Article

Validation of Nutritrauma Strategy for Detection of Harmful Effects of Medical Nutritional Treatment in Critically Ill Patients in Real Life

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Abstract: Aims: Medical Nutritional Treatment (MNT) can be complex and associated to potential metabolic complications, which has been recently described as Nutritrauma. There is no data on the effect of applying this strategy in clinical practice. The aim of our work is to describe if application of Nutritrauma concept in real live is useful to detect metabolic complications associated to the prescription of MNT. Methods: In this descriptive prospective study at a single center, we enrolled 30 consecutive critical ill patients of a 14 beds medical – surgical Intensive Care Unit. The Nutritrauma strategy implementation was based in four M steps: Metabolic screening, MNT prescription, Biochemical Monitoring and Nutritional Management. The primary endpoint was to describe the metabolic complications of the MNT detected with Nutritrauma strategy. Secondary endpoint was to describe the most frequent causes of inappropriate prescription. Results: We analysed 28 patients (mean age 69,7 ± 11,3 years; APACHE II 18,1 ± 8,1, SOFA 7,5 ± 3,7; Nutric Score modified 4,3 ± 2,01 and mean BMI 27,2 ± 3,8). The most frequent disease on admission was sepsis (46,4%). Length of ICU stay was 20,6 ± 15,1 days and 39,3% died during the ICU stay. Enteral nutrition (82,1%) was more frequent than parenteral nutrition (17,9%). During nutritional monitoring 54 specific analytical determinations were made. Hyperglycemia was the most frequent metabolic alteration (83,3% of the determinations). Electrolyte disturbance were hypocalcemia (50%), hypophosphatemia (29,6%) and hypokalemia (27,8%). The most frequent lipid profile abnormality were hypocholesterolemia (64,8%) and hypertriglyceridemia (27,8%). Furthermore, nutritional prescription was modified in the 53,6% of patients: increase protein dosage (25%), increase caloric dosage (21,4%) and change to an organ-specific diet (17,8%). Conclusions: The application of Nutritrauma strategy facilitate the detection of metabolic complications and the evaluation of the appropiate prescription of the MNT. conclusions.

Keywords: metabolic complications; critically ill; nutritrauma; medical nutrition therapy; enteral nutrition; parenteral nutrition

1. Introduction

Treatments for organ failure can present deleterious effects on critically ill patients. Mechanical ventilation or dialysis are essential despite an incorrect prescription on ventilation parameters can produce harmful effects. Barotrauma or dialytrauma has been introduced as syndromic entities, new concepts that has facilitated the general diffusion of these questions, increasing awareness to avoid iatrogenia, and consequently increasing patient's safety (1,2).

Medical nutritional treatments (MNT) in critically ill patients can be complex, mainly during the first days of illness. The ideal prescription of calories, proteins, fiber or electrolytes is difficult, because is affected by basal patient conditions, impact of acute illness, endogenous production, route for

 doi:10.20944/preprints202306.1237.v1

administration… so an special monitoring is suggested (3,4). Over and under prescription of macronutrients is associated to worse prognosis. Moreover, critically ill patients can present comorbid conditions predisposing to refeeding syndrome (5,6).

Recently, Nutritrauma (4) has been described as a structured strategy to increase alert and facilitate the detection of metabolic complications potentially associated to the MNT. The aim of this work was to describe how Nutritrauma strategy implementation in real life help us to detect metabolic complications and inappropriate prescription of MNT in critically ill patients.

2. Materials and Methods

2.1. Subjects and Study Design

A unicenter prospective study was developed in a Medical-Surgical intensive Care Unit with 14 beds of a University Hospital. We included 30 consecutive critically ill patients that received MNT during first trimester of 2020. Patients were monitored from admission to ICU discharge.

