/FiO_2 – oxygen tension in arterial blood/oxygen fraction in gas mixture
PN – parenteral nutrition
TAABS – total antioxidant activity of blood serum
TBI – traumatic brain injury
TF – transferrin
TG – triglycerides

INTRODUCTION

In critical patients with intracranial hemorrhages (ICH), hypercatabolism syndrome develops, which is characterized by disregulatory changes in "anabolism-catabolism" — growing demand for energy donator, constructive material, and energy, developing abnormal tolerance of body tissues to ordinary nutrients. As a result, in patients with ICH, severe forms of protein-energy malnutrition develop, accompanied by a significant increase in complications and mortality [1-3]. Thus, in patients with severe traumatic brain injury (TBI), reduction of energy value of introduced artificial feeding by 10 kcal/kg per day, is accompanied by an increase in mortality by 30-40% and the delayed initiation of nutrition support (on day 5 or 7 after trauma) leads to an increase in mortality by 2 and 4 times, respectively [4, 5]. The exact timing and severity of hypercatabolism syndrome in the early postoperative period in patients with ICH have not been finally determined. Nitrogen losses in these patients may be as high as 30 g per day (180-200 g of protein, or 750 g or muscle mass) or more, and the severity of catabolism significantly differs between patients with different extent and type of brain lesions.

One of the main ways to treat hypercatabolism syndrome is artificial feeding, ensuring the patient's energy needs and nutrient substrates. Mixed parenteral and

enteral nutrition (EN-PN) is often used to provide energy needs of patients. Modern three-component mixtures for parenteral nutrition (PN) include all the necessary nutrients and components of the immune power.

However, the problem of digestibility and safety of PN in critical patients with remains relevant.

The aim of our study was to evaluate the effectiveness and safety of PN as a component of mixed EN-PN, including the impact on parameters of oxidative stress in the early postoperative period in patients with ICH.

MATERIAL AND METHODS

We examined 20 patients with ICH and 13 points or less according to Glasgow Coma Scale in the early postoperative period. The average age of patients was 46.8±10 years. There were 13 (65%) male patients and 7 (35%) female patients. Two patients (10%) had severe traumatic brain injury, 13 (65%) patients had subarachnoid hemorrhage due to the rupture of an arterial aneurysm of the brain, 3 (15%) patients had hemorrhagic stroke, and 2 (10%) patients had the rupture of arteriovenous malformation (AVM) of the brain.

All patients in the acute period of ICH underwent surgeries: exclusion of aneurysm from the blood flow in patients with an aneurysm rupture, removal of intracranial hematomas and foci of brain contusion-crush in patients with severe traumatic brain injury, removal of intracerebral hematoma in patients with hemorrhagic stroke, excision of AVM in patients with AVM rupture. Of 20 cases, 10 patients died.

The standard intensive therapy was performed in the postoperative period. Upon initiation of the study, 3 patients (15%) breathed independently, in 17 patients (85%) artificial lung ventilation (ALV) was performed.

Enteral nutrition (EN) was started in all patients on the 1st day of the postoperative period. In connection with the impossibility of providing adequate nutritional support using only EN, we added PN in all patients at different times of the postoperative period which was initiated on day 4 (3;5) of the postoperative period. To assess the degree of catabolism, we analyzed the nitrogen balance.

The protein need was calculated according to the formula: protein needs (g)=(nitrogen excretion in urine (g)+4 g (extrarenal losses))×6.25.

The energy need was calculated according to the formula: nitrogen excretion in urine (g)×160 Kcal/day.

For PN we used a 3-component mixture SmofKabiven (Fresenius Kabi) in volume of 1.477 ml (infusion rate 82 ml/h, while the infusion rate of the fat emulsion was 0.03 g/kg/h) or 1.970 ml (infusion rate 109 ml/h, while the infusion rate of the fat emulsion was 0.04 g/kg/h). SmofKabiven 3-component mixture included SmofLipid fat emulsion, which contains 30% soybean oil, 30% medium-chain triglycerides (TG) 25% olive oil (alpha-tocopherol), 15% fish oil. The ratio omega-6/omega-3 fatty acids is 2.5:1.

