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NUTRITIONAL STRATEGY IN PATIENTS WITH SEVERE ACUTE PANCREATITIS - RELATION AND IMPORTANCE TO CYTOKINE CONCENTRATION

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ABSTRACT

Introduction - Nutritional support in patients with severe acute pancreatitis is a critical aspect in the management of this condition. Inability to use gastrointestinal tract in patients with severe disease may lead to exacerbation of the stress response and severity. Therefore the establishment of proper nutrition strategy determines individualized therapeutic approach and modulation of appropriate treatment decisions.

Aim - This study investigated and analyzed all available medical information related to strategies for nutritional support in patients with acute pancreatitis. The evidences about statements, optimal way of delivery of nutritients, time and effect of nutritional strategy in these patients were systematicly examined.

Scope – We analyzed the available literature published in PUBMED and MEDLAIN systems in period from January 1986 to December 2011. So we concluded that only severe acute pancreatitis requires creation of individual nutritional support, because in mild and moderate forms nutritional support does not improve the outcome. EN has better results than parenteral feeding and it is a new „gold standard" in nutritional support of acute pancretitis. Nasogastric and nasojejunal feeding have comparable results but remain the question if using NGEN is justified in conditions of acute pancreatic disfunction. Standard polimeric formula is characterized with less tollerance and stronger pancreatic stimulation than semielemental diets. Despite all this there is no unified approach for nutritional support which provides complex therapeutic strategy in management of patients with acute pancreatitis. Using imunoenchanced nutritional formulas and probiotics does not improve clinical otcome which make their earli applying unreasonable.

Conclusions – Efforts of several teams in recent years were directed to prove and enforce the enteral nutritional strategy in daily practice. This is aparent from published data in all international guidelines. Implement standards allowed the creation of strategies for nutritional support in condition of severe acute pancreatitis. Despite all the advantages of enteral nutrition - reduction of infected complications, hospital stay, need of surgical intervention and mortality, implementation of therapeutic effect remains unclear. Examination of cytokines serum concentration in the course of EN may evaluate and prove the impact on immunoinflamatory response. According to several authors the effect of enteral nutritional strategy is due to modulation of stress response during the AP. The activation of cytokine cascade is too complex to be able to claim that initiation of EN would affect it completely, and even if there is influence, it is limited. Nevertheless the effects of EN have been proven by number of authors and it application in patients with acute pancreatitis is not just a formula for nutritional supporft, but also a major part in the complex therapeutic strategy.

Key words – acute pancreatitis, clinical course, nutritional support, EN, intestinal barrier function, complications, clinical outcome.

INTRODUCTION

Acute pancreatitis is a surgical disease beginning as aseptic inflammation, of demarcation nature with pancreatocyte necrobiosis and enzymatic autoagression at its background, with potential for development of gland necrosis with subsequent infection of necrotic tissues, sepsis and multiorgan failure complications. In many aspects, this disease is still a clinical challenge with annual incidence of 4.9 – 80/100 000 and tends to increase during the last two decades (1).

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More than 80% of patients exhibit clinically mild acute pancreatitis. In general, the initial treatment of this form consist of "nothing through the mouth", controlled haemodilution and adequate analgesia. No nutrition strategy is needed, as the oral intake is reinstated after 3 to 7 days (1, 2, 3).

The other 20% of cases are those of a severe disease with local and systemic complications. This form is accompanied by a severe energy deficiency and serious metabolic disturbances with high mortality (up to 15%) (4,5,6,7,8). Until the mid 1990s, the therapeutic strategy in such patients included intensive reanimation, monitoring and protection of organ dysfunction and total parenteral nutrition (TPN) after stabilisation of the haemodynamics and the glucose disbalance. This approcha was associated with lower incidence of morbidity and mortality that the strategy without nutritional support.

During the last years, a number of clinical surveys have outlined enteral nutrition (EN) as a safe strategy for nutritional support and a therapeutic approach determining the clinical course of the disease. A number of disputable questions about its application have still remained: the route of nutrient delivery (nasogastric or nasojejunal probe), the dietary substrate formula, the use of pre-, probiotics and immunomodulators, the time to begin the nutritional support and the potential for real evaluation of its effects.

EN or TPN

The early nutritional support is a main part of the therapeutic approach in patients with really severe pancreatitis, but the question about the best and, at the same time, safest strategy (enteral or parenteral) is still controversial. TPN ensures a rapid attainment of desired nutritional goals, it is indicated for patients with severe intestinal paresis, severe compartment syndrome, but was associated with catheterisation-related septic conditions that could worsen inflammatory response. More frequently, it results in disturbances and difficult glucose metabolism regulation that, in a number of cases, significantly narrowed the therapeutic window.