Inclusion criteria were: patients admitted to intensive care unit aged 18 years or older with at least 2 organ failures who needs enteral or parenteral nutrition for, at least, 48 hours. Exclusion criteria were patients with a high subjective probability of receive oral nutrition or dead during the first 72h. The present study was approved by the Ethics Committee of the Consorci Sanitari del Maresme (Ref. 52/2019).

2.2. The "Nutritrauma strategy" implementation

A preliminary multitdisciplinary formative session was conducted. Informative posters were designed and a specific biochemical profile was created in the biochemical laboratory petitionary. The strategy was structured in four M steps: Metabolic screening, MNT Design, Monitoring and Management (Figure 1).

2.2.1. Metabolic screening

During first 24 hours of admission, severity of illness [Sequential Organ Failure Assessment (SOFA) (7), Acute Physiology and Chronic Health Evaluation II (APACHE II) (8)], evaluation of nutritional risk (modified Nutric Score) (9) and risk of refeeding syndrome (10) were performed.

2.2.2. MNT prescription

Initial nutrition prescription was according institutional protocol. Caloric and protein requirements were estimated separately, using weight-based formulas (using adjusted weight if BMI was >30). The initial caloric prescription was 10-15 Kcal/kg/day if there was a refeeding syndrome risk, and 20 kcal/kg/day if was no risk. Caloric prescription was increased progressively according to the clinical status. Enteral and/or parenteral route was used to achieve caloric objectives. Protein prescription was adjusted to clinical status (from 1,2 to 2 g/kg/day or 2g/Kg/day if BMI was between 30 or 40) (11).

2.2.3. Biochemical monitoring

A specific blood analytic profile was created (named Nutritrauma) that included:

- Electrolytes: sodium (Na); potassium (K), phosphorus (P), magnesium (Mg), calcium (Ca).
- Liver function analysis: Gamma-Glutamyl Transferase (GGT), Glutamic Oxaloacetic Transaminase (GOT), Glutamic Pyruvic Transaminase (GPT), Alkaline Phosphatase (ALP), Total Bilirubin (and indirect and direct bilirubin if it was anormal)
- Proteins: total proteins, albumin, prealbumin, transferrin
- Lipids: total cholesterol, triglycerides
- Inflammation: C Reactive Protein (CRP), lymphocytes.

2.2.4. Nutritional management

 doi:10.20944/preprints202306.1237.v1

Physicians must design their patient's treatment according to institutional protocol, based on SEMICYUC Guidelines (11). The Nutritrauma blood analysis was performed at the nutrition initiation (day 0), at clinical criteria in presence of abnormal values or nutritional risk, on days 2 and 5, and weekly. Every Wednesday a one-hour multidisciplinary clinical session was performed with presence of the medical ICU staff, a nutritionist, a pharmaceutic, a rehabilitation physician and a physiotherapist.

2.3. Data Collection

The study data included age, sex, weight, and height, Body Mass Index (BMI), APACHE-II and SOFA. Blood levels of total proteins, albumin, prealbumin, transferrin, triglycerides, total cholesterol, CRP, liver function (GGT, GOT, GPT, ALP), and electrolytes (Na, K, Ca, Mg, P] were recorded for each study participant.

During de Wednesday multidisciplinary clinical session nutritional treatment changes were collected as increase of protein and/or caloric dosage, change into an "organ-specific diet" (L-arginina enriched diets, specific diabetic diets and diet for enteral nutrition associated diarrhea) or change to a fiber enriched diet.

2.4. Statistical Analysis

Data were collected in Excel® and exported for analysis to SPSS version 26.0 statistical package (IBM SPSS, Armonk, NY, USA) to perform descriptive analysis of means or medians based on normality for quantitative variables and of proportions for descriptive variables. Normality was analyzed using Shapiro¬–Wilk tests.