The emulsion had been administered for 18 hours (11:30 am-05:30 am), then there was a 6-hour interval (05:30 am-11:30 am).

The duration of PN was 7 (4; 10) days. We discontinued PN due to septic shock development in 4 patients, progressive multiple organ failure in one patient, and in 5 patients – due to severe hemodynamic instability in the background of increasing doses of

intravenously administered sympathomimetics and increase of osmolarity above the allowable values in blood plasma. In 10 patients, we discontinued PN as the degree of catabolism had fallen and the proper artificial nutrition had become possible using only EN.

From day 1 to day 10 of EN-PN we studied changes of nitrogen excretion in urine, transferrin concentration in blood serum, concentration of total protein, albumin, urea, triglycerides, glucose in blood serum, ratio of oxygen tension in the arterial blood to the oxygen fraction in the gas mixture (PaO_2/FiO_2).

Total protein concentration in blood serum was determined by biuret, concentration of TG – by peroxidase method, glucose – by hexokinase method, albumin concentration was measured photometrically using bromocresol green and biochemical analyzer *Olympus AU2700* (Beckman Coulter, USA). Ultraviolet kinetic determination of urea in blood serum (urease test) was also performed with the biochemical analyzer *Olympus AU2700* (Beckman Coulter, USA).

The concentration of triglycerides and the ratio of PaO_2/FiO_2 was determined 4 times a day as follows:

- point 1 — prior to EN-PN (11:00 am-11:30 am);
- point 2 — 2 hours after the beginning of EN-PN (01:30 pm);
- point 3 — 12 hours after the beginning of EN-PN (11:30 pm);
- point 4 — 18 hours after the beginning of EN-PN (05:00 am-05:30 am).

To assess the degree of oxidative stress we measured concentration of lipid peroxidation (LPO) and antioxidant system (AOS) products in blood on day 1,3,5,7, and 10 of the research prior to EN-PN (point 1). Concentration of lipid peroxidation products was studied according to the level of malondialdehyde (MDA) in blood serum, which was measured by the method of V.B. Gavrilov [6]. AOS status was evaluated according to the total antioxidant activity of blood serum (TAABS), which was measured with photometric method by biochemical analyzer *Olympus AU270* (Beckman Coulter, USA) using reagents *Randox* (United Kingdom). To determine boundaries of normal values of the studied parameters, we examined 25 healthy people of mean age 32.7±8.6 years, the ratio *male/female* was 17/8.

STATISTICAL ANALYSIS OF RESULTS

Statistical data processing was performed using the standard package of *Microsoft Office Excel* software and *StatSoft STATISTICA* 10. The findings are presented in the format M± ∫ (M — arithmetic mean, ∫ — standard deviation) for "normal" distribution and Median format (25 and 75% percentiles) for "abnormal" distribution. We used non-parametric methods of statistical analysis. Evaluation of intragroup differences were performed using the Wilcoxon test. Intergroup comparisons were performed by Mann-Whitney test. Differences were considered statistically significant at a significance level criterion $p<0.05$.

RESULTS

At the beginning of EN-PN all patients had expressed protein catabolism (Fig. 1).

The concentration of transferrin (TF) measured before the start of EN-PN was 1.52 (1.32; 1.66) g/l. In 19 of 20 patients with ICH at the beginning of EN-PN transferrin concentration was below the normal value. On day 1-5 of observation, the TF level slightly decreased, a gradual increase in TF concentration was observed on day 7, indicating the improvement in protein-energy status of patients (Table. 1).