Enteral nutrition is characterised with reduced incidence of infection complications, faster resolution of the disease process, and lower treatment costs. It is indicated in all patients without signs of paralytic ileus, severe compartment syndrome or any intolerance. It is associated with better glycaemic control and its beginning is not directly dependent on the haemodynamic status of the patient. Patient with EN were associated with lower incidence of infective necrosis and sepsis as well as to shorter in-hospital stay in intensive care units as compared to TPN patients (10, 11, 12, 13). McClave et al. (14), and later Windsor et al (10) have related EN to a significant reduction of infection complications – $p = .001$ and hospitalisation duration - $p < .0001$, although no correlations with the extent of necrosis and the development of organ failure in such patients was found out. In his survey from 2007, Petrov et al. (15) achieved a reduced mortality in the enterally fed group. A meta analysis (16) of 6 randomised studies (2, 10, 17, 18, 19) aimed at comparing enteral and total parenteral nutrition methods (EN; TPN) established a significant correlation of EN with the frequency of infection complications, surgical interventions and the duration of hospitalisation without change in CTSI scores and the appearance of systemic complications (20, 21). These results are confirmed also in the meta analysis of Petrov MS et al. (22). Thus, EN could probably become the new "gold standard" in the nutritional support of patients with severe acute pancreatitis, supported by its inclusion in the last guidelines in the United Kingdom, Japan and the USA, but the lack of define standards of application leaves it still far away from the daily clinical practice (24, 25, 11, 12, 13, 23).

When to begin EN

EN provides maintenance of intestinal integrity with reduced translocation of enteropathogens and modulation of inflammatory response with improved intestinal metabolism. The bacterial translocation occurs within several hours after the symptoms of severe acute pancreatitis. This implies that there is a very narrow time window for influencing this process (26, 27, 28)

In comparative studies on the initiation of EN during the first 24 h with gradual increase in energy supply, a better resolution of the disease, lower incidence of infection complications and lower hospital ICU stay duration were demonstrated (27, 28, 29). A systematic review made in 2009 outlined a better outcome in patients with severe acute pancreatitis with early start of EN (30).

The first 24-72 h are the therapeutic window that largely determines the necrosis spread, the impact on MODS and the outcome in patients with severe acute pancreatitis. This period is adequate for exact evaluation of severity and initiation of early reanimation measures aimed at control of organ dysfunction, prevention of organ failure and improvement of pancreatic microcirculation. Furthermore, in conditions of haemodynamic instability, compromised blood circulation to the splachnicus and MODS manifestations of intolerance to nutrients, the incidence of aspiration pneumonia and intestinal ischaemia is high. That is why we suppose that the early hours should be used for stabilisation of the condition and then, with pancreatic necrosis evidence, to start EN for protection against infection and influence on persisting cytokine response (31).

So far, there are no categorical indications in the available literature as to when to begin enteral nutrition. The large multi centre survey - PYTHON, is designed to prove whether the initiation of EN within 24 h after the symptoms' manifestation has a positive effect on the course of severe acute pancreatitis (32). The results from this large-scale project could throw light and define the exact moment to begin EN in patients with severe acute pancreatitis but at present, it is determined by the clinician on the basis of his own experience.

NGEN or NJEN

In a randomised study, Eatock et al have demonstrated a surprising tolerance to nasogastric enteral nutrition (NGEN) with low incidence of complication from the nutrition itself, and prevention of pancreatic complication comparable to that of nasojejunal enteral nutrition (NJEN) (33, 34). Similar results were reported in the randomised studies of Kumar et al. (NGEN vs. NJEN) and Eckerwall et al. (NGEN vs. TPN) (35, 31).

It was established that nasogastric nutrition yielded no worse results about reduction of APACHE II score, CRP concentrations, relapse of pain syndrome, the doses of analgesics or mortality as compared to nasojejunal nutrition (25). A study published in 2011 (36) reported 23.1% complication in NGEN vs 35.9% in NJEN. Further, blood biochemical nutritional parameters such as serum albumin and prealbumin in early NGEN were well preserved, without any significant difference vs NJEN (35). The data provided by Eckerwall et al. (31) demonstrated a higher incidence of pseudocysts in the 3-month follow-up of patients that could be associated to the stronger stimulation of the pancreas in the acute stage. Anyhow, the mechanism of the more frequent formation of pseudocysts remains unclear and a larger randomised set is needed to confirm these results.

