Clinical Study

Parenteral and enteral nutrition in the management of neurosurgical patients in the intensive care unit

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Abstract

The iatrogenic malnutrition of neurosurgical patients in intensive care units (ICU) is an underestimated problem. It may cause a decrease in plasma albumin and oncotic pressure, leading to an increase in the amount of water entering the brain and increased intracranial pressure (ICP). This study was conducted to test the hypothesis that combined high-protein parenteral and enteral nutrition is beneficial for neurosurgical patients in ICU. A total of 202 neurosurgical patients in ICU (mean age ± standard deviation, 56 years ± 16 years; male:female = 1.2:1) were studied. Two consecutive 1-year time periods were compared, during which two different nutritional regimens were followed. In the first time period (Y1) patients were given a low-protein/high-fat formulation parenterally, followed by a standard enteral regimen. In the second time period (Y2) a protein-rich, combined parenteral and enteral diet was prospectively administered. The Glasgow Outcome Score was measured at 3–6 months after discharge. The following clinical parameters were recorded during the first 2 weeks after admission: ICP; albumin; cholinesterase (CHE); daily hours of ICP > 20 mmHg and cerebral perfusion pressure < 70 mmHg; and Acute Physiology and Chronic Health Evaluation II (APACHE II) score. It was found that overall albumin (32.4 g/L ± 4.1 g/L vs 27.5 g/L ± 3.6 g/L) and CHE was higher during Y2, although the total energy supply, glucose and fat intake was lower. Higher GOS scores were seen when patients had lower APACHE II scores and received the Y2 nutritional regimen. During Y2, the total hours of ICP > 20 mmHg were fewer. With the Y2 nutrition, maintenance of adequate cerebral perfusion required less catecholamine medication and colloidal fluid replacement. Therefore, adequate nutrition is an important parameter in the management of neurosurgical patients in ICU.

1. Introduction

Iatrogenic malnutrition is an important issue in hospitals worldwide, with weight loss being reported in up to 66% of patients during hospital stays.1,2 Malnutrition has been defined as an alteration of the body’s composition that occurs as a result of a lack of major or minor nutrients. Malnutrition can develop as a result of insufficient nutritional input, an increased need or an altered utilization of nutrients, and can result in malfunctioning organs, pathological laboratory values, a reduction in body mass and unfavorable clinical outcomes.3 Within one year the death rate of undernourished hospital patients has been reported to be 30%.4 Critically ill patients frequently suffer from a hypermetabolic state that leads to a reduction in the body’s fat and protein stores. This is one explanation for the increased risk of infection and impaired wound healing.5,6

Neurosurgical patients in intensive care units (ICU) have special needs. After a traumatic brain injury (TBI), more than 50% of patients do not tolerate enteral nutrition; vomiting, abdominal distension and increased gastric residual volume have been reported.7 Although the cerebral–intestinal relationship has yet to be fully elucidated, reduction of epithelial cells, villous atrophy and oedema in villous intestinal tissue have been observed after TBI.8 Patients with a low Glasgow Coma Scale score have shown prolonged gastric emptying. Increased intracranial pressure (ICP) may reduce gastric contractility by 80%, but normalisation of ICP may restore contractility.9 Stress may be one contributing factor as corticotrophin-releasing factor reduces gastric function in rats by up to 80%.

The recently reported “Guidelines for the Management of Severe Traumatic Brain Injury” recommend the administration of 140% and 100% of the calories required for baseline metabolism to patients with and without neuromuscular blockades for relaxation, respectively.10 They further recommend that nutrition should be given enterally or parenterally, and 15% of calories should be...
administered as protein after day 7 post-TBI. However, even with optimal nutrition, albumin and CHE serum levels will decrease over time.

This study was conducted to test the hypothesis that a structured combination of enteral and parenteral nutrition, where the proportion of amino acids is double those recommended by the above Guidelines, will improve protein synthesis and decrease ICP. Also, we hypothesize that the neurological outcome may be improved, and the new nutritional regimen should lead to a decreased need for catecholamines in neurosurgical patients in ICU.

