ImpACt of very high protein Content enteral nUtrition formulas on protein metabolism and residual gastric volume in critically ill MUltipLe trAuma paTiEnts – ACCUMULATE trial -

Study Protocol

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Imp**AC**t of very high protein **C**ontent enteral n**U**trition formulas on protein metabolism and residual gastric volume in critically ill **MU**ltip**L**e tr**A**uma pa**T**i**E**nts

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Background and rationale:

Despite an increased survival among critically ill patients, many of the ICU "survivors" may develop prolonged functional disabilities(1). It has already been proven that nutritional therapy is essential, considering that an adequate provision of calories and proteins may influence patients prognostic(1).

Multiple trauma patients are on a particular nutritional risk, since their high nitrogen demands and associated nutritional therapy challenges, caused by repeated surgical intervention or multiple imagistic procedures(2). Although nutritional therapy impact on mortality is still in debate, clear, positive results were obtained in decreasing ICU and hospital stay after adequate nutritional support(3).

According to ESPEN guideline on clinical nutrition in the ICU early enteral nutrition (within 48 h) should be initiated in order to assure an adequate calorie and protein intake(4). Beside optimal timing, the management of nutrition therapy in critically ill patients should also integrate the optimal route and caloric/protein targets(4).

Energy requirements monitoring through indirect calorimetry has been proposed as a standard-of-care method for critically ill patients, considering its proven superiority towards predictive equation(5).

Beyond calorie intake, proteins proved to play a central role in maintain lean body mass, healing wounds and supporting immune function(5).For multiple trauma patients it was reported that protein losses may reach 14 % of the total body stores, thus this type of patients are exposed to a particular increased risk of protein deficits(6). If calorie administration benefits from a proper monitoring tool, protein requirements are still based on predictive equation(6). The impact of protein administration is also lacking of direct measurements techniques(7). Lean body mass evaluation by ultrasound and computerized tomography has been reported to have a good correlation with hospital stay and pots-ICU functional capacity(7). Moreover muscle function evaluation through a hand-grip dynamometer was also tested with good results in patients with ARDS(7).

Source of administered protein may also influence nitrogen balance, considering that whey proteins (rich in leucine) promote a slower hydrolysis and allow a longer period for absorption(8).

Reaching the recommended goals is often impeded by gastric intolerance manifested through increased gastric volume residues(4). It has been already demonstrated that large gastric volume residues are associated with impaired absorption and an increased incidence of aspiration pneumonia(9).

Gastrointestinal dysfunction in multiple trauma patients admitted to the intensive care unit (ICU) is an important yet underrecognized consequence(10). There are various

causes of gastrointestinal tract dysfunction mostly related to patients general health condition and to their diagnostics(11). Gastrointestinal failure may be induced by several factors like immunological, biological and mechanical barrier disruption and it may be manifested through stress ulceration, bacterial translocation, ileus, intra-abdominal hypertension, diarrhoea and constipation(2).

Whether residual gastric volume monitoring should be regularly performed has been extensively discussed. Although the results from some randomised trials which focused on monitoring gastric residual volume, did not find any difference in outcomes, this measurement was far for being abandoned(12). Moreover, gastric residual volume monitoring is still an essential component of enteral nutrition patient care(13).

Although several monitoring methods for gastric volume residue measurements were described, there is no generally accepted technique for daily use(12,13).

Body composition monitoring

Objective:

This prospective observational randomized study aims to determine energy, protein intake and gastrointestinal tolerance while using enteral nutrition formulas with very high protein content and enteral nutrition formulas with normal protein content.

Outcomes will be assessed as:

- **Primary outcome parameter:**

  - Differences regarding achieving protein and calorie daily targets in grams per kilogram of body weight (g/kg BW) at day 5 of the intervention period and at day 10 when using enteral nutrition formulas with different protein content

  - Differences regarding residual gastric volume when using enteral nutrition formulas with different protein content

Secondary outcome parameter:

Differences regarding body composition when using enteral nutrition formulas with different protein content:

a) Quadriceps rectus femoris thickness measured by B-mode ultrasonography on admission, on day 5, on day 10 and 15.

b) Body composition assessment (Fat-Free mass, Total Body water, Phase angle) using bioimpedance analysis after patient has been stabilized (24 hours after extubation and on day 5 after extubation)

c) Plasmatic levels of prealbumin and inflammatory markers (C reactive protein) on day 5 and on day 10;

d) Muscle function evaluation using handgrip dynamometer after extubation and sedation cessation. (24 hours after extubation and on day 5 after extubation)

- **Safety points:**
  - Clinical parameters – vomiting, diarrhoea
  - Biochemical parameters – base excess, urea levels
  - Daily gastric residual volume evaluation using ultrasound gastric antrum measurements after 24 hours of continuous enteral nutrition administration using both types of formulas;

Study population

Consecutive patients with multiple trauma intubated and mechanical ventilated, admitted to the intensive care unit (ICU).

Inclusion criteria:

- Adult patients (>18 yrs) admitted to the ICU
- Multiple trauma (Injury severity score > 18)
- Intubation and mechanical ventilation upon admission in ICU or during the first 24 hours of admission, for at least 48 h

Exclusion criteria

- Age < 18 years
- Pregnant women
- Patients not intubated or not mechanically ventilated or receiving only non–invasive ventilation
- Patients with enteral feeding contraindication 48 h after admission
- Patients with recent gastrointestinal surgical intervention
- Patients on chronic therapy with corticosteroids

Sample size calculation

Since the hypotheses of the study are exploratory, no formal sample size calculation has been performed. This prospective observational study aims to recruit >60 multiple trauma patients.

Randomization:

Simple randomization method will be used to assign subjects into two groups A and B.

Group A – Nutrison Protein Plus with 6.3 g/100 ml protein

Group B - Nutrison Protein Intense with 10 g/100 ml protein

Ethical considerations:

This study will be conducted in full conformity with the Declaration of Helsinki and Good Clinical Practices.

Local ethical committee approval will be asked before any patient will be included.

Considering that nutritional support has become a standard-of-care in every intensive care unit in the world, it is considered that this research is based on collecting data routinely available for every critically ill patient. Although no intervention is performed an informed consent will be provided.

Taking into account that the included patients are not able to provide informed consent at the time of recruitment (on ICU admission), a Power of Attorney or a Legal tutor will act as Consultee and will be asked to consent/decline participation to the study on legal behalf of the patient. If patients have Advance Decision Plan including participation in research studies the Plan will be respected and recruitment pursued/abandoned accordingly.

After regaining capacity, all patients will be asked to provide Informed Consent for using their personal data and will be given the possibility to:

- Provide Informed Consent for the acute data and follow-up.
- Deny research participation and request destruction of acute data collected.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to the Data Manager and the Statistician of the study.

Expected impact of the study

KNOWLEDGE

Investigators aim to provide a detailed description of protein administration using two different types of enteral formulas. The main objectives of the study are to evaluate energy, protein intake and gastrointestinal tolerance while using enteral nutrition formulas with different protein content. Nevertheless, investigators want to provide data about the impact of these different enteral nutrition formulas on body composition as well as on functionality.

Regarding of the obtained data a change on local and national recommendation considering enteral nutrition in multiple trauma patients is to be expected.

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