Clinical Nutrition xxx (2016) 1–10

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Evaluation of a new concept of immune-enhancing diet in a model of head-injured rat with infectious complications: A proof of concept study

Christine Charrueau [a, 1], Christophe Moinard [b, 1], Saskia Brinkmann [b], Caroline Choisy [b], Marie-José Butel [c], Michel-Francis Bureau [d], Servane Le Plénier [b], Françoise Brignole-Baudouin [e], Nathalie Neveux [b, f], Luc Cynober [b, f, *], Jean-Pascal De Bandt [b, f]

[a] Laboratoire de Pharmacie Galénique, EA4466, Faculté des Sciences Pharmaceutiques et Biologiques, Université Paris Descartes, Sorbonne Paris Cité, 4 avenue de l'Observatoire, 75270 Paris Cedex 06, France
[b] Laboratoire de Biologie de la Nutrition, EA4466, Faculté des Sciences Pharmaceutiques et Biologiques, Université Paris Descartes, Sorbonne Paris Cité, 4 avenue de l'Observatoire, 75270 Paris Cedex 06, France
[c] Laboratoire de Microbiologie, EA 4065, Risk in Pregnancy Department, Faculté des Sciences Pharmaceutiques et Biologiques, Université Paris Descartes, Sorbonne Paris Cité, 4 avenue de l'Observatoire, 75270 Paris Cedex 06, France
[d] Unité de Technologies Chimiques et Biologiques pour la Santé (UTCBS) CNRS UMR 8258-INSERM U1022, Faculté des Sciences Pharmaceutiques et Biologiques, Université Paris Descartes, Sorbonne Paris Cité, 4 avenue de l'Observatoire, 75270 Paris Cedex 06, France
[e] Laboratoire de Toxicologie, Faculté des Sciences Pharmaceutiques et Biologiques, Université Paris Descartes, Sorbonne Paris Cité, 4 avenue de l'Observatoire, 75270 Paris Cedex 06, France
[f] Service de Biochimie, Hôpital Cochin, Hôpitaux Universitaires Paris Centre, APHP, Paris, France

ARTICLE INFO

Article history:
Received 19 August 2015
Accepted 8 April 2016

Keywords:
Trauma
Enteral nutrition
Sepsis
Arginine
Glutamine

SUMMARY

Immune-enhancing diet (IED) utilization in critically ill septic patients is still debated. A new concept of IED has been proposed combining extra glutamine sequentially with either antioxidants or other amino acids, in order to match patient requirements according to their response to injury. We evaluated whether this new IED elicits a more favorable response to stress when compared with two existing IEDs both enriched in arginine but with different levels of anti-oxidants, in a validated rat model combining head injury (HI) and infectious complications. Forty-eight HI rats were randomized into four groups ($n = 11–13$ per group) to receive, for 4 days, standard enteral nutrition (S), one of the two existing IEDs (IED1, IED2), or the new IED (IED3; providing glutamine and antioxidants for two days and glutamine and specific amino acids for two days). Two days after HI, the rats received an enteral bolus of luminescent *Escherichia coli* Xen14 to induce infection, and bacterial dissemination was evaluated. Body weight (BW) was recorded daily. Four days after HI, animals were euthanized; blood was sampled; organs were weighed; cumulated nitrogen balance (CNB) and nitrogen efficiency were determined. IED3 was more efficient than IED1 and IED2 in improving BW recovery from D3 (D3 *vs.* D1, $p < 0.05$) after HI. It significantly improved CNB and net protein utilization (IED3 *vs.* S, IED1, IED2, $p < 0.05$). An IED with sequential administration of anti-oxidants and glutamine may be better suited to meeting nutritional requirements in severe catabolic states.

1. Introduction

Immune-enhancing diets (IEDs) have demonstrated their efficacy when given to patients in perioperative care [1,2]. However, despite intense debate over the last decade [3–5], the use of IEDs in critically ill patients is still controversial. Indeed, while some studies have demonstrated a beneficial effect of such diets in

* Corresponding author. Faculté de Pharmacie, UP Nutrition (case 16), 4 avenue de l'Observatoire, F-75270 Paris Cedex 06, France. Tel.: +33 1 53 73 99 45/99 47; fax: +33 1 53 73 99 52.
E-mail address: luc.cynober@parisdescartes.fr (L. Cynober).
[1] These two authors contributed equally to this work.

http://dx.doi.org/10.1016/j.clnu.2016.04.018
0261-5614/

critically ill patients, others suggest that IEDs may increase mortality, in particular in septic situations [3], possibly because of a too-high arginine (Arg) supply, leading to excessive nitric oxide (°NO) production [6]. To the best of our knowledge, this claim is not clearly supported by clinical data. Moreover, in a recent trial in which medical intensive care patients received an enteral diet solely enriched with Arg (200 mg/kg/d), there was no over-mortality and even the SOFA score tended to improve compared to non-supplemented patients [7]. Similar results were obtained in traumatized rats [8] or in diabetic obese critically ill rats [9]. According to the SCCM/ASPEN guidelines, trauma patients are clearly defined as appropriate candidates for the use of IEDs (Grade B) while caution should be observed in patients with severe sepsis [10].

