Arch Argent Pediatr 2018;116(4):e515-e521 / e515

Results of the implementation of a nutritional support protocol for major burn pediatric patients hospitalized in the intensive care unit

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Funding:
None.

Conflict of interest:
None.

Received: 8-2-2017
Accepted: 1-23-2018

ABSTRACT

Introduction. "Major burn" is used to describe a person who suffers thermal damage affecting more than 30% of his/her total body surface area (TBSA). The secondary hypercatabolism causes lean body mass loss and delayed wound healing.

Objective. To describe and analyze the results of implementing a nutritional support protocol for pediatric burn patients hospitalized in the intensive care unit in the first 6 weeks.

Population and methods. Analytical, prospective, observational, and longitudinal design. Weight, height, %TBSA, length of stay in the intensive care unit, and mortality were measured. The basal metabolic rate was measured by indirect calorimetry and the Schofield equation, and protein and energy intake, prealbumin, C-reactive protein, vitamins A, D, E, copper, and zinc levels were analyzed every week.

Results. Eighteen patients were included (mean: 3.9 years old, 49%TBSA). The mean energy target was achieved by week 2 and protein requirements were met by week 6. Twelve patients required complementary parenteral nutrition and there were no complications. Hypermetabolism parameters were observed, which returned to normal 4-6 weeks after hospitalization, except for C-reactive protein. Vitamins A and E and trace elements (zinc and copper) were reduced at the time of admission and showed a subsequent improvement. Vitamin D remained low. One patient died.

Conclusions. Implementing the protocol was useful to cover the total energy requirement; the coverage of protein requirements was delayed until week 6. It is necessary to focus on solving limitations to achieve the latter.

Key words: *burn unit, nutritional support, micronutrients, nitrogen balance, basal metabolism.*

http://dx.doi.org/10.5546/aap.2018.eng.e515

To cite: Tramonti N, Lema J, Araujo MB, et al. Results of the implementation of a nutritional support protocol for major burn pediatric patients hospitalized in the intensive care unit. *Arch Argent Pediatr* 2018;116(4):e515-e521.

GLOSSARY

ANOVA: analysis of variance.
BMI: body mass index.
BMR: basal metabolic rate.
CMIA: chemiluminescence microparticle immunoassay.
CO_2: carbon dioxide.
CPG: clinical practice guideline.
CRP: C-reactive protein.
GRADE approach: Grading of Recommendations Assessment Development and Evaluation.
HPLC: high pressure liquid chromatography.
IC: indirect calorimetry.
ICU: intensive care unit.
NB: nitrogen balance.
NGT: nasogastric tube.
O2: oxygen.
PN: parenteral nutrition.
RV: reference value.
UUN: urine urea nitrogen.
%TBSA: percentage of total body surface area burned.

INTRODUCTION

"Major burn" patients have been defined as those who suffer thermal damage affecting more than 30% of total body surface area (TBSA).[1]

They require exclusive nutritional solutions because the metabolic consequences are deep and account for a constant challenge. The extent of burn wounds directly affects rehydration, nutritional support, and interventions.

The hypermetabolism secondary to the secretion of counterregulatory hormones (adrenaline, cortisol, and glucagon) determines that the skeletal muscle acts as the main mandatory fuel, while the ability to use fat as a source of energy is reduced,[2] which causes a great loss of lean body mass over few weeks following the injury. A delayed escharotomy, transient and definite wound coverage, and sepsis also contribute to rhabdomyolysis[3] due to an even greater increase in basal metabolic rate.[4]

Such great metabolic display starts immediately after the burn. The acute phase takes place in the first 8-12 weeks of the burn wound[5] and causes lean body mass loss, muscle weakness, and delayed wound healing. This process worsens in the case of insufficient energy and protein intake, which may lead to infections, organ dysfunction, and finally, death.

Besides, micronutrients play a key role in immunity, protein synthesis, and antioxidant activity. Micronutrient stores are depleted due to the increased production of free radicals and lipid peroxidation and the loss through wounds, urine, drainages, diarrhea[6] and suction devices.[7] Assessment is also hindered by the acute phase response and the reduction in carrier proteins and micronutrient redistribution. In addition, there is no consensus regarding the dose and route of supplementation due to the interaction in absorption when given enterally and the potential toxicity in the case of sustained high doses.[6]

For these reasons, providing intensive nutritional support is essential for the management of these patients because it reduces mortality.[2]

In order to optimize nutritional support, a protocol was developed based on a non-systematic review of the bibliography under the GRADE approach, which was subsequently published as a clinical practice guideline (CPG 2016) by Hospital de Pediatría Garrahan.[8]

The objective of this study was to describe and analyze the results of the nutritional support protocol implemented in patients with burns in more than 30%TBSA hospitalized in the intensive care unit (ICU) during the first six weeks of admission.

