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Enteral and Parenteral Nutrition in Cancer Patients - Complication Rates Compared: Updated Systematic Review and Meta-Analysis

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ABSTRACT

Background: The aim of this systematic review and meta-analysis is to compare the complication rates of enteral nutrition (EN) (oral or tube feeding) and parenteral nutrition (PN) in patients with any cancer.

Methods: A systematic review of the literature until 2024 was conducted, including randomized controlled trials comparing EN and PN with respect to one or more of four endpoints: (i) infection, (ii) nutrition support complications, (iii) major complications, and (iv) mortality. Meta-analysis was conducted to generate summary effect estimates. Analysis was stratified by pediatric (≤21 years old) versus adults (>21 years old) patients. Subgroup analyses were conducted, based on including patients with (vs without) protein-energy malnutrition and type of enteral nutrition. Cumulative meta-analysis and leave-one-out analysis was conducted. Type I error was set at 0.05.

Results: 49 studies reporting on 6,361 patients were included: 41 reported on adults and 8 on children. Among adults, the infection rate was higher for PN compared to EN (RR=1.07, 95% CI: 1.00-1.14), with no differences in rates of nutrition support complications, major complications or mortality. Among children, there were no differences in all four endpoints. On cumulative meta-analysis, EN was overall marginally superior to PN for infection, although results fluctuated over time between superiority and no difference. Subgroup analysis found no differences in effects among patients with (vs without) protein-energy malnutrition, and patients provided with EN options of standard care vs tube feeding.

Discussion: From the perspective of complications, EN and PN are equivalent, with EN demonstrating marginal superiority for infection among adults.

Keywords: cancer, weight loss, cachexia, nutrition support, enteral nutrition, parenteral nutrition, complications, infection, morbidity, mortality

INTRODUCTION

Weight loss in cancer patients receiving non-palliative therapy is a poor prognostic indicator for disease progression and mortality.[1-3] It therefore follows that to counter weight loss during treatment with nutritional support, enterally or parenterally, will lead to improved outcomes.[3-7] The provision of enteral nutrition (EN), defined as feeding by oral route or enteral route, and parenteral nutrition (PN) has been extensively studied in the past, notably with two systematic reviews published in 2016[8] and 2020.[9]

The review published in 2016 compared complication rates of EN and PN in patients with cancer, specifically assessing the rates of infection, nutrition support complications, major complications and mortality. With 36 articles included in the review, it found that only infection rates were slightly higher among PN patients, and otherwise EN and PN were equivalent for rates of nutrition support complications, major complications and mortality.[8]

In 2020, an updated review was published with an addition of 7 articles, leading to a total of 43 articles in the review. Meta-analysis yielded similar conclusions as the 2016 review, and additional cumulative meta-analysis reported that there has been no significant change in summary effect estimates since 1997.[9]

Since then, several new articles have been published comparing EN and PN in patients with cancer receiving non-palliative therapy, which report on complication rates. The aim of this review is to update the previously-published systematic reviews and meta-analyses, to compare complication

rates of EN and PN in patients with cancer receiving active treatment as reported in randomized controlled trials (RCT).

METHODS

Literature Search

A literature search was carried out with the assistance of an information specialist (CW). Databases of Medline, Embase, and Cochrane Central Register of Controlled Trials were utilized, employing similar strategies to the two previous reviews.[8,9] Restrictions were placed for English-language articles, RCTs, and time restriction from 2018 to 2024. The search strategy is reported in Appendix 1. Backwards reference screening, of reviewing reference lists of included articles in this review, was also conducted. The 43 articles from the prior review were added to screening.

Selection Criteria

After a calibration exercise of 10 articles, two authors (RC, LMT) independently and in-duplicate screened records through level 1 title & abstract and level 2 full text screening. In case of discrepancies, discussion occurred between the two authors to achieve consensus; if unable to achieve consensus, a third author participated in discussion to help achieve consensus. In level 1 screening, articles were eligible for level 2 screening if they reported on a randomized controlled trial of EN vs PN. In level 2 screening, articles were assessed for data extraction if they reported on a sample population where over 50% of patients had cancer, in keeping with criteria used in previous reviews.[8,9] Articles were ultimately included in this review if they had extractable data, reporting on one of four endpoints as detailed subsequently.