2. Methods and materials

The local ethics committee approved the study design. Neurosurgical patients who were younger than 16 years were admitted to the University’s children’s hospital, and patients with concurrent injuries to the chest, abdomen or pelvis were admitted to the general ICU. Thus we studied adult intubated neurosurgical patients who stayed longer than 5 days in the neurosurgical ICU (NICU) across 2 consecutive time periods (Y1 and Y2). The following parameters were recorded for 14 days after admission: (i) total amount of nutrition specified in carbohydrates, proteins and lipids; (ii) haemodynamic parameters (daily average values of ICP, mean arterial pressure [MAP] and cerebral perfusion pressure [CPP], daily hours of ICP > 20 mmHg, daily hours of MAP < 90 mmHg, daily hours of CPP < 70 mmHg); (iii) amounts of catecholamines administered; (iv) liver function tests (thromboplastin time [TPT], prothrombin time [PT], partial thromboplastin time [PPT], as well as serum concentrations of albumin, cholinesterase [CHE], glutamate-oxaloacetate-transaminase [GOT], glutamate-pyruvate-transaminase [GPT] and gamma-glutamyltransferase [GGT]); (v) infection status (white blood cell [WBC] count,); (v) amino acid metabolism (urea, creatinine); (vi) blood gas parameters (partial pressure of oxygen [PaO2], partial pressure of carbon dioxide [PaCO2], fraction of inspired oxygen, blood pH, lactate, and blood glucose); and (vii) severity of disease (Acute Physiology and Chronic Health Evaluation II [APACHE II] score). Blood gas parameters were measured every 6 hours and the daily values represent the mean ± standard deviation (SD) of all four measurements. GPT, GOT, GGT and CHE were measured at a body temperature of 37°C (98.6°F).

During the first time period (Y1) a standard diet low in amino acids was administered either enterally via a nasogastric tube or parenterally as tolerated. As shown in Fig. 1, the ratio of enteral/parenteral nutrition remained constant over the first 2 weeks after admission. Amino acids accounted for <20% of the total intake of calories (Fig. 2).

During the second time period (Y2) the diet was formulated by a nutritional support team (Table 1). The data was collected prospectively, whereas patients in time period Y1 served as historical controls and their data was collected from their paper charts. All patients were fed the study formulation after admission, but the ratio of enteral to parenteral nutrition increased over time. By the end of the first 2 weeks, almost 80% of patients received nutrition enterally. The amount of amino acids in the diet was double the amount in the Y1 group. On average, 30% of total calories were administered as amino acids. ICP, MAP and CPP were recorded every 10 minutes.

2.1. Estimation of nutritional status – the role of albumin and cholinesterase

Long-term and short-term nutritional variations were estimated by the serum values of albumin and CHE, respectively. Both, albumin and CHE were measured in the hospital’s central laboratory once daily. Albumin is synthesised in liver tissue and has a biological half-time of 20 days. Thus, albumin is an ideal marker...
for long-term changes in nutrition. Albumin is not stored in liver tissue, but is directly released into the serum. During a 24-hour period, 0.2 g/kg of body weight of albumin are synthesised. The synthesis of albumin depends on the protein content of the liver interstitial tissue. With low colloid osmotic pressure (COP), the synthesis of albumin depends on the protein content of the liver interstitial tissue.

CHEs are enzymes that hydrolyse choline esters. CHE is also an enzyme that hydrolyses choline. CHE is also a member of the choline ester hydrolase family. CHE is also expressed in the liver, and is a member of the choline ester hydrolase family.

Table 1
Standardized diet developed by a nutritional team and administered in the Y2 time period of the study to neurosurgical intensive care patients

<table>
<thead>
<tr>
<th>Day No.</th>
<th>Parenteral</th>
<th>Enteral</th>
<th>Total calories</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No nutrition; stabilisation of metabolism</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Aminomix 2 (1500 mL) plus 500 mL Intralipid 20% or Nutriflex lipid special (1875 mL) plus 500 mL Aminoplasmal 10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Aminomix 2 (1500 mL) plus 500 mL Intralipid 20% or Nutriflex lipid special (1875 mL) plus 500 mL Aminoplasmal 10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Aminomix 2 (1500 mL) or Nutriflex lipid special (1875 mL) plus 500 mL Aminoplasmal 10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Aminomix 2 (1500 mL) or Nutriflex lipid special (1875 mL) plus 500 mL Aminoplasmal 10%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1 x Novasource start (1000 mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1 x Novasource start (1000 mL) or Nutrison energy multifibre (1000 mL) plus 1/2 water (1000 mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 x Fresubin original fibre (1000 mL) plus 1/2 water (1000 mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>From Day 7</td>
<td>1 x Nutrison energy multifibre (1000 mL) plus 1/2 water (1000 mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>or</td>
<td>1 x Nutrison energy multifibre (2000 mL) plus 1/2 water (1000 mL)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ca. = approximately.