POPULATION AND METHODS

Analytical, prospective, observational, and longitudinal design. All male and female children and adolescents younger than 16 years with burns affecting more than 30%TBSA admitted to the ICU of Hospital Garrahan between October 2014 and August 2015 were included by consecutive sampling. In all cases, the informed consent was obtained from their parents or legal guardians. The study was supported by the hospital's Research Ethics Committee.

The following criteria from the nutritional support protocol were applied to all patients, which was developed based on the algorithm below.

Brief protocol description: Initially, the energy target (indirect calorimetry or Schofield equation + 30%) and the protein intake target (3 g/kg/day for children and 1.5-2 g/kg/day for adolescents), which will be achieved mainly by enteral route, are defined. Following hemodynamic stabilization, in the first 24-48 hours of hospitalization, enteral feeding is started (using a nasogastric tube [NGT] except contraindications [ileus and/or altered intestinal perfusion]) in the form of continuous enteroclysis with lactose-free formula at an ideal nonprotein calories to nitrogen ratio of 100:1. Then formula is used based on the specific algorithm. If the target volume (70%) is not achieved by 72 hours of intake initiation, after attempting to solve limitations (e.g., transpyloric tube changing to hydrolyzed formula), complementary parenteral nutrition (PN) is started. PN starts without lipids, at a maximum glucose flow of 5-7 mg/kg/min, and amino acids at a rate of 30 g/L.

In the case of exclusive PN, by day 7, lipids should be added at a rate of 0.5 g/kg/day and increased to 1 g/kg/day after 24 hours if triglycerides are < 250 mg/dL. Enteral tolerance should be reassessed on a daily basis and PN should be reduced as enteral feeding progresses. Micronutrient requirements (vitamins A, E, and D, and trace elements, zinc and copper) are covered with both enteral multivitamin supplementation and PN. Micronutrient intake is trebled, in average, by adding the formula given by enteral feeding.

Study outcome measures

Weight was measured upon admission using a bed-scale, and height was registered in the dorsal recumbent position using an infantometer. The body mass index (BMI) and the corresponding Z-scores were estimated. Sex, age, percentage of total body surface area (%TBSA), etiology, and length of stay in the ICU in days were registered.

The basal metabolic rate (BMR) (energy required to keep the normal physiological functioning at rest) was measured by indirect calorimetry (IC) using gas exchange with measurement of oxygen (O_2) uptake and carbon dioxide (CO_2) production (CCM Express by MEDGRAPHICS) during 20 minutes. For patients who could not have an IC, BMR was estimated using the Schofield equation.[8,9]

Energy intake was defined as BMR + 30% to avoid requirement underestimation.

The weekly average of enteral and parenteral intake was obtained from the nursing records and was used to estimate energy (calories/kg) and protein (grams of proteins/kg) intake. Energy and nitrogen balance (NB) was estimated until oral feeding was started.

A 24-hour kinetic assay for urine urea was done with urease and glutamate dehydrogenase (reference value [RV]: 12-20 g/24 hours). NB was estimated according to the following formula:

NB = protein intake – urine nitrogen (N) – stool/skin N – N loss from burn wound

N from protein intake: proteins in g/6.25. Urine N: (urine urea from 24 hour collection/2.1) + 20%. Stool/skin N: 2 g/day for children < 4 years old, 3 g/day for children between 4 and 10 years old, and 4 g/day for children > 10 years old. N loss from burn wound: 0.12 g/kg/day.

The following lab tests were done: prealbumin and C-reactive protein (CRP), both using an automated immunoturbidimetric method (RV: 20-40 mg/dL and < 5 mg/L, respectively), vitamins A and E by high pressure liquid chromatography (HPLC) (RV: 20-50 mcg/dL and from 600 mcg/dL, respectively). Trace elements: copper and zinc, by atomic absorption spectroscopy (RV: 66-166 mcg/dL and 50-120 mcg/dL, respectively), and vitamin D by chemiluminescence microparticle immunoassay(CMIA) (RV: > 30 ng/mL).

All measurements were obtained in weeks 1, 2, 3, 4, and 6 after hospitalization.

Outcome variables

The time to initiation of enteral feeding, weekly energy and protein intake, and mortality were assessed.

An acceptable intake was defined as achieving 70% of the energy and protein target.