Endpoints

The two primary endpoints were the percentage of patients who did not experience infection and who did not experience nutrition support complications. The two secondary endpoints were the percentage of patients who did not experience major complications and who did not experience mortality.

These endpoints are in-keeping with those used in the previous 2016 and 2020 reviews.[8,9] As previously published, infection was defined as "minor infections" including wound infection, pneumonia and sepsis. Nutrition support complications included nausea, vomiting and diarrhea. Major complications include major complications and morbidity, as reported by studies. Mortality was recorded as reported in literature. Where clarification was needed between study definitions and definitions used in our meta-analysis, corresponding authors were contacted for clarification of endpoints and collection of more data

Data Extraction

As with screening, two reviewers (RC, JHBI) independently and in-duplicate extracted data for each study included in this review. Endpoints, as previously described, were noted. Patient demographics of mean age, percentage female, study reporting on children (≤ 21 years old) or adults (>21 years old), cancer diagnosis and whether patients were malnourished or had protein-energy malnutrition (PEM) were noted. If studies did not report the population to have PEM or be malnourished, it was assumed there were no malnourished patients. Descriptions of EN (including tube feeding (TF) vs standard care (SC)) and PN were recorded.

For each study, quality assessment was conducted using Cochrane Risk of Bias tool version 2[10] and results presented visually using robvis.[11]

Statistical Analysis

Meta-analysis was conducted using random-effects DerSimonian Laird model.[12] Summary effect estimate of risk ratio (RR) and corresponding 95% confidence intervals (CI) were calculated for each endpoint for all included studies, stratified by age group (children vs adults). Cumulative meta-analysis was conducted. Sensitivity analysis with leave-one-out meta-analysis was conducted. Subgroup analysis was conducted based on whether studies included patients with PEM/malnourishment, type of EN (TF vs SC) and study quality based on quality assessment. Heterogeneity was assessed using I^2, with > 50% suggesting notable heterogeneity. Egger's test[13] and funnel plots were conducted to assess for publication bias. Type I error was set at 0.05. All analyses were conducted using StataBE 18.0.

RESULTS

After literature search and duplicates removed, 311 records were screened in addition to the 43 in the prior review, and ultimately 49 articles were included in this updated review (Appendix 2). Quality assessment found low risk of bias for the majority of studies, with another one-third having some concern, predominantly driven by concern with respect to bias from the randomization process (Appendix 3).

Study demographics are presented in Supplemental Table 1. Eight studies reported on pediatric patients,[14-21] and 41 on adult patients.[22-62] 34 studies administered TF (1 pediatric study, 33 adult studies), and 15 studies (7 pediatric studies, 8 adult studies) administered SC for EN.

Infection

37 studies reported on infection; 33 studies reported on adults and 4 studies reported on children. Among adults, there was a higher rate of infection for PN compared to EN (RR=1.07, 95%CI: 1.00-1.14, I^2=0.00%, Figure 1). Cumulative meta-analysis found that summary effect estimates initially reported no difference from 1977 up until 1997, at which point PN was noted to have higher rates of infection than EN (RR=1.15, 95%CI: 1.00-1.31, Appendix 4.1). From 2001 to 2018, summary effect estimates reverted to reporting no difference. In 2018, effect estimates briefly reported significant differences (RR=1.07, 95%CI: 1.00-1.14, Appendix 4.1), before again reverting to reporting no differences. With the inclusion of the last study in 2021, summary effect estimate changed again from reporting no difference to reporting higher rates of infection for PN (RR=1.07, 95%CI: 1.00-1.14, Appendix 4.1). Leave-one-out analysis identified no single influential study (Appendix 4.2). There was no concern for publication bias (p=0.396, Appendix 4.3). Subgroup analyses found no difference by studies reporting on PEM patients (p=0.69, Appendix 5.1), type of EN (p=0.39, Appendix 5.2) and study quality (p=0.91, Appendix 5.3).

Among children, there was no difference in infection rates between EN and PN (RR=1.26, 95%CI: 0.88-1.79, I^2=0.00%, Figure 1). Cumulative meta-analysis found the summary effect estimate to be unchanged over time (Appendix 6.1). Leave-one-out analysis suggested there was one study by van Eys et al[17] that may have had a larger impact on the summary effect estimate than other studies

(Appendix 6.2). There was no concern for publication bias (p=0.341, Appendix 6.3). Subgroup analyses found no differences by PEM (p=0.94, Appendix 7.1) and study quality (p=0.87, Appendix 7.3); all studies used SC, for EN.