The conclusion from these randomised clinical surveys was that nasogastric nutrition was well tolerated and with equally good results as NJEN with regard to infection complications and immuno-inflammation acute phase response, despite the anticipated higher incidence of late complications. NJEN was associated with more difficult probe placement, higher frequency of aspiration complications, more frequent probe migration and thus more frequent need for probe replacement than NGEN. Yet, in conditions of severe pancreatic dysfunction, this route of nutrition seems more secure from pathophysiological point of view.

Nutrition formulas

The EN of patients with severe acute pancreatitis uses three main formulas: elemental, semi-elemental and polymeric. The elemental formula comprises amino acids, simple sugars and essential fatty acids. The semi-elemental formula contains peptides with various chain length, sugars, glucose polymers or starch and middle-chain triglycerides. The polymeric formula is composed of proteins, complex carbohydrates and long-chain fats.

The comparison of elemental and polymeric formulas reveals a substantial correlation between NGEN and the secretion of trypsin, amylase and lipase, as well as a lack of correlation for elemental diet and placebo (10, 37, 38). Semi-elemental formula was associated with better reduction of morbidity, better nitrogen balance, shorter hospitalisation and lower weight reduction compared to the polymeric (39, 40). In their meta analysis however Petrov et al concluded that the utilisation of the polymeric formula did not results in worsened tolerance, more complications or higher mortality than semi-elemental/elemental ones, but when the intrajejunal route was used (41). It should be nevertheless stated that semi-elemental nutrition is 7 times more expensive and that its advantages to polymeric formula delivered by

nasojejunal probe are not quite clear. The guidelines of ESPEN from 2006 recommend a start with polymeric diet and if it is not tolerated, transition to a (semi-)elemental formula. We suggest that the semi-elemental formula was more appropriate for NGEN (42).

The utilisation of immunomodulatory nutrition formulas (glutamine, arginine and omega 3 fatty acids) and probiotics did not guarantee a clinical outcome and reduction of the incidence of complications, which does not justify their early application. Their immunomodulatory effect is disputable and compared to that of the other enteral nutrition formulas (41, 43). Probiotics should not be routinely included in the nutritional strategy of severe acute peritonitis due to the high incidence of intestinal ischaemia (43).

Evaluation of EN effect on inflammatory response

The manifestations of SIRS in patients with severe acute pancreatitis (SAP) are due to activation of cellular humoral immunity and release of inflammatory mediators as IL – 1, TNF –alfa, IL6; IL8; cell activating factor, NO, PG E2, LT B4, reactive oxygen species etc. Thus, the evaluation of the efficacy and the effect of early EN on immunoinflammatory response of patients with SAP could be performed by monitoring the dynamics of blood serum cytokine and CRP concentrations.

In 1998, Windsor et al. (10) showed a significant reduction of CRP ($p<0.005$) until the 7th day after EN start and lack of changes on blood CRP concentrations in the groups of patients fed parenterally. The authors reported a significant decrease in APACHE II scores for the same period ($p<0.0001$). Similar results were published by Brian E et al. in 2005 (44). In 2006, Callum et al. (45) demonstrated reduced cytokine 6 and 10 concentrations in the course of disease with patients with EN and related these findings to the lower APACHE II scores and the morbidity. Zhou et al (2011) reported a considerable reduction of the IL-10/TNF-α ratio and CD4+; CD8+ by the 6th day of the therapy when EN was early initiated (46). All this suggests that EN could modulate the inflammatory response and determine the morbidity in SAP patients. The effect of EN for protection from infection necrosis is beyond any doubt, but several research teams have outlined the lack of effect in the early immuno-inflammation stage of the disease (47, 31, 48, 49). In the study of Powell et al (47), the serum inflammation markers were statistically insignificantly lower in patients on EN, so the authors assumed that EN in patients with severe pancreatitis did not modify the inflammatory response. Similar results were shown by Karsenti et al., Casas et al. and Eckerwall et al. (31, 48, 49) – the authors did not observe any statistically significant difference in IL6 and CRP concentrations between EN and TPN groups. In general, the activation of the inflammatory cascade in acute pancreatitis is rather intricate to affirm that enteral nutrition could modify it, but if any effect is present, it would be limited. So far, there is no meta analysis on the results of the large-scale randomised studies distinguishing the role of EN to systemic inflammatory response provided that available literature data are rather controversial.

DISCUSSION

The nutritional support is an essential element of the therapeutic strategy in SAP patients, which determines the subsequent development of infection complications and the outcome of the disease.

