Nutrition support in hospitalised adults at nutritional risk: a Cochrane systematic review of randomised clinical trials

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Danish Abstract

Baggrund

Litteraturstudier har vist modsigende resultater med hensyn til ernæringsterapi. Vores formål var at undersøge fordelene og ulemperne ved ernæringsterapi sammenlignet med ingen intervention, sædvanlig behandling eller placebo hos hospitaliserede patienter i ernæringsrisiko.

Metoder

Vi udførte en Cochrane systematisk oversigtsartikel med meta-analyse og Trial Sequential Analysis. Vi søgte på Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS, Science Citation Index Expanded og fem yderligere databaser indtil februar 2016. Vi inkluderede alle lodtrækningsforsøg der inkluderede hospitaliserede patienter i ernæringsrisiko vurderet ved enten screeningsværktøjer, specifikke sygdomme associerede med er at være i ernæringsrisiko eller ved forsøgsinvestigators definition. Vores primære effektmål var mortalitet, alvorlige skadelige hændelser og livskvalitet.

Fund

244 forsøg der inkluderede i alt 28.619 deltagere. All forsøg var i høj risiko for bias. Vores meta-analyser viste, at ernæringsterapi (set som én overordnet intervention) ikke påvirkede mortaliteten (RR 0·94, 95% CI 0·86 to 1·03, P = 0·16, I^2 = 0%, 21.758 deltagere, 114 forsøg) eller alvorlige skadelige hændelser (RR 0·93, 95% CI 0·86 to 1·01, P = 0·07, I^2 = 0%, 22.087 deltagere, 123 forsøg). Trial Sequential Analyses viste, at vi havde nok information til at afvise en relativ risiko reduktion på mere end 10%. Når vi analyserede de forskellige slags ernæringer hver for sig, virkede enteral ernæring (sondeernæring) til at reducere både mortaliteten og alvorlige skadelige hændelser ved maksimal opfølgning. De resterende slags ernæringsterapier (general ernæring, beriget

ernæring, oral ernæring og parenteral ernæring) virkede ikke til at have en effekt på mortalitet eller alvorlige skadelige hændelser. Kun 16 forsøg undersøgte livskvalitet og ernæringsterapi virkede ikke til at have nogen effekt.

Tolkning af resultater

Vi fandt ingen kliniske vigtige fordele eller ulemper ved at give ernæringsterapi til hospitaliserede voksne i ernæringsrisiko. Enteral ernæring (sondeernæring) er måske den eneste form for ernæring, som kan være fordelagtig at give til hospitaliserede patienter. Fremtidige forsøg der undersøger ernæringterapi bør udføres med lav risiko for bias, lav risiko for tilfældige fejl og inkludere livskvalitet som et effektmål.

Finansiering af studiet

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English abstract

Background

Reviews have shown contradictory results with regard to the effects of nutrition support. Our objective was to assess the benefits and harms of nutrition support versus no intervention, treatment as usual, or placebo in hospitalised adults at nutritional risk.

Methods

We conducted a Cochrane systematic review with meta-analysis and Trial Sequential Analysis. We searched the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS, Science Citation Index Expanded, and 5 additional databases until February 2016. We included all randomised clinical trials of hospitalised participants at nutritional risk according to screening tools, specific diseases, and trialists' judgement. Our primary outcomes were mortality, serious adverse events, and quality of life.

Findings

244 clinical trials randomising a total of 28,619 participants were included. All trials were at high risk of bias. Meta-analyses showed that nutrition support (analysed as one overall intervention) did not affect mortality (RR 0·94, 95% CI 0·86 to 1·03, P = 0·16, I