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Review

Systematic review and meta-analyses of the effect of lipid emulsion on microbial growth in parenteral nutrition

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SUMMARY

Background: As lipid in parenteral nutrition (PN) purportedly enhances microbial growth, recommendations limit infusion of lipid PN (or lipid emulsion) from a single container to 24 h (48 h for lipid-free PN). However, the associated evidence base is ambiguous.
Aim: To examine factors affecting microbial growth in PN.
Methods: A systematic review with meta-analyses examined effects of nutrients on microbial growth in PN infusates over a 48-h period using the growth ratio {GR=$\log_{10}$[colony-forming units (cfu)/mL at 48 h/cfu/mL at time zero]}.
Findings: Factors influencing GR in PN included glucose, microbial species, temperature, osmolarity, presence of vitamins, trace elements and lipid, and amino acid profile. Using unmatched datasets (N=306), a general linear model found that lipid inclusion in PN represented 3.3% of the variability, which was less than that due to glucose concentration (5.8%), microbial species (35.3%) and microbe–infusate interaction (4.4%). Using matched datasets (N=38 pairs), lipid inclusion in PN represented 5.4% of the variability (P=0.076), which was less than that due to glucose concentration (8.5%; P=0.025), microbial species (75.5%; P<0.001) and microbe–infusate interaction (13.3%; P=0.382). Using meta-analyses of matched datasets, the presence of lipid in PN at fixed glucose concentrations did not significantly increase GR of *Candida albicans*, *Escherichia coli* or *Staphylococcus epidermidis* (P=0.352, P=0.025 and P=0.494, respectively; overall P=0.175).
Conclusion: Lipid inclusion in PN is only one of several factors that may influence microbial growth in PN. Any recommendations about the duration of PN infusion from a single container should account for all these factors, and should be weighted according to microbial species likely to contaminate PN.

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Introduction

Parenteral nutrition (PN) is of great value to patients with intestinal failure, but can cause severe morbidity, and even death, when inadvertently contaminated with microbes.[1–7] PN is often considered an ideal microbial growth medium, and slow administration at room temperature offers the opportunity for microbes to multiply and cause adverse effects. Therefore, multiple approaches are used to prevent inadvertent microbial contamination of PN, and to limit growth of any microbes present, including PN preparation under aseptic technique in pharmaceutical facilities meeting recognized standards (e.g. those applicable in the USA[8] or UK [9,10]) and less frequent bag changes. In addition, the Healthcare Infection Control Practices Advisory Committee (HICPAC) concluded that lipid inclusion in PN poses a specific risk for microbial growth.[11] It therefore recommended that administration sets linked to lipid PN (or lipid emulsion) should be replaced within 24 h after infusion commencement, but the replacement could be delayed for up to 48 h for lipid-free PN. The Cochrane Collaboration[12] and the UK epic project[13] supported the HICPAC recommendations after finding no evidence to challenge them. Other organizations such as the European Society for Clinical Nutrition and Metabolism (ESPEN) have also reported lipid PN to be an infection risk should administration sets be used beyond 24 h.[14] Collectively, these developments have had a profound impact on clinical practice by restricting administration of lipid PN from a single bag to no more than 24 h in situations when it might otherwise have been infused over longer periods, such as when starting or weaning. However, there may be disadvantages in replacing lipid PN bags more frequently, such as workload increases for those preparing PN and for nurses changing bags more frequently, and more bag changes may increase the risk of sepsis. An alternative approach to meet the HICPAC recommendations is to replace 48-h infusions of lipid PN with lipid-free PN, but this may confuse staff, and cause hyperglycaemia which increases the risk of sepsis.

The evidence base underpinning the above recommendations consists of a small number of studies of variable quality which sometimes did not compare lipid and lipid-free PN, and which sometimes reported conflicting results. In addition, certain guideline recommendations have been based on expert opinion alone. Where published evidence has been used as the basis of recommendations, little or no consideration appears to have been given to confounding variables and methodologies used; moreover, several studies have been omitted from guideline formulation, including one (published in 1987 prior to any of the guideline group reviews) which reported that growth of a range of microbes was no more likely in PN containing lipid compared with lipid-free PN.[15]

The main aim of this study was to critically examine the robustness of evidence suggesting that microbial growth is greater in lipid PN compared with lipid-free PN, taking into account confounding variables. It also aimed to make research recommendations around any uncertainties.

Methods

This systematic review was undertaken using the recommendations of the Cochrane Collaboration,[16] the UK National Health Service Centre for Reviews and Dissemination,[17] and PRISMA.[18]

Primary outcome

The primary outcome was the extent of microbial growth promotion or suppression over 48 h in lipid emulsion, lipid PN and lipid-free PN, expressed as a microbial growth ratio {GR=$\log_{10}$ [colony-forming units(cfu)/mL at 48 h/cfu/mL at time zero]}.

Inclusion and exclusion criteria

The inclusion criteria were publications (journal articles) in the English language of laboratory-based microbial growth studies in lipid emulsion, lipid PN or lipid-free PN over a 48-h period. Abstracts reporting work subsequently published as full papers were excluded. Publications were also excluded if they duplicated previous work or if cfu/mL were not reported at both time zero and at 48 h (except for one publication[19] that reported cfu/mL at time zero and at 40 h). Furthermore, studies that did not define infusate composition were excluded.

Literature search

The literature search undertaken on 22nd February 2014 used all available years in three databases: Medline (OvidSP) from 1946, Embase (OvidSP) from 1947, and the complete Cochrane Library. Supplementary File I shows the search terms (including variations and pleural terms) used in combination and the corresponding numbers of identified publications. In total, 14,700 publications were identified: 7546 from Medline, 6145 from Embase, and 1009 from the Cochrane Library. Removal of duplicates left 10,623 publications. Eight additional publications were identified by cross-referencing, hand-searching and discussion with experts in the field.[20–27] Of the total 10,631 publications, 10,562 were excluded by review of the abstracts. The complete texts of the remaining 69 records were examined; 45 further records were excluded (Figure 1), leaving 24 full-text papers for detailed review.[15,19–41]

Data extraction

Different strains of the same microbial species were grouped. For each microbial species in each infusate type in each record, the cfu/mL at time zero and at 48 h were taken from the text or a magnified version of graphically represented results, or the raw cfu/mL data from three records[20–22] published by the authors' group. Data were excluded for unspecified or unclear infusate formulations, or if there was no practical way to establish the cfu/mL accurately at both time points. GR >0 indicates microbial growth (an increase in cfu/mL) and GR<0 indicates microbial decline (a decrease in cfu/mL). One record reported the cfu/mL of *Enterococcus durans* in lipid emulsion at 48 h to be zero,[22] which is described narratively as it could not be included in the present analyses due to the mathematical difficulties of taking $\log_{10}$ of zero.

Statistics

Two main sets of analyses were undertaken: an unmatched analysis of all identified data, except for *E. durans* in lipid emulsion (see above); and a matched analysis based on within-study methodologies. Matched analyses involved GR estimation