Table 1

Changes of TF concentration in patients upon EN-PN

Indicators (normal 2.1-3.6 g/l)	Time after initiation of EN-PN (days)				
	1	3	5	7	10
Concentration of TF, g/l	1.52 (1.32; 1.66)	1.38 (1.26; 1.53)	1.38 (1.34; 1.49)	1.51 (1.24; 1.62)	1.51 (1.46; 1.72)

Notes: EN-PN – enteral and parenteral nutrition; TF – transferrin

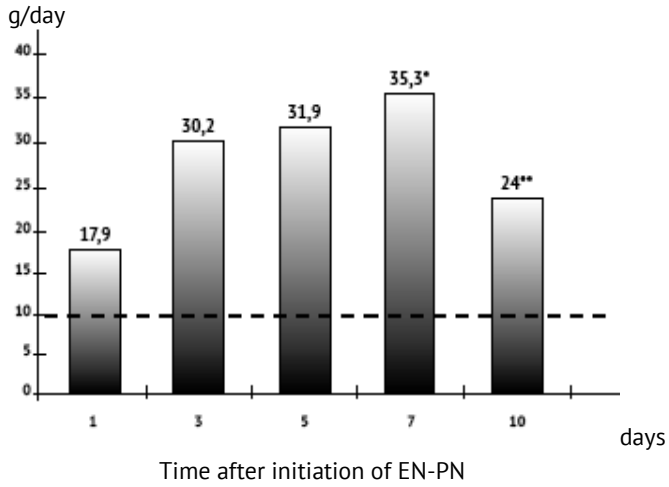

Fig. 1. Changes of nitrogen excretion in urine at different times of EN-PN (the dashed line marks the level of nitrogen excretion 10 g/day. The exceedance over this value shows the development of expressed *hypercatabolism)* (n = 25)

Notes: * — $p<0.05$ compared to the 1st day of EN-PN; ** — $p<0.05$ compared to the 7th day of EN-PN. EN-PN — enteral and parenteral nutrition

Despite the large volume of administered protein (1.5-2 g/kg of the body weight), the need for that was extremely high. So, we have noted an increase in the protein deficit from the 1st to 5th day of EN-PN. On the 5th day of observation the protein deficit was the highest and amounted to -83.4 (-117.0; 4.0) g/day ($p<0.05$ compared to the 1st day of study) (Table 2). Only on the 10th day after initiation of EN-PN, the amount of infused protein became sufficient to provide a zero nitrogen balance.

Table 2

Changes of indicators of protein and energy metabolism in examined patients

Timing of EN-PN (days)	Number of patients	Параметры				
		Nitrogen loss, g/day	Need for protein, g/day	Infused protein, g/day	Protein deficit, g/day	Infused, kcal/day
1	20	17.9 (14.5; 21.4)	111.9 (91.3; 133.5)	153.8 (135; 160)	53.8 (4.1; 64.2)	3,400 (3,100; 3,700)
2	20	–	–	145 (127; 178.2)		3,475 (3,025; 3,756)
3	19	30.2 (19.0; 32.3)	188.6 (118.7; 201.7)	140 (123; 177.8)	−41.1 (−58.1;47.1)	3,550 (2,800; 3,850)
4	15	–	–	142 (123; 160.8)		3,100 (2,800; 3,775)
5	14	31.9 (23.7; 38.6)	210.9 (148.4; 246.7)	142 (118.1; 158.6)	−83.4 (−117; 4)*	2,900 (2,688; 3,700)
6	12	–	–	160.3 (142; 177.3)		3,400 (3,050; 3,850)
7	10	35.3 (33.1; 37)*	225.7 (202.2; 237.0)*	154,5 (137.9; 172)	−76.1 (−91.4; −27.8)*	3,100 (2,950; 3,813)
8	9	–	–	159 (142; 175,5)		3,100 (3,100; 3,850)
9	8	–	–	160,3 (146,3; 177,3)		3,400 (3,100; 3,850)
10	8	24,0 (23,0; 27,1)§	150,1 (143,8; 169,6)§	160,3 (146,3; 177,3)	−2,6 (−19,6; −1,9)§	3,400 (3,100; 3,850)

Notes: * – p <0.05 compared to the value on day 1; § – p <0.05 compared to the value on day 7. EN-PN – enteral and parenteral nutrition

During the entire period of observation, we noted hypoproteinemia and hypoalbuminemia, and also statistically significant increase in urea concentration in the blood serum from day 5 to day 10 of EN-PN (Table. 3).