1 B. Braun, Melsungen, Germany.
2 Fresenius Karbi, Bad Homburg, Germany.
3 Novartis, Nürnberg, Germany.
4 Prümmer Nutricia, Erlangen, Germany.

2.2. Outcome

The Glasgow Outcome Scale (GOS) score was assessed at around 6 months after admission. Our department’s general policy is to follow-up patients at this time.

2.3. Statistical analysis

Data were collated using Microsoft Access (Microsoft, Redmond, WA, USA), and the software used for analysis was Statistica 6 (Statsoft, Hamburg, Germany). Mixed-effects regression models were calculated at the University’s Institute of Biostatistics. Student’s t-test was used for the univariate analysis. When serial laboratory parameters were compared to single categorical parameters, such as GOS score, the laboratory parameters were averaged over both patients and time. The resulting average value was compared to the categorical parameter using an analysis of variance.

3. Results

3.1. Description of the cohort

A total of 202 patients were studied. As shown in Table 2, patients in both groups were very similar and there was no statistical difference between the proportion of patients with different diseases. About two-thirds of the study population comprised

Table 2
Characteristics of the cohort

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Y1 n = 101 (%)</th>
<th>Y2 n = 101 (%)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>55.9 ± 16.1</td>
<td>56.7 ± 15.8</td>
<td>0.72</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>52:49</td>
<td>60:41</td>
<td>0.25</td>
</tr>
<tr>
<td>SAH</td>
<td>34 (33.6%)</td>
<td>38 (37.6%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Chronic SDH</td>
<td>9 (8.9%)</td>
<td>4 (4%)</td>
<td>0.66</td>
</tr>
<tr>
<td>TBI</td>
<td>18 (17.8%)</td>
<td>17 (16.8%)</td>
<td>0.85</td>
</tr>
<tr>
<td>AVM</td>
<td>4 (4%)</td>
<td>3 (3%)</td>
<td>0.90</td>
</tr>
<tr>
<td>Unruptured aneurysms</td>
<td>1 (1%)</td>
<td>2 (2%)</td>
<td>0.85</td>
</tr>
<tr>
<td>ICH</td>
<td>34 (33.7%)</td>
<td>29 (28.7%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Miscellaneous (pituitary or complex spine cases)</td>
<td>1 (1%)</td>
<td>8 (7.9%)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

AVM = arteriovenous malformation, ICH = intracranial haemorrhage, SAH = subarachnoid haemorrhage, SDH = subdural haematoma, TBI = traumatic brain injury, Y1 = first time period, Y2 = second time period.

 Patients with chronic subdural hematomas and unruptured aneurysms experienced rebleeding and intraprocedural complications, respectively. Intensive care unit treatment for more than 14 days was required.
patients with a subarachnoid haemorrhage (SAH) or TBI. Patients who had unruptured aneurysms were included when they suffered complications after coiling or clipping and needed ICU treatment.

3.2. Time course of albumin and cholinesterase

Serum values of albumin decreased over time in both groups (Fig. 3). During Y2, albumin remained significantly higher from the time of admission to the end of the observation period. During Y1 and Y2, 62.3% and 93.2% of serum albumin values were > 26 mg/dL, respectively. The difference at day of admission to the NICU was statistically significant, where mean albumin level (±SD) was 30 mg/dL ± 5.9 mg/dL and 35.7 mg/dL ± 6.4 mg/dL in Y1 and Y2, respectively (p < 0.001). Serum values of CHE also decreased over time in both groups. During Y2 the time course was more stable and average values never decreased below 4000 U/L. On average (±SD), the patients’ fluid intake was significantly higher during Y1 (Y1: 5.7 L/day ± 2.2 L/day; Y2: 2.6 L/day ± 2.2 L/day; p < 0.001), but mixed-effects regression analysis revealed that the higher albumin values seen in Y2 were due to nutrition rather than dilution.

3.3. Nutrition and laboratory values

In addition to albumin and CHE, GOT, GPT, GGT and urea increased with protein-enriched enteral and parenteral nutrition (Y2). (Table 3). This increase in transaminases and urea suggest that the amino acid mixture being used was not an appropriate balance to support the acute-phase response. As a consequence, amino acids were wasted by deamination into urea and oxidation via the Krebs cycle. Levels of serum lactate and WBC were lower with improved nutrition. Coagulation values such as the TPZ and PTT were not affected by nutrition, but the time to clotting (TZ) was longer during Y2. Blood gas analysis (PaO2, PaCO2) was not affected.