Nutrition Support Complications

24 studies reported on nutrition support complications; 21 studies reported on adults and 3 studies reported on children. Among adults, there was no difference in nutrition support complications between EN and PN (RR=0.99, 95%CI: 0.92-1.06, I^2=0.00%, Figure 2). Cumulative meta-analysis found no change in summary effect estimate over time (Appendix 8.1). Leave-one-out analysis found no single study with significant influential effect on the summary effect estimate (Appendix 8.2). There was no concern for publication bias (p=0.875, Appendix 8.3). Subgroup analyses found no difference by whether studies reported on patients with PEM (p=0.58, Appendix 9.1), type of EN (p=0.56, Appendix 9.2) and study quality (p=0.90, Appendix 9.3).

Among children, there was no difference in nutrition support complications between EN and PN (RR=1.09, 95%CI: 0.68-1.75, I^2=0.00%, Figure 2). Cumulative meta-analysis was stable over time (Appendix 10.1). Leave-one-out analysis reported no significant influential study (Appendix 10.2). There was no concern for publication bias (p=0.900, Appendix 10.3). Subgroup analyses by PEM (p=0.92, Appendix 11.1) and study quality (p=0.91, Appendix 11.3) found no differences; all studies used SC for type of EN.

Major Complications

23 studies reported on major complications; all studies reported on adult patients. There was no difference between EN and PN with respect to major complications (RR=1.04, 95%CI: 0.96-1.12, I^2=0.00%, Figure 3). Cumulative meta-analysis found no change in summary effect estimate over time (Appendix 12.1). Leave-one-out analysis reported no significantly influential study (Appendix 12.2). There was no concern for publication bias (p=0.419, Appendix 12.3). Subgroup analysis found no difference by PEM (p=0.27, Appendix 13.1), type of EN (p=0.97, Appendix 13.2) and study quality (p=0.94, Appendix 13.3).

Mortality

37 studies reported on mortality; 31 studies reported on adults and 6 studies reported on children. Among adults, there was no difference in mortality between EN and PN (RR=1.00, 95%CI: 0.94-1.06, I^2=0.00%, Figure 4). Cumulative meta-analysis found no difference in conclusion since the first publication in 1977 (Appendix 14.1). Leave-one-out analysis identified no single influential study (Appendix 14.2). There was no concern for publication bias (p=0.873, Appendix 14.3). Subgroup analyses found no difference by studies reporting on PEM patients (p=0.93, Appendix 15.1), type of EN (p=0.92, Appendix 15.2) and study quality (p=0.91, Appendix 15.3).

Among children, there was no difference in mortality between EN and PN (RR=1.01, 95%CI: 0.76-1.34, I^2=0.00%, Figure 4). Cumulative meta-analysis found no difference in conclusion since the first publication in 1980 (Appendix 16.1). Leave-one-out analysis identified no single influential study (Appendix 16.2). There was no concern for publication bias (p=0.826, Appendix 16.3). Subgroup analyses found no difference by PEM patients (p=0.96, Appendix 17.1), type of EN (p=0.99, Appendix 17.2) and study quality (p=1.00, Appendix 17.3).

DISCUSSION

In this updated systematic review and meta-analysis, we report on 49 articles and 6,361 patients comparing EN and PN with respect to complication rates. In keeping with the previous reviews in 2016[8] and 2020[9], there was no difference between EN and PN with respect to any complication except for infection rates in adults, for which EN was marginally superior. Cumulative meta-analysis reported no change in summary effect estimate with publication of each additional trial across nearly 3 decades for all outcomes, with the exception of adult infection rates. Leave-one-out meta-analysis found only one significantly influential study with large effect on the summary effect estimate regarding infection in children.

We report an increased volume of literature and robustness of summary effect estimate for adults compared to pediatric patients. There are limited studies included in our review for pediatric children, and therefore the emphasis of interpretation and generalization should be limited to the adult population. As well, it is notable that most studies reporting on hematologic malignancies are in the pediatric setting, where patients tend to be more neutropenic and therefore at higher risk of infection. Given the higher rate of infection for PN compared to EN in adults, further studies are needed to determine whether infection rates are also higher with PN in children.