Statistical analysis

A descriptive and analytical assessment was done. The behavior of each outcome measure was analyzed and, according to their distribution, they were described as normal, mean and standard deviation or as biased, median, and range. Student's t test and the Wilcoxon rank-sum test were used for normal and biased distribution outcome measures, respectively. Categorical outcome measures were analyzed using the χ^2/Fisher test. An analysis of variance (ANOVA) was done to identify the differences between the serial measurements of the same outcome measure. A two-tailed test and a statistical significance of $p < 0.05$ were assumed. The statistical software package used was STATA 10.

RESULTS

Eighteen patients who met the inclusion criteria were recruited. Demographic data are described in *Table 1*. Patients' median age was 3.9 years (0.2-14.9). Twelve patients were male. From an anthropometric perspective, all patients had a normal nutritional status based on their BMI Z-score. The %TBSA was 49% (34-87%); 55% of patients suffered a burn caused by direct fire. Twelve patients (66%) started enteral feeding in the first 48 hours of admission. The median length of stay in the ICU was 45 days (10-144 days).

Energy requirements and enteral and parenteral intake are shown in *Table 2*. Given that enteral intake was analyzed until oral intake was started, the number of patients analyzed each week reduced as follows: week 1, 100% (18/18); week 2, 94% (17/18); week 3, 83% (15/18); week 4, 72% (13/18), and week 6, 61% (11/18).

The total energy and protein intake was increased significantly on a weekly basis (ANOVA p 0.03). As observed in *Table 2*, the mean energy requirement coverage was achieved by week 2 of hospitalization, whereas the mean protein target was achieved only by week 6.

Complementary PN was required by 67% (12/18) of patients at some point during hospitalization.

Figure 1 shows that 6/18 patients achieved an acceptable energy target in the first week, while all patients did it as of week 2 after hospitalization.

In relation to protein intake, 10/18 patients achieved an acceptable protein intake by week

Table 1. *Demographic data (n= 18)*

Outcome measure	Mean ± SD/median (range)
Age (years)	3.9 (0.2-14.9)
Weight Z-score	0.7 (-0.6 to 2.3)
Height Z-score	1.1 (-1.2 to 2.4)
BMI Z-score	19.2 (± 2.2)
Total body surface area burnt (%)	49 (34-87%)
Length of stay at the ICU (days)	45 (10-144)

BMI: body mass index; ICU: intensive care unit; SD: standard deviation.

2, which was increased on a weekly basis. When analyzed as a continuous outcome measure, the mean protein requirement was covered by week 6.

The mean prealbumin level in this population was reduced at the time of hospitalization (6.9 ± 3.2) and increased in a statistically significant manner by weeks 3, 4, and 6 ($p < 0.01$); however, PCR levels remained high. Urine urea nitrogen (UUN) increased from hospitalization to week 3 (8.2 ± 3.8 versus 13.1 ± 3.8; p 0.03) and then reduced in a statistically significant manner. In addition, NB varied significantly: it was negative at initiation and became positive by week 6 *(Table 3)*.

Table 4 shows the weekly micronutrient determinations and the percentage of patients with normal values. Vitamins A and E reduced at the time of hospitalization and subsequently increased (ANOVA $p < 0.01$). Vitamin A returned to normal in all patients by week 6, whereas vitamin E did it by week 3. No statistically significant differences were observed between copper and zinc levels at the time of hospitalization and the subsequent determinations; however, they returned to normal in 60% of the studied population by week 6. Conversely, vitamin D remained reduced during the study period.

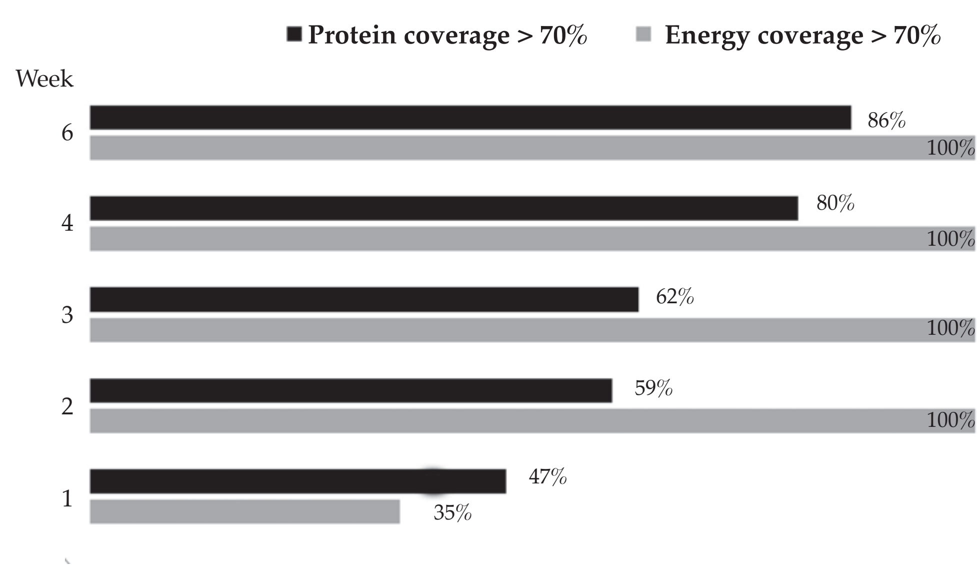
No significant differences were observed in micronutrient levels among patients who would have complementary PN or not.