3.4. Hemodynamic parameters

Monitoring of ICP was used in only 27% and 56% of patients during Y1 and Y2, respectively. The MAP was higher for patients during Y1. Although the mean ICP did not differ between the two time periods, the average hours of ICP > 20 mmHg were significantly higher in Y1. However, hours of CPP < 70 mmHg were more frequent during Y2 (Table 4).

Fig. 3. The time course of serum (a) albumin and (b) cholinesterase concentrations showing that despite the lower average total daily intake of calories in Y2 (see Fig. 2), both albumin and cholinesterase concentrations were higher during Y2 than Y1. Solid symbols = daily mean, open box = standard error of the mean, bars = standard deviation of the mean.
The percentage of favourable outcome (GOS score 4 and 5) was 46.5% outcome was similar during both observation periods. The GOS score was assessed 3.8 months after admission. Clinical

### 3.6. Nutrition and outcome

Outcome data were available for all 202 patients. On average, the GOS score was assessed 3.8 months after admission. Clinical outcome was similar between both observation periods. The percentage of favourable outcome (GOS score 4 and 5) was 46.5% and 39.6% in Y1 and Y2, respectively (p = 0.32). However, when all patients were pooled regardless of the time period, the improved outcome was associated with increased albumin concentration (Fig. 4). Univariate analysis revealed that a favourable outcome was achieved with higher concentrations of albumin and CHE, and lower urea, blood glucose and total amount of energy (Table 5). Unsurprisingly, a favourable outcome was primarily seen in patients who had lower APACHE II scores. In a multiple regression model that included all of the previously mentioned predictors, the APACHE II score was the only factor that was statistically significant.

### 4. Discussion

#### 4.1. Summary of findings

This retrospective study of 202 randomly selected NICU patients showed that during the first 14 days after admission, a combined enteral and parenteral nutrition regimen maintained both albumin and CHE concentrations and lowered the need for colloidal fluid replacement and catecholamine administration. Although there was no difference in clinical outcome in both observation periods, the cumulative doses of catecholamines and plasma expanders such as fresh frozen plasma (FFP), human albumin and hydroxyl-ethyl starch (HES), were lower in Y2. The cumulative doses of catecholamines and plasma expanders were administered in lower amounts during Y2. Only the differences in total administered volume of human albumin and CHE reached statistical significance, while FFP showed a statistical trend (Y1 versus Y2: HES of 1045.84 mL ± 543.4 mL vs. 541.8 mL ± 201.75 mL, p < 0.001; human albumin of 161.8 mL ± 69 mL vs. 79.5 mL ± 39.3 mL; p < 0.001; FFP of 781.3 mL ± 708.5 mL vs. 490.9 mL ± 297.9 mL; p = 0.08).

### Table 4

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Y1 Mean ± SD</th>
<th>n</th>
<th>Y2 Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP (mmHg)</td>
<td>101</td>
<td>12.6 ± 6.6</td>
<td>101</td>
<td>12.3 ± 5.9</td>
<td>0.32</td>
</tr>
<tr>
<td>CPP (mmHg)</td>
<td>101</td>
<td>12.2 ± 6.4</td>
<td>101</td>
<td>11.8 ± 6.1</td>
<td>0.51</td>
</tr>
<tr>
<td>Hours of CPP &lt; 1000 mmHg</td>
<td>101</td>
<td>11.8 ± 6.4</td>
<td>101</td>
<td>11.8 ± 5.9</td>
<td>0.16</td>
</tr>
<tr>
<td>Hours of CPP ≥ 1000 mmHg</td>
<td>101</td>
<td>12.2 ± 6.4</td>
<td>101</td>
<td>11.8 ± 6.1</td>
<td>0.51</td>
</tr>
</tbody>
</table>

CPP = cerebral perfusion pressure, MAP = mean arterial pressure, Y1 = first time period, Y2 = second time period.
periods, higher albumin values were associated with higher GOS scores.