Table 3

Changes of biochemical parameters in the blood serum of examined patients

Timing of EN-PN (days)	Number of patients	Parameters		
		Total protein, g/l	Albumin, g/l	Urea, mmol/l
1	20	52.3 (44,2; 54.7)	30.4 (27.4; 32.7)	5.5 (4.2; 7.0)
2	20	50.9 (47.8; 55.9)	31.3 (29.4; 34.0)	6.2 (5.1; 8.3)
3	19	55.6 (47.5; 60.1)	30.0 (27.9; 32.5)	7.1 (5.6; 8.0)
4	15	52.0 (48.0; 53.0)	29.2 (26.2; 31.8)	7.8 (6.6; 8.7)
5	14	50.4 (47.9; 55.4)	30.3 (27.6; 33.1)	7.8 (7.2; 8.9) *
6	12	51.5 (48.2; 57.0)	32.0 (27.8; 34.7)	9.1 (7.9; 11.5) *
7	10	53.0 (48.8; 58.0)	29.5 (26.2; 30.9)	9.1 (7.1; 13.9) *
8	9	52.6 (50.6; 59.0)	29.9 (27.9; 31.5)	9.4 (7.9; 9.6) *
9	8	54.4 (47.8; 60.8)	–	9.1 (7.8; 9.2) *
10	8	60.2 (53.0; 63.5)	24.9 (24.4; 29.7)	10.1 (9.0; 12.0) *

Notes: * – p<0.05 compared to the value on day 1. EN-PN – parenteral and enteral nutrition

Introduction of 3-component PN was not accompanied by a significant increase in concentration of triglycerides, indicating normal absorption of fat emulsion, included into the mixture, and did not lead to any impairments of pulmonary gas exchange (table 4, 5).

Table 4

TG concentration in blood serum of examined patients (normal values — 1.71 mmol/l or less)

Indicators	Stages			
	Prior to PN	2 hours after PN initiation	12 hours after PN initiation	18 hours after PN initiation
TG concentration in blood serum, mmol/l	1.37 (0.95; 1,68) (*n*=130)	1.55 (1.08; 2.01) (*n*=129)	1.50 (1.03; 2.01) (*n*=128)	1.38 (0.97; 1.91) (*n*=126)

Notes: n — the number of observations; PN — parenteral nutrition; TG — triglycerides

Table 5

Changes of ratio PaO_2/FiO_2 in examined patients

Pulmonary gas exchange	Ratio PaO_2/FiO_2			
	Prior to PN	2 hours after PN initiation	12 hours after PN initiation	18 hours after PN initiation
Normal functioning (ratio $PaO_2/FiO_2 \geq 300$)	365 (343; 451)§ (*n*=88)	382 (341; 434)§ (*n*=82)	371 (312; 453)§ (*n*=82)	365 (301; 449)§ (*n*=78)
Acute disorder (ratio $PaO_2/FiO_2<300$)	246 (200; 273) (*n*=37)	270 (214; 328) * (*n*=37)	289 (219; 338) * (*n*=34)	324 (255; 382) * (*n*=35)

Notes: * — $p<0.05$ compared to the value prior to PN; § — $p<0.05$ as compared to the corresponding value in patients with normal lung function; n — observations. PP — parenteral nutrition

When lung functioning was initially normal (the ratio $PaO_2/FiO_2 \geqslant 300$), the gas exchange remained unchanged, and in the presence of acute lung injury (the ratio $PaO_2/FiO_2<300$) there was an increase and normalization of pulmonary gas exchange within a day.