3. Results

3.1. Patients Characteristics

From January to march of 2020, 30 consecutives patients were included. Two of them died before initiation of MNT. Mean age was 69,7 ± 11,3 years, the 50% were female with an admission APACHE II 18,1 ± 8,1, admission SOFA 7,5 ± 3,7, and modified Nutric Score 4,3 ± 2,01. The mean body weigh was 77,4 ± 12,9 kilograms and the mean BMI was 27,2 ± 3,8. Four patients (14,4%) had risk of refeeding syndrome. The most frequent disease on admission was sepsis (46,4%), followed by cardiovascular disease (21,4%) and respiratory failure (17,8%). The main MNT route of administration was enteral nutrition (82,1%). The starting time of the nutritional treatment was appropriate in 92,8% of the patients. The patients remained 20,6 ± 15,1 days in ICU and 39,3% died during the ICU stay. Main characteristics of the 28 patients are described in Table 1.

Table 1. Main patient's characteristics.

Main patient's characteristics	N = 28
Age (years); mean (± SD)	69,7 ± 11,3
Male / Female	14 (50%) / 14 (50%)
Weigh (Kg); mean (± SD)	77,4 (± 12,9)
BMI; mean (± SD)	27,2 (± 3,8)
APACHE II; mean (± SD)	18,1 (± 8,1)
SOFA Score; mean (± SD)	7,5 (± 3,7)
Nutric Score; mean (± SD)	4,5 (± 1,9)
Risk of refeeding syndrome; n (%)	4 (14,4%)
Disease on admission; n (%)	
Sepsis	13 (46,4%)
Cardiovascular	6 (21,4%)
Respiratory	5 (17,8%)
Miscellanea	4 (14,4%)

 doi:10.20944/preprints202306.1237.v1

Enteral / Parenteral nutrition	23 (82,1%) / 5 (17,9%)
Adequacy of starting time; n (%)	26 (92,8%)
Hiperglycaemia; n (%)	23 (83,3%)
Fluid overload; n (%)	28 (100%)
Length of ICU stay (days); mean (± SD)	20,6 (± 15,1)
Mortality; n (%)	11 (39,3%)

T Kg: Kilograms; BMI: Body Max Index; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment; ICU: Intensive Care Unit.

3.2. Detection of Metabolic Complications

During follow-up, 54 analytical determinations were made (Table 2). Hyperglycemia was the most frequent metabolic alteration during evolution (83,3% of patients). Electrolyte disturbances were also frequents: hypocalcemia, adjusted for albumin (50%), hypophosphatemia (29,6%) and hypokalemia (27,8%). After identifying the ion deficit, supplementation was started in 100% of the cases. Regarding liver function, 31,5% of the patients had bilirubin elevation > 2 times its baseline value, not being associated, in this case, with MNT. Similarly, 85,2% of the patients presented cholestasis, none of them being treated with parenteral nutrition. Analyzing the lipid profile, hypocholesterolemia (64,8%) was the most frequent laboratory abnormality followed by hypertriglyceridemia (27,8%), and during serial tests both cholesterol and triglyceride levels normalized without specific treatment. All the protein-related biochemical parameters were low during practically the entire follow-up: hypoproteinemia (90,7%), hypoalbuminemia (88,8%), low transferrin (87%) and low prealbumin (72,2%). Finally, 100% of the patients presented anasarca in the evolution.

Table 2. Detected metabolic complications

Analytical determinations		**N = 54**
Inflammation		
Lymphopenia; (n %)		31 (57,4%)
C Reactive Protein; mean (± SD)		16,5 ± 15,3
Glycaemia		
Hyperglycaemia; (n %)		48 (88,8%)
Electrolytes		
Phosphorus	Hypophosphataemia; (n %)	16 (29,6%)
	Hyperphosphataemia; (n %)	5 (9,2%)
	Normal phosphorus; (n %)	33 (61,1%)
Magnesium	Hypomagnesaemia; (n %)	4 (7,4%)
	Hypermagnesaemia; (n %)	7 (12,9%)
	Normal magnesium; (n %)	28 (51,8%)
Calcium	Hypocalcemia; (n %)	27 (50%)
	Hypercalcemia; (n %)	3 (5,5%)
	Normal calcium; (n %)	24 (44,4%)
Potassium	Hypokalaemia; (n %)	15 (27,8%)
	Hyperkalaemia; (n %)	3 (5,5%)
	Normal potassium; (n %)	35 (64,8%)
Lipids		
Cholesterol	Hypercholesterolaemia; (n %)	3 (5,5%)