4.2. Methodological issues

This study was designed to test whether the addition of amino acids enterally and parenterally may improve albumin concentrations and decrease the need for plasma expanders. During Y2, nutritional specialists (AH, JG) were consultants on the NICU and developed the parenteral and enteral feeding formulations. In contrast, during Y1 the nutritional therapy was organised by neurosurgeons. The data were collected prospectively during Y2, but was collected retrospectively as historical controls in Y1. Due to this semi-prospective approach, some of the important laboratory values such as COP and nitrogen balance were not routinely measured. Nutrition support teams (NST) are well-established in Anglo-American countries, but in Germany and German-speaking countries, however, only 3% of hospitals have organised NST.17,18

4.3. Enteral vs. parenteral nutrition

The optimal rate of feeding for critically ill patients is under debate and two recent meta-analyses could not resolve the controversy.19,20 According to the Guidelines of the European Society for Clinical Nutrition and Metabolism, enteral feeding is recommended in preference to parenteral nutrition for critically ill patients.21 Nasogastric tube feeding has been associated with an improved clinical outcome.22 Intestinal permeability is maintained and bacterial translocation from the intestinal lumen into the bloodstream, which results in septic complications, is less likely.23–27 However, discrepancies between the prescription and the delivery of nutrition can cause significant complications in critically ill patients.28 Many of the patients in ICU are frequently sedated using midazolam and fentanyl, and are artificially ventilated. Opioids are known to decrease gastrointestinal mobility by inhibiting the release of acetylcholine from the mesenteric plexus. Consequently, colonic muscle tone is increased and propulsive activity in the gastrointestinal (GI) tract is reduced.29 Other reasons for the discrepancy are the cessation of feeding for airway management and diagnostic procedures.28 Overall, although it offers some benefits, the enteral feeding route does not guarantee that nutrition is adequately delivered, digested and absorbed.

With parenteral nutrition only, atrophy of intestinal villi, overfeeding and hyperglycaemia were reported.22,24,30 A reduction of enzymes such as disaccharidase in the GI tract may lead to an increased risk of sepsis.23–27 Overall, from a pathophysiological perspective, sole parenteral feeding seems to be less beneficial for patients in ICU.

The combined enteral and parenteral nutrition approach guarantees a sufficient supply of nutrients for the patient and may avoid the GI complications associated with sole parenteral nutrition. Overfeeding is a possible complication and care must be taken to avoid it.

4.4. Composition of nutrition

Over the last 25 years, hypermetabolism and nitrogen wasting have been documented in neurosurgical patients, especially after TBI. The increase over the expected metabolic expenditure ranged from 120% to 250%.31 There are no recommendations available regarding a specific neurosurgical diet, the protein content being the exception. In general, parenteral formulas contain 50% to 60% carbohydrates, 20% to 30% lipids and 15% to 20% proteins.32 The protein content for neurosurgical patients should not be less than 15% of total calories. Critically ill patients may benefit from more than 2 g of amino acids/kg normal body weight per day instead of the 1.5 g of amino acids/kg normal body weight per day recommended by some guidelines.33 The rational behind the excess parenteral administration of amino acids in this study was to provide enough substrate for protein biosynthesis, especially albumin. After surgical procedures, about 6% of body protein is wasted.34 An enriched nutrition with amino acids was thought to reduce the mobilisation of glutamine and alanine from skeletal musculature.

4.5. Clinical impact of adequate nutrition

The administration of amino acids seems to be beneficial for maintaining the concentrations of albumin and other proteins. Excess amino acids are desaminated and then enter carbohydrate metabolism, where they are metabolised to energy carriers such as adenosine triphosphate (ATP).35 This could be one possible explanation for the higher GOT and GPT values in patient who received protein-enriched nutrition during Y2. Urea was significantly higher, but none of the patients needed hemofiltration or hemodialysis.

4.6. Special neurosurgical considerations

In neurosurgical patients, the maintenance of normal albumin values, and thus normal COP, is of critical importance. In patients with cerebral oedema, high normal COP may help to stabilise ICP. In instances of low COP, the interstitial water content may increase regardless of the organ system.36 As a result, ICP may deteriorate.

The influence of nutrition on the outcome of neurosurgical patients was reported more than 20 years ago in several case series. In all of these, abnormal laboratory values were corrected with hypercaloric alimentation.37,38 Our study was statistically underpowered and could not answer the question of whether the applied nutritional regimen had beneficial effects on the GOS scores. The only predictor of a favourable outcome was the APACHE II score, which was averaged across the first 14 days of observation. It is assumed that patients who are in better health throughout the study period will have higher albumin values.

5. Conclusion

With amino acid-enriched enteral and parenteral nutrition, albumin and CHE levels are maintained within nearly normal ranges, while ICP seems to be better controlled. The amount of colloid replacement and catecholamines needed is significantly less than seen with low amino-acid nutrition. In order to investigate the influence of nutrition on the GOS score, a randomised controlled trial is warranted.

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References