One patient died due to multiple organ failure secondary to sepsis.

Table 2. *Energy requirement and enteral and parenteral intake (initial n = 18)*

	Energy intake from enteral feeding (cal/kg/day)	Protein intake from enteral feeding (g/kg/day)	Energy intake from parenteral feeding (cal/kg/day)	Protein intake from parenteral feeding (g/kg/day)	Total energy intake (cal/kg/day)	Total protein intake (g/kg/day)	% received of energy target	% received of protein target
Week 1	28	0.8	16.5	1.3	31	1.2	61	60
N = 18	(8.8-93)	(0.3-2.7)	(5.8-32.6)	(0.3-2)	(13.5-93)	(0.45-4)	(26-138)	(15-106)
Week 2	59	1.8	12	1.5	59	2.1	115	73
N = 17	(22-98)	(0.8-2.9)	(5.4-32)	(0.4-2)	(22-98)	(1.2-3.9)	(76-182)	(17-140)
Week 3	54	1.3	18.5	1.2	58	2.2	121	93
N = 15	(26-96)	(0.7-2.8)	(8.3-25)	(0.7-1.9)	(27-96.7)	(1.5-3.8)	(72-172)	(35-126)
Week 4	44	1.4	19	1.3	53	2.1	109	94
N = 13	(10-79)	(0.3-2.5)	(10-42)	(0.9-2.2)	(13.5-95)	(1.6-3.8)	(75-170)	(60-126)
Week 6	54	1.8	17.8	1.3	80	3.2	139	110
N = 11	(35-102)	(1-3.5)	(8-45)	(0.7-2.2)	(35-102)	(1-4)	(110-166)	(50-133)

Figure 1. *Percentage of patients who achieved 70% of the energy and protein intake target*



DISCUSSION

It is worth noting the importance of using a nutritional support protocol for critically-ill burn patients. There is ample bibliographic evidence in favor of its use to boost nutritional support success.[2] Hamilton et al.[10] found a significant decrease in enteral feeding interruptions and in the time to achieve energy requirements by implementing a protocol to this end.

The total energy intake increased significantly on a weekly basis and the mean energy requirement coverage was achieved by week 2 of hospitalization, whereas the mean protein target was achieved only by week 6. The delayed achievement of protein intake may have been due to clinical limitations, such as hemodynamic instability, acute renal failure, etc., and to the use of enteral formulas, which, despite having a lower nonprotein calories to nitrogen ratio compared to formulas for non-critically-ill children, are still less effective to achieve protein intake in patients with a high requirement. Complementary PN was used if there were limitations that prevented the achievement of the energy/protein intake target by enteral feeding.[11-13] In this regard, a cautious use of PN has been supported by experts for critically-ill pediatric patients if an adequate intake cannot be achieved with enteral feeding.[14,15] If the energy requirement is exceeded, overfeeding may lead to increased CO_2, fatty liver, increased urea nitrogen, and hyperglycemia.[11]

The increase in prealbumin levels observed in weeks 3, 4, and 6, compared to the first week values, was statistically significant, and no differences were seen in acute phase reactants (PCR), which was simultaneous to the positivization of NB. The increased protein catabolism has been widely described together with a greater UUN loss and a negative NB until the second week after the burn.

Diaz et al. characterized the rate of protein synthesis in 87 children with severe burn wounds for 24 months and found that it had remained high in the first year following the burn.[16]

Once determinations are made, protein synthesis increases, which is indispensable for wound healing and graft adhesion. The achievement of energy and protein intake targets reduces, but does not cancel, protein catabolism.