The enteral nutrition should be preferred to parenteral provided that the tolerance of the patient is good (50, 51, 52). It is recommended in the revised guideline of ESPEN from 2006 (42) In several studies, EN has been associated with reduction of morbidity (24-28), septic complications (25-27), the duration of ICU stay (27), the duration of hospitalisation (28, 24), the need of surgery (12, 13, 29) and treatment costs (24, 26, 27, 28). That is why this method is regarded upon not only as a method of nutritional support, but also as therapy strategy modulating the immuno-inflammation response and improving the outcome (29, 30). Only in a comparative study from 2006, TPN has yielded better results than EN (31). The authors reported a substantial frequency of infection complications and poorer outcome in the EN group. Newer meta analyses published in 2008 and 2011 (22, 53) established lower risk of infections (relative risk of 0.556, 95% confidence interval 0.436 to 0.709, P = .000), lower incidence of surgical interventions (relative risk of 0.501, 95% confidence interval 0.378 to 0.663, P = .000) and lower mortality rate (relative risk of 0.395, 95% confidence interval 0.272 to 0.573, P = .003) in the EN group. At the same time, non-infectious complications including ARDS,

pancreatic cyst and fistula, diarrhoea, abdominal distention and removal of the nasojejunal probe without counting the multiorgan failure, were considerably more frequent in patients receiving EN than those on TPN (relative risk of 2.697, 95% confidence interval 1.947 to 3.735, P = .994).

TPN is indicated in all patients with intolerance to EN, severe paralytic ileus and compartment syndrome during the disease course. It ensures an adequate energy supply, fast and easy satisfaction of calculated energy needs. Its start is not dependent on the gastrointestinal tract state, it is application – friendly and does not result in pancreatic stimulation. Nevertheless, TPN could worsen the inflammation and lead to metabolic and blood electrolyte disturbances and changes in the intestinal barrier function. Further, the need form central venous catheterisation could trigger septic complications (17).

Despite all advantages of EN evidenced in a number of randomised studies and confirmed by meta analyses, The Italian Society of Pancreatology informed that only 20% of patients with severe pancreatitis received enteral nutritional support (54). In the Netherlands, a multi-centre study has concluded that 50% of severe pancreatitis received early EN (55). None of these studies reports about contraindications for initiating an enteral nutrition in the other part of the cohort. These results were most probably due to the lack of standards about the time of EN start, the route of nutritional support, the choice of dietary formula, and the yet insufficient experience of many surgeons or reanimation specialists.

It was supposed that in SAP patients, the position of the nutritional probe was largely determining the efficacy and the outcome of enteral nutrition. The meta analysis from 2007 (56) did not show any significant difference in the total mortality between early NGEN and conventional groups (NJEN, TPN). There was not any statistically significant difference in the mean in-hospital stay between NGEN and NJEN groups (P = 0.43), in infection complications as sepsis and infected pancreatic necrosis (RR = 1.41, P = 0.41), in MODS manifestations (RR= 0.97, P = 0.97) and pain relapse after transition to the usual diet (RR = 0.94, P = 0.96). These data were confirmed by the systemic survey of Petrov et al. (57) by showing that the NGEN was tolerated by over 79% of patients with insignificantly increased risk of diarrhoeic syndrome (RR=1.42). Both meta analyses allowed concluding that the nasogastric route for EN of SAP patients should be routinely used and first choice of nutritional support strategy, whereas NJEN should be applied when NGEN is not tolerated. Nevertheless, it was proved that nasogastric nutrition results in stimulation of the pancreatic secretion, which, even being on a basal level, leaves the question about its adequacy in conditions of severe gland dysfunction still open.

Enteral nutrition in acute pancreatitis patients is not only a nutritional support, but a therapeutic strategy. The effect of EN for preventing infection complications is undeniable but some research teams have shown the lack of therapeutic effects in the early immuno-inflammation stage of the disease (47,31,48,49). This could be due to the fact that the modulation of gastrointestinal tract-dependent immunocompetent cells is not sufficient to exert an effect on systemic response. In general, the activation of the inflammation cascade in acute pancreatitis is too complex to affirm that enteral nutritional strategy could modify it. Further, the early release of cytokines was hardly due to translocation of endotoxins and bacterial products from the metabolically compromised gastrointestinal tract, but rather to activation of monocytes by the early autodigestion of the gland tissue. This way, in patients with really severe pathology, the effect of EN consists in preventing the development of infection necrosis, whereas the effects related to the cytokine cascade and the early SIRS are disputable. There is a need for a meta analysis to sum up and analyse results reported so far, but its results would barely be optimistic. In any way, EN is an independent gold standard for nutritional support as seen from all large meta analyses and guidelines and its application would become more and more popular (24, 25, 42,58, 59, 60, 61).

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