Clinical Nutrition 33 (2014) 785–792

Contents lists available at ScienceDirect

Clinical Nutrition

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

Original article

Cost-effectiveness of omega-3 fatty acid supplements in parenteral nutrition therapy in hospitals: A discrete event simulation model

Lorenzo Pradelli [a,*], Mario Eandi [b], Massimiliano Povero [a], Konstantin Mayer [c], Maurizio Muscaritoli [d], Axel R. Heller [e], Eva Fries-Schaffner [f]

[a] AdRes HE&OR, Turin, Italy
[b] Pharmacology, Università degli Studi di Torino, Via Pietro Giuria 13, I-10100 Torino, Italy
[c] Lung Transplant Program, Internal Medicine, Pulmonary Medicine, Intensive Care Medicine, Sleep Medicine, Department of Internal Medicine, Justus-Liebig University Giessen, Klinikstrasse 36, D-35392 Giessen, Germany
[d] Internal Medicine, Università La Sapienza, Via del Policlinico 155, I-00161 Rome, Italy
[e] Clinic for Anaesthesiology and Intensive Therapy, University Dresden, Fetscherstraße 74, D-01307 Dresden, Germany
[f] Fresenius Kabi Deutschland GmbH, Rathausplatz 12, D-61348 Bad Homburg, Germany

ARTICLE INFO

Article history:
Received 11 July 2013
Accepted 27 November 2013

Keywords:
Parenteral
Nutrition
Omega-3
Model
Cost
Pharmacoeconomics

SUMMARY

Background & aims: A recent meta-analysis showed that supplementation of omega-3 fatty acids in parenteral nutrition (PN) regimens is associated with a statistically and clinically significant reduction in infection rate, and length of hospital stay (LOS) in medical and surgical patients admitted to the ICU and in surgical patients not admitted to the ICU. The objective of this present study was to evaluate the cost-effectiveness of the addition of omega-3 fatty acids to standard PN regimens in four European countries (Italy, France, Germany and the UK) from the healthcare provider perspective.

Methods: Using a discrete event simulation scheme, a patient-level simulation model was developed, based on outcomes from the Italian ICU patient population and published literature. Comparative efficacy data for PN regimens containing omega-3 fatty acids versus standard PN regimens was taken from the meta-analysis of published randomised clinical trials ($n = 23$ studies with a total of 1502 patients), and hospital LOS reduction was further processed in order to split the reduction in ICU stay from that in-ward stays for patients admitted to the ICU. Country-specific cost data was obtained for Italian, French, German and UK healthcare systems. Clinical outcomes included in the model were death rates, nosocomial infection rates, and ICU/hospital LOS. Probabilistic and deterministic sensitivity analyses were undertaken to test the reliability of results.

Results: PN regimens containing omega-3 fatty acids were more effective on average than standard PN both in ICU and in non-ICU patients in the four countries considered, reducing infection rates and overall LOS, and resulting in a lower total cost per patient. Overall costs for patients receiving PN regimens containing omega-3 fatty acids were between €14 144 to €19 825 per ICU patient and €5484 to €14 232 per non-ICU patient, translating into savings of between €3972 and €4897 per ICU patient and savings of between €561 and €1762 per non-ICU patient. Treatment costs were completely offset by the reduction in hospital stay costs and antibiotic costs. Sensitivity analyses confirmed the robustness of these findings.

Conclusions: These results suggest that the supplementation of PN regimens with omega-3 fatty acids would be cost effective in Italian, French, German and UK hospitals.

1. Introduction

In Italy, France, Germany and the UK, a substantial part of hospital budgets is dedicated to ICU costs, owing to the technological and personnel resources required.

Critically ill and surgical patients receive parenteral nutrition (PN) when oral or enteral nutrition is impossible, insufficient, or contra-indicated. Interest in omega-3 fatty-acid rich fish oil-

* Corresponding author.
E-mail addresses: l.pradelli@adreshe.com (L. Pradelli), mario.eandi@unito.it (M. Eandi), m.povero@adreshe.com (M. Povero), Konstantin.Mayer@uglc.de (K. Mayer), maurizio.muscaritoli@uniroma1.it (M. Muscaritoli), Axel.Heller@uniklinikum-dresden.de (A.R. Heller), Eva.Fries-Schaffner@fresenius-kabi.com (E. Fries-Schaffner).

http://dx.doi.org/10.1016/j.clnu.2013.11.016

containing lipid emulsions as part of a PN regimen has increased in recent years, with the recognition that they supply not only energy and essential fatty acids, but also very long-chain fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acids (DHA), which are considered to be clinically beneficial.

A meta-analysis conducted on 23 studies – thirteen conducted in 762 patients admitted to an ICU, and ten in 740 elective surgical patients, not admitted to ICU[1] – showed that the use of fish oil-containing lipid emulsions as part of a PN regimen was associated with statistically significant and clinically relevant reductions in infection rate and of hospital and (where appropriate) ICU lengths of stay (LOS). Furthermore, supplementation with omega-3 fatty acids confers important benefits, including increased serum concentrations of alpha-tocopherol, increased EPA and DHA content of phospholipids, and enhanced leucocyte activity, together with a possible hepato-protective action (as evidenced by less elevation of ALT and AST), and a significantly greater reduction in interleukin-6 (IL-6) during the first days after initiation of the PN regimen.