 doi:10.20944/preprints202306.1237.v1

	Hypocholesterolaemia; (n %)	35 (64,8%)
	Normal cholesterol; (n %)	16 (35,2%)
Triglycerides	Hypertriglyceridaemia; (n %)	15 (27,8%)
	Low triglycerides; (n %)	0 (0%)
	Normal triglycerides; (n %)	39 (72,2%)
Liver function analysis		
Alteration of GGT and ALP; (n %)		46 (85,2%)
Alteration of bilirubin; (n %)		17 (31,5%)
Proteins		
Total proteins	Hypoproteinaemia; (n %)	49 (90,7%)
	Normal proteins; (n %)	5 (9,2%)
Albumin	Hypoalbuminaemia; (n %)	48 (88,8%)
	Normal albumin; (n %)	6 (11,1)
Prealbumin	Low prealbumin; (n %)	39 (72,2%)
	High prealbumin; (n %)	1 (1,8%)
	Normal prealbumin; (n %)	14 (25,9%)
Transferrin	Low transferrin; (n %)	47 (87%)
	Normal transferrin; (n %)	7 (12,9%)

* % expressed the number of described alterations respect the analytical determinations. GGT: Gamma-Glutamyl Transferase; ALP: Alkaline Phosphatase.

3.3. MNT Modifications during multidisciplinary sessions

During the multidisciplinary sessions inappropriate prescription was detected in 53,6% of patients. All of them suffered at least one MNT modification, 3,6% of the patients suffered two modifications and another 3,6% suffered three modifications during their evolution in the ICU. The most frequent modification made was the increase in protein dosage (25%), followed by the increase in caloric dosage (21,4%) and the change to an organ-specific diet (17,8%). The change to a fiber-enriched diet was made in 10,7% of the patients (Table 3).

Table 3. Treatment modifications.

Variable		n = 28
Patients with treatment modifications; n (%)		15 (53,6%)
Number of modifications	1; n (%)	15 (53,6%)
	2; n (%)	1 (3,6%)
	3; n (%)	1 (3,6%)
Type of modification	Increase protein dosage	7 (25%)
	Increase caloric dosage	6 (21,4%)
	Change to organ-specific diet	5 (17,8%)
	Diabetic diet; n (%)	4 (14,2%)
	L-arginina enriched diet; n (%)	1 (3,6%)
	Change to a fiber-enriched diet	3 (10,7%)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 16 June 2023 doi:10.20944/preprints202306.1237.v1