Additional PN was accompanied by the development of hyperglycemia. Increased serum glucose concentration was observed 2 hours after the start of emulsion administration and during the whole period of 3-component mixture infusion (table 6).

Table 6

Glucose concentration in blood serum of patients with ICH under PN

Timing of EN-PN (days)	Number of patients	Glucose comcentration in blood serum (normal 3.8-6.1 mmol/l)			
		Prior to PN	2 hours after PN initiation	12 hours after PN initiation	18 hours after PN initiation
1	20	7.2 (6.5; 8.5)	8.8 (7.9; 10.6)*	9.2 (7.9; 10.2)*	9.4 (6.5; 12.4)*
2	20	8.1 (7.2; 9.2)	10.8 (10.0; 14.5)*§	10.2 (8.5; 14.1)*	9.5 (7.5; 10.9)*
3	19	7.9 (7.1; 9.2)	10.5 (7.6; 13.1)*	9.0 (8.4; 14.1) *	8.8 (7.0; 12.8)
4	15	7.4 (6.8; 9.3)	11.1 (8.9; 14.9)*	8.4 (7.6; 12.7)	10.2 (8.3; 13.8)
5	14	9.4 (7.2; 10.6)	9.0 (8.0; 12.2)	8.4 (7.9; 15.4)	7.9 (7.6; 12.8)
6	12	8.0 (6.5; 9.4)	9.0 (7.2; 11.7)	9.7 (7.1; 11.2)	7.3 (6.1; 8.9)
7	10	7.2 (6.9; 7.5)	9.4 (7.8; 12.4)*	8.8 (6.4; 10.8)	9.2 (6.9; 11.6)
8	9	7.8 (7.0; 8.7)	8.2 (6.3; 10.6)	11.1 (7.2; 15.5)	11.3 (6.8; 14.9)
9	8	6.1 (5.7; 10.0)	9.1 (7.6; 10.3)	8.1 (7.6; 12.0)	9.2 (7.1; 11.7)
10	8	6.9 (6.3; 10.0)	9.3 (7.4; 12.4)	10.5 (8.3; 16.6)	11.8 (9.5; 12.0)

Notes: * — $p<0.05$ compared to the value prior to PN; § — $p<0.05$ compared to the corresponding value on day 1 of observation. ICH — intracranial hemorrhage; PN — parenteral nutrition; EN-PN — enteral and parenteral nutrition nutrition

Analyzing the parameters of oxidative stress, we observed an increase in MDA concentration in blood serum compared to normal values (Table. 7). However, TAABS was in the normal range throughout the observation.

Table 7

Changes of oxidative stress indicators in examined patients

Timing of EN-PN (days)	Indicators of oxidative stress			
	MDA, mcmol/l		TAABS, mmol/l	
	Normal values	Value	Normal values	Value
1	2.3 (2.1–2.5)	3.4 (3.0; 3.7)*	1.6 (1.6–1.7)	1.4 (1.3; 1.5)
3		3.6 (3.4; 4.0)*		1.6 (1.3; 1.7)
5		3.7 (3.5; 4.2)*,§		1.5 (1.2; 1.6)
7		3.7 (3.5; 3.9)*		1.4 (1.3; 1.7)
10		3.8 (3.5; 4.4)*,§		1.3 (1.2; 1.6)

Notes: * — p <0.05 compared to normal values; § — p<0.05 compared to the value on day 1. TAABS — total antioxidant activity of blood serum; MDA — malondialdehyde, EN-PN — enteral and parenteral nutrition