Vitamins A and E were reduced at the time of hospitalization and subsequently increased (ANOVA $p < 0.01$). Most studies agree that, two weeks after the burn, these vitamins are

TABLE 3. *Prealbumin, C-reactive protein, urine urea nitrogen from 24-hour collection and nitrogen balance levels (n = 18)*

	Week 1	Week 2	Week 3	Week 4	Week 6
Prealbumin (mg/dL)	6.9 ± 3.2	9.5 ± 4.7	13.8 ± 7.8#	11.3 ± 5.6*	18.4 ± 8#
CRP (mg/dL)	143 ± 105	125 ± 90	143 ± 126	185 ± 139	135 ± 161
Urine urea nitrogen, 24 h (g/day)	8.2 ± 3.8	9.6 ± 5.3	13.1 ± 3.8#	7.9 ± 3.4*	7.8 ± 5.5*
Nitrogen balance (g/day)	-2.3 ± 4.7	-0.7 ± 4.5	1.3 ± 2.9	-0.4 ± 1	2 ± 2#

CRP: C-reactive protein.
* p < 0.01 compared to week 1.
# p < 0.005 compared to week 1.

TABLE 4. *Plasma determinations of vitamins A, E, and D and trace elements zinc and copper, and percentage of micronutrient determinations in the normal range (n = 18)*

	Week 1		Week 2		Week 3		Week 4		Week 6	
Vitamin A	18	22%	21	55%	22.5	62%	37	80%	53	100%
20-50 mcg/dL	(10-40)		(15-34)		(9-63)		(17-45)		(35-100)*	
Vitamin E	537	44%	837	77%	1339	100%	1421	100%	1432	100%
> 600 mcg/dL	(403-1832)		(432-1271)		(912-2016)*		(898-2334)*		(938-2207)*	
Vitamin D	10.8	0%	13.5	0%	13.2	0%	12.3	0%	17.4	0%
> 30 ng/mL	(6.8-26.8)		(7.6-23.8)		(9-25.9)		(9-19)		(9-21.7)	
Copper	50	0%	40	11%	35	12%	52.8	33%	62	63%
66-166 mcg/dL	(18.9-63.9)		(22-68)		(30-76)		(51-60)		(30-117)	
Zinc	51	45%	44	22%	39.5	5%	51.5	75%	63	65%
50-120 mcg/dL	(22-108)		(29-61)		(32-44)		(37-54)		(25-110)	

* p < 0.01 compared to week 1.

reduced[17] and that alpha-tocopherol, a marker of vitamin E store in adipose tissue, decreases on a daily basis.[18] The normalization of plasma levels has been described in adults by day 21 following the burn with enteral feeding supplementation.[19]

In this study, vitamin D levels decreased since the time of hospitalization and remained below the normal range. This is consistent with previous studies that confirmed the reduced levels of vitamin D and its carrier protein, and consider that part of such alteration might be caused by the hypoproteinemia typical of the acute phase of patients with major burns. Other authors[20] have confirmed, in adults with a history of a burn in >50%TBSA, a reduction in bone formation and mineral stores compared to healthy controls. Such alteration may be caused by multiple factors: hypoalbuminemia, inflammatory cytokines, endogenous and exogenous corticosteroids, immobilization, inadequate intake, in addition to loss from wounds and the inability to conduct synthesis at the level of the epidermis.[21] In addition, Klein et al. observed a persistent vitamin D deficiency in children with a history of a burn of >40%TBSA, even up to 7 years later.[22]

In our study, low copper and zinc levels were observed at the time of hospitalization, which returned to normal by week 6 in 60% of the studied population. Both minerals, as well as their carrier proteins (albumin and ceruloplasmin), and their redistribution from the muscle and bone to the wound and other tissues, have been described to be reduced.[2] Studies conducted in children with burns of >40%TBSA receiving enteral supplementation three times the recommended dose were not able to establish that plasma levels returned to normal at the time of discharge from the hospital.[23] In addition, Berger et al. demonstrated, in a prospective study in adults with severe burn wounds, that intravenous supplementation with copper, zinc, and selenium improved wound healing, the number of infections,[24] and protein catabolism.[25] The dose and route of administration of micronutrients are still controversial.

Further studies are required that focus specifically on micronutrient supplementation, wound healing, and mortality.

CONCLUSIONS

The implementation of the nutritional support protocol was useful to achieve a mean energy requirement by week 2, although protein intake requirements were delayed until week 6. For this reason, it was necessary to enhance enteral intake with a formula with a lower nonprotein calories to nitrogen ratio or with complementary parenteral nutrition. ■

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