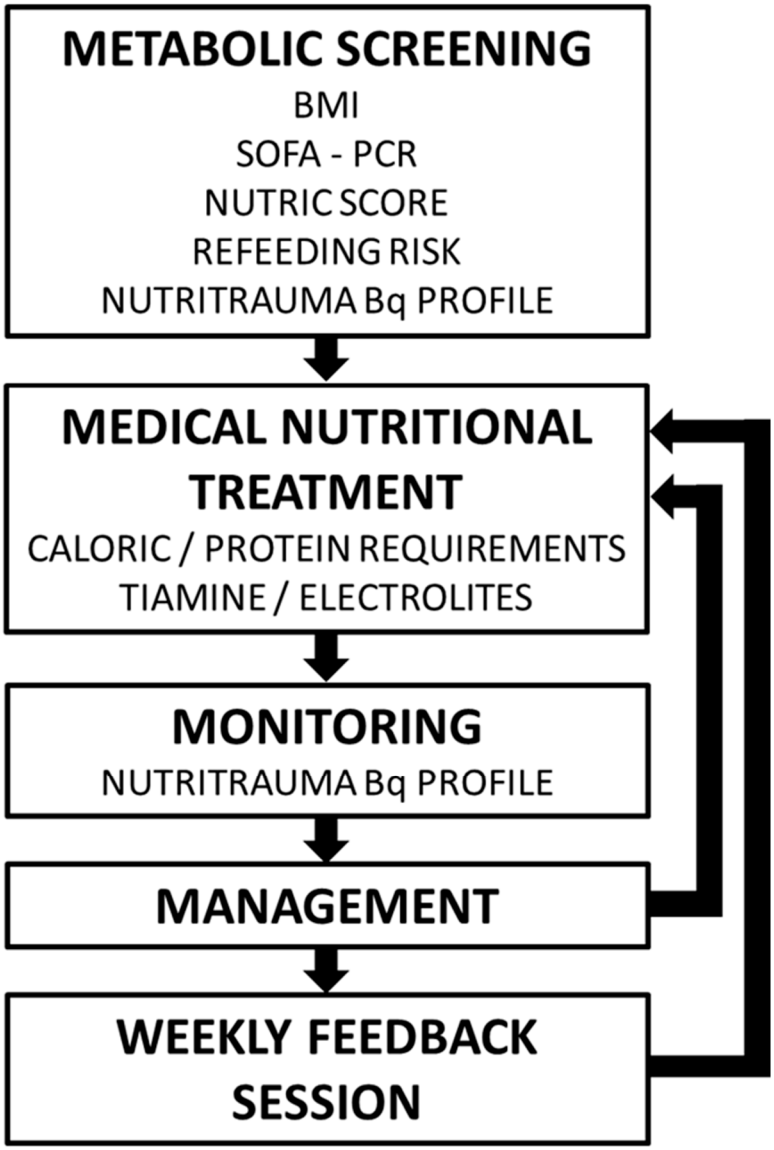

Figure 1. Schema for incorporating the concept of nutritrauma into clinical practice.

4. Discussion

Our work is the first clinical report of the application of nutritrauma concept. In our experience, the grouping of the different complications associated with MNT under the nutritrauma concept facilitated the spread of the concept that inadequate nutritional prescription can be associated with deleterious metabolic effects. The strategy allowed to detect that near 30% of patients presented hypophosphatemia, 50% hypoalbuminemia, and 83% hyperglycemia. Moreover, the combination of the analytical screening with periodical clinical multidisciplinary session facilitated the systematic reevaluation of the MNT, modifying MNT in the 53% of patients.

Glucose blood levels alteration is quite common in critically ill patients. Its prevalence is difficult to know, it depends on the cut-off point we consider hyperglycemia. In our sample, 83,3% of patients presented glucose levels above 150 mg/dL, this data is consistent with that literature describe. Hyperglycemia may be related to overfeeding, insulin resistance in the acute phase of metabolic response, or even insufficient insulin treatment (12). It is described that hyperglycemia is associated with poor clinical outcomes, increase mobidity and mortality (13),alters the immune response, causing increased risk of infection, reduces vascular reactivity and nitric oxide, compromising blood flow and increases proteolysis, being associated with a greater risk of cardiac and renal complications (14). Although treatment of hyperglycemia is associated with better results, strict control is not

 doi:10.20944/preprints202306.1237.v1

recommended, which is associated with higher mortality. That is why most scientific societies recommend glucose levels between 140 – 180 mg/dL (15). Avoiding hyperglycemia is not enough, it is increasingly important to control glycemic variability, which is also associated to mortality (14,15).