Based on all literature to date, EN has marginally lower infection rates than PN. However, it is intriguing to note that these two are nearly equivalent in infection rates since 2001, with significant difference in summary effect estimate only noted fleetingly after one study in 2018 and now also noted after the latest study in 2021. Otherwise, there is equipoise between EN and PN with respect

to nutrition support complications, major complications and mortality. Furthermore, there was no difference in effect based on whether patients had protein energy malnutrition, or type of enteral nutrition provided.

From the perspective of complications from nutritional support, our findings support the current guidelines by the European Society of Clinical Nutrition and Metabolism (ESPEN),[5] European Society of Medical Oncology (ESMO)[6] and Multinational Association of Supportive Care in Cancer (MASCC)[7] to prefer EN over PN if possible, when oral nutrition or tube feeding is adequate. Aside from the marginal difference in infection rates, we suggest that when considering whether to employ EN or PN, other factors aside from complication rates should be considered.[9] As previously reported,[9] EN has a noted benefit of lower cost[28] and easier initiation and maintenance, making it potentially superior for community and lower complexity centers. On the other hand, PN requires less time to improve nutritional status, leading to shorter hospital stays.[63] PN is also less likely to be interrupted if patients need to have oral intake restricted or interrupted (NPO) for diagnosis or treatment.[26]

The quality of literature is high, with a low risk of bias for the majority of included studies. Subgroup analyses found no difference in effect by study quality. From Egger's test and funnel plots, there was no publication bias. Additionally, the lack of significant results from cumulative meta-analysis aside from infection and leave-one-out meta-analyses suggest that the existing literature is robust. It is unlikely that any new high-quality studies will significantly change summary effect estimate, and therefore unnecessary for further studies to focus exclusively on complication rates in adults, although further studies specifically in children are needed.

This meta-analysis has several advantages compared to the prior analyses. This is the most comprehensive and robust meta-analysis to date, and with 49 articles and a sample size of 6,361, the statistical power of this meta-analysis well-surpasses that of previous analyses. The 2020 analysis added to the results from the 2016 analysis[8] by conducting subgroup analysis by age and cumulative meta-analysis.[9] In this study, we conducted analysis stratified by age, and subgroup analyses by type of EN and nutrition status within these strata, recognizing that pediatric and adult patients are different and distinct populations with unique treatment considerations. Furthermore, we augmented assessment for publication bias by completing Egger's test, and reported on leave-one-out analysis to identify any substantially influential studies impacting the summary effect estimate.

This study was not without limitations. As inherent in systematic review methodology, the strength of the meta-analyses' conclusions depend on the strength of the underlying literature. The literature on adult populations is robust, with overall good quality. There is limited literature on pediatric populations; thus less emphasis and generalization should be placed on the results pertaining to children. Additionally, as a consequence of including studies across 5 decades and in a dynamic field of research, there are heterogeneous definitions and recording methods for infections, nutrition support complications and major complication outcomes, for which corresponding authors were contacted where necessary for clarification of endpoints and collection of more data.[9]

In conclusion, this meta-analysis reports no difference in rates of nutrition support complications, major complications and mortality between enteral and parenteral nutrition in patients with cancer.

EN is associated with a marginally lower rate of infection in adults. From the perspective of complications, enteral and parenteral nutrition are equivalent, with marginal superiority noted for EN. There already exists robust data in the literature over the past 5 decades, and it is unlikely new studies will provide substantial added value to the literature, particularly in adults; future studies should focus on pediatric populations and on investigating other rationales for selecting enteral or parenteral nutrition.

STATEMENTS

Contributorship statement: RC is responsible for study conception and design. RC, LMT, JHBI and CW are responsible for acquisition of data. All authors (RC, JHBI, JA, EDF, LMT, DQ, SB, CW, GW, ML, EP, LE, CZ, EB) contributed significantly and substantially to the conduct and reporting, and all (RC, JHBI, JA, EDF, LMT, DQ, SB, CW, GW, ML, EP, LE, CZ, EB) are guarantors.

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Figure 1. Infection

Figure 2. Nutrition Support Complications

Figure 3. Major Complications

Figure 4. Mortality