DISCUSSION OF RESULTS

One of the important directions of therapy for hypercatabolism syndrome in patients with ICH is artificial nutrition sufficient to ensure the patient's needs for energy and nutrients. In connection with the impossibility of adequate artificial feeding in the acute period of ICH, EN is often supplemented with PN. This concept corresponds to current guidelines of the European Society for Clinical Nutrition and Metabolism (*ESPEN*), which say that in case of impossibility or failure of enteral nutrition therapy within first 24-48 hours, EN-PN or full PN should be initiated [7]. However, PN is associated with the risk of infectious complications, hyperglycemia, acute lung injury, disorders of homeostasis [8, 9]. In the past few years, the results of three randomized multicenter studies have been reported using different protocols of mixed EN-PN in critical patients [10-12]. However, research results have appeared to be extremely controversial. Thus, in *EPaNIC* study the use of PN was accompanied by longer stay in the intensive care unit (ICU) and higher incidence of infectious complications, which can be explained by the use of concentrated solutions of glucose and insulin on day 1-2 under the early onset of PN [10]. *C.P. Heidegger et al.* found that additional PN, started on the 4th day of stay in the ICU, had not lead to an increase in the length of stay in the ICU, and had helped reduce the incidence of infectious complications [11]. *G.S. Doig, et al.* found that the beginning of the PN on day 1 after admission to the ICU had helped reduce the duration of ALV and had had no effect on the incidence of infectious complications [12]. To increase the efficiency and reduce the frequency of PN complications, new compounds are now being developed. A mixture "three-in-one", used in our study, has one of the most promising composition today.

The results of our study showed that critical patients with ICH needed PN to be added to EN on day 4 (3;5) of the postoperative period. At this time, there was a sharp increase in catabolism such as higher nitrogen losses, hypoproteinemia and growth of urea concentration in blood serum. Measurement of TF concentration in the blood serum on day 1-10 of EN-PN helped assess the severity of hypercatabolism syndrome and the effectiveness of artificial nutrition over time. The growth of TF level with the 7th day after EN-PN initiation indicated a gradual decrease in the level of catabolism. In spite of the serious condition of patients, the digestibility of mixed feeding was good, and introduction of the fat emulsion did not lead to deterioration of pulmonary gas exchange, and even contributed to its improvement.

One of the common complications of PN is hyperglycemia. According to international recommendations, the rise of glucose by 10 mmol/L or more in critical patients should be managed [7, 13]. We noted the development of hyperglycemia in excessing 10 mmol/L 2 hours after the start of PN on day 2,3,4 of observation, followed by normalization of glucose concentrations in blood serum 12 and 18 hours after the start of PN.

The brain is very sensitive to oxidative stress due to the peculiarities of its composition (the highest content in humans of phospholipids, fatty acids, Fe^{2+} and low vitamin *A*, low activity of glutathione peroxidase and almost complete lack of catalase), high oxygen demand and lack of antioxidant protection factors in the medulla [14]. The analysis of oxidative stress indicators in patients with ICH who had underwent EN-PN revealed an increase of MDA concentration in blood serum compared to normal values. According to the results previously obtained in our clinic, the MDA concentration in patients with subarachnoid hemorrhage due to the rupture of an arterial aneurysm reaches much higher values (8.34 (6.64; 10.98) mcmol/L) [15]. Increasing MDA was not accompanied by a significant decrease in concentration of metabolites characterizing TAABS. This balanced state of LPO indicators and AOS can be explained by the presence of polyunsaturated fatty acids in the ratio of omega-6/omega-3 2.5:1 and alpha-tocopherol in the the fat emulsion used in PN.

CONCLUSIONS

1. The mixed parenteral-enteral nutrition in patients with intracranial hemorrhages and in a state of hypercatabolism, helps improve the protein metabolism and is not accompanied by an increase in triglyceride concentration of blood serum or impaired pulmonary gas exchange.

2. Introduction of "three-in-one" emulsion for parenteral nutrition may be accompanied by the development of hyperglycemia which the peak is observed 2 hours after the start of infusion.

3. A three-component mixture containing polyunsaturated fatty acids in the ratio of omega-6/omega-3 2.5:1, and olive oil, used for parenteral nutrition for critical patients with intracranial hemorrhage contributes to maintaining a balanced state of indicators of lipid peroxidation and antioxidant system of blood serum.

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