The aim of the present study was to evaluate the cost-effectiveness of adding omega-3 fatty acids to standard PN regimens by merging evidence on the clinical outcomes in the Italian population with clinical effectiveness estimates from the aforementioned international meta-analysis and health resource consumption strategy in Italian hospitals. These cost-effectiveness results for Italy were then extrapolated using health resource consumption data from France, Germany and the UK in order to judge whether difference clinical practices resulted in similar pharmacoeconomic outcomes. The four national scenarios investigated represented different clinical practices for PN: in Italian and French settings, three-chamber bags are used for PN; in the UK, lipid emulsion units are used as a component of compounded PN admixtures; in the German setting, both of these systems are used (three-chamber bags or single bottles/bags).

2. Methods

For the present evaluation we used a decision analytic Discrete Event Simulation (DES) pharmacoeconomic model that includes: (i) outcomes from the Italian ICU patient population and from published literature; (ii) partially re-elaborated efficacy data from a meta-analysis of published randomised clinical trials that included 23 studies with a total of 1502 patients receiving PN supplemented with omega-3-rich fatty acids or PN standard regimens[1]; (iii) national Italian cost data; and (iv) extending these results to three further national scenarios by using French, German and UK cost data. Standard PN may be defined as those containing non-enriched lipid emulsions, namely, soybean oil, medium-chain triglycerides/long-chain triglycerides or olive/soybean oil emulsions. Please note that further details on the methods used in this study are available as a Supplementary on-line appendix.

2.1. Italian model

2.1.1. Model structure

The model was built using a DES scheme designed with the use of TreeAge Pro 2009 (TreeAge Software Inc., Williamstown, MA) software. In a DES, changes in the individuals' state are modelled over time in terms of events that occur and the consequences of those events. This DES strategy, rather than a Markov model, is used as it is particularly suitable for non-chronic situations where the timing and chronology of events are important, such as in patient groups under consideration in this study (surgical and ICU patient populations given PN).

The model simulates two treatment alternatives for patients needing PN: parenteral omega-3 enriched emulsions or standard lipid emulsions. Moreover, two patient populations are considered in this study: (i) medical and surgical patients with an ICU stay and (ii) surgical patients without an ICU stay. The following events are considered: transfers between ICU and ward, nosocomial infections, discharge from the hospital, and death, with the last two events determining the end of treatment. A simplified model structure is shown in Fig. 1(a) and (b) (for ICU and non-ICU patients, respectively). For ICU patients the publicly available *Progetto Margherita* report data are used as this is extensive and representative of the ICU population, but no such comparable source is available for non-ICU patients, therefore we used international clinical trial data for this population.[2–7]

2.1.2. Probability and outcomes

The main clinical outcomes simulated by the model are: death rate in the ICU, infection rate in the ICU, death rate in the ward, and length of hospital stay (LOS) which is divided into LOS pre-ICU, LOS in the ICU, and LOS in the ward (post-ICU for ICU patients).

The data source used for estimating the probability distributions of these outcomes in the ICU population is the 2009 edition of the *Progetto Margherita* report, an annual publication on behalf of the *Gruppo Italiano* per *la Valutazione degli Interventi in Terapia Intensiva* (GIVITI) that includes data collected in 230 Italian ICUs from a total of over 77 000 patients.[8] The GIVITI network, which covers more than half of all ICUs operating in Italy, is coordinated at the Mario Negri Institute of Pharmacology in Milan, and conducts constant monitoring of the activities and outcomes of participating ICUs. These range from medium to large in scale, university-affiliated and non-university-affiliated ICUs, and reflect the range of ICUs found in Italy. Data are collected at the patient level using standardised computer software.

The outcomes after ICU admission for this population are: (i) death in ICU (19.0%); (ii) transfer to a general ward (79.7%), or (iii) discharge from the ICU directly to home (1.3%). Among patients transferred to the general ward after ICU discharge, the mortality rate is 7.9%. In this patient population, the risk of new nosocomial infections acquired in the ICU is 11.4%. For the elective surgical population, the outcomes are: (i) death in the ward (4.76%) or (ii) discharge from ward (95.24%), and the risk of nosocomial infections is 23.0%: these represent weighted averages of the control groups included in the recent meta-analysis.[1]

The *Progetto Margherita* reports detailed information regarding hospital and ICU lengths of stay, with data given for the overall population and for subgroups of ICU/hospital outcomes. Distribution curves were fitted to these data to mathematically represent these distributions in the model, giving simulation input data for ICU patients (as shown in Table 1). For non-ICU patients, the same curve-fitting procedure was applied to data from the literature.[2–7] The times-to-events applied to the simulated patients are drawn from these fitted distributions.

2.1.3. Simulation and sensitivity analysis

In our model, the simulation takes into account the variability among individuals, while the probabilistic sensitivity analysis (PSA) allows us to consider the uncertainty of key parameters and its effect on the estimated outcomes, verifying the robustness of the numerical outcomes. This was done using a two-level Monte Carlo simulation. A deterministic sensitivity analysis (DSA) was also used. This allows us to investigate which input parameters had the greatest impact on incremental total cost and LOS. The parameters employed in the PSA and DSA analyses and their related distributions are reported in Tables 1and 2. Further details on the simulation and these sensitivity analyses is provided in the Supplementary on-line appendix.