Electrolyte disorders, as hypocalcemia (50%) and hypophosphatemia (29,6%) were very frequent. Calcium is the most plentiful mineral in the body. It has skeletal functions, such as bone tissue building and non-skeletal ones. The latter are divided in structural, like organelles or cell membranes formation and regulatory, such as enzymatic reactions to modify cell functions (16). Hypocalcemia may have severe consequences, such as seizures, laryngospasm, prolonged QT or cardiac dysfunction (17). In critically ill patients, abnormal calcium values can be a marker of severity, and it is often corrected spontaneously when the primary disease is solved. There is not enough evidence on the hypocalcemia management, although generalized administration is discouraged to normalize its values and it is concluded that treatment should be guided by basic decision-making principles (18).

Phosphate has several functions in the body (19), as energy function (it is part of adenosine triphosphate, ATP), structural function (it is a component of the phospholipids of cell membranes and nucleic acids), activation of proteins through their phosphorylation, intracellular buffering effect and mineralization of the bone matrix. Hypophosphatemia produces a wide spectrum of symptoms when there is a depletion of intracellular phosphate. Its deficit produces an increase in the affinity of hemoglobin for oxygen, reducing its delivery at the tissues and, the ATP deficit produces alterations in the cellular functions affecting neurological, cardiopulmonary, muscular and hematological systems. In critically ill patients, hypophosphatemia, in addition to the described symptoms, is a risk marker for refeeding syndrome, a syndrome associated with high morbidity and mortality (10). As reflected in the latest ASPEN consensus recommendations on refeeding syndrome (20), the identification of hypophosphatemia can help to identify patients at risk of presenting refeeding syndrome.

During the Nutritrauma strategy the MNT prescription was optimized in 53,6% of patients. In our experience, one of the most frequent difficulty of MNT for not expert physicians, is to adapt de prescription of MNT to the metabolic situation (21) and syndromic characteristics (22–24). Many studies show that the amount of calories and proteins that critical ill patients receives is lower than calculated requirements (25,26). This is associated with worse evolution (27). The evaluation of daily nutritional requirements could minimize this concern. Despite our patients were in a not blinded observational study, underfeeding remained the most frequent complication related with doses. Consequently, the increase of protein (25%) and caloric dosage (20%) were the most frequently modifications.

The qualitative characteristics of the diets can also affect the patient evolution. We introduced changes in the prescription of organ-specific diet in a 17,8% of patients (22). The SEMICYUC recommendations for specialized nutritional – metabolic management of the critical patient includes soluble and insoluble fiber diets to prevent complications such as diarrheal, constipation and tolerance to enteral nutrition (28). We detected a significant percentage of patients that were not receiving fiber-enriched diet, so the prescription of fiber-enriched diet was very common (10,7%).

Finally, the positive effects of multidisciplinary meetings is difficult to measure. To share weekly doubts and interpretations of nutritional practice with experts allows, not only identify wrong dosages and metabolic disorders, but also the increasing of MNT knowledge.

Our work has some limitations. This is a not blinded observational study designed to evaluate applicability of the nutritrauma strategy. In our opinion, the main limitation is that it has been developed in a single center with a low number of patients. However, this is the first clinical application reported of the nutritrauma concept, and the benefits observed encourage us to presents our protocol and results.

5. Conclusions

The concept nutritrauma has been useful to spread the concept that MNT must be carefully designed and monitored to avoid harmful effects. The application of Nutritrauma strategy facilitate

the detection of metabolic complications and the evaluation of the appropriate prescription of the MNT. The weekly multidisciplinary session results in a powerful assistential and educational strategy.

Author Contributions: Conceptualization JCY, IMdL, JP, LC. Methodology all authors. Investigation, IMdL, JP. Formal analysis JCY, IMdL, JP. Review and editing, All authors. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Ethics Committee of Hospital de Mataró (protocol code 52/2019).

Informed Consent Statement: Patient consent was waived due to the observational nature of the project.

Data Availability Statement: Data included in this work is available contacting with the Unitat de Recerca de l'Hospital de Mataró (recerca@csdm.cat).

Conflicts of Interest: The authors declare no conflict of interest.

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