It must be emphasized that, besides varying Arg content, IEDs also contain other immuno-modulatory compounds in varying amounts and these nutrients may interact with each other [11,12]. For instance, trace element and micronutrient supply also varies among IEDs (e.g. from one- to nine-fold for vitamin C content) (see Table 1). Glutamine (Gln) is also present in some IEDs, such a supplementation being indicated in trauma situations (Grade B) [10]. While Gln is generally considered as safe this has been questioned recently [13]. Indeed, Heyland et al. [13] suggested that Gln supplementation in ICU patients might be harmful. However, the significance of these results seems limited as their patients suffered multiple (at least two) organ failure, Gln-supplemented patients received extraordinary large doses of Gln (60–80 g/day) resulting in greatly unbalanced diet, and some of them only received very low energy and protein supply outside their Gln supplement [14–16].

While there are plenty of experimental studies on the effects of individual immunonutrients, only a limited number has evaluated the complete products available on the market. While they do not enable to define the specific role of each nutrient within the product, such studies may be very useful as a rationale for future nutritional care strategy. From the data presented above, it appears clearly that every new IED has to be evaluated to determine its clinical utility in specific clinical situations.

Recently, a new concept of IED has been proposed taking into account the fact that the response to injury is not a linear process. Indeed, the initial response includes a major oxidative stress and inflammation possibly evolving into Systemic Inflammatory Response Syndrome (SIRS), septic shock and multiple organ failure. The second phase is a compensatory anti-inflammatory response possibly leading to a depression of immunity and Compensatory Anti-inflammatory Response Syndrome (CARS) which may lead to fatal secondary infections [17]. It makes sense that nutritional requirements could be very different in these two phases justifying a disease-specific time-dependent diet approach [18]. Thus the proposed IED has been developed as two supplements associating extra Gln and cysteine (Cys) with either some anti-oxidants or some other amino acids (but not Arg) added to a conventional diet and administered sequentially in order to prevent exaggerated responses to stress, i.e. SIRS and CARS respectively [17]. In the first supplement, specific amino acid addition aims at preventing inflammation-induced alterations and promoting nitrogen equilibrium since i) cysteine is rate-limiting for glutathione synthesis and thus promote the protection against oxidative stress, ii) threonine and serine are abundant in acute phase proteins and in mucins which protect intestinal mucosa from physical–chemical damages, and iii) aspartate plays a key role in intermediary nitrogen metabolism [18]. In the second supplement, vitamins C and E, β-carotene, zinc and selenium addition aimed at improving immune response [19].

We hypothesize that the use of this new sequential nutrition could lead to a more favorable response to stress in catabolic states than conventional IED enriched with Arg with or without pharmacological levels of anti-oxidants. The present study therefore set out to compare this new concept with two existing IEDs enriched with Arg. For this purpose, a validated rat model combining Head Injury (HI) and infectious complications was used [8,20]. This model mimics the biphasic response to injury and the metabolic alterations observed in head trauma patients with infectious complications. Since this situation is characterized by alterations in protein metabolism, nutritional status, and immune status [21,22], we focused our attention on related biomarkers.

Table 1
Composition of the enteral products under study (per liter of mixture).

	Sondalis HP®	IED1 (high arginine)	IED2 (high arginine, high antiox)	ID3[a] glutamine cysteine	
				+Antiox	+3 other AA
Energy (kcal/L)	1500	1010	1500	–	–
Proteins[b] (g/L)	75	56[c]	94[c]	–	–
Carbohydrates (g/L)	170	134	135	–	–
Lipids (g/L)	58	28	66	–	–
ω-3 fatty acids (g/L)	1.5	3.4	3.8	–	–
Free arginine (g/L) (Arg)	–	12.8	12.5	–	–
Protein-bound Arg (g/L)	2.3	1.4	2.0		
Free taurine (g/L) (Tau)	–	–	0.15	–	–
Free glutamine (g/L) (Gln)	–	–	–	24	12
Free cysteine (g/L) (Cys)	–	–	–	5	5
Free threonine (g/L) (Thr)	–	–	–	–	3
Free serine (g/L) (Ser)	–	–	–	–	9.2
Free aspartate (g/L) (Asp)	–	–	–	–	3.8
Vit C (mg/L)	110	67	600	260	–
β-Carotene (mg/L)	–	–	0.54	12	–
Vit A (μg RE/L)	900	1000	2100	–	–
Vit E (mg ET/L)	18	30	65	40	–
Zinc (mg/L)	14	15	36	12	–
Selenium (μg/L)	60	47	98	100	–

[a] IED3: Gln, cysteine and antioxidants on one hand and Gln, cysteine, threonine, serine, aspartate on the other hand were provided as powder mixtures and mixed with Sondalis HP® before use.
[b] Provided as whole (Sondalis, IED1) or partially hydrolyzed (IED2) casein.
[c] Including free L-arginine.

Please cite this article in press as: Charrueau C, et al., Evaluation of a new concept of immune-enhancing diet in a model of head-injured rat with infectious complications: A proof of concept study, Clinical Nutrition (2016), http://dx.doi.org/10.1016/j.clnu.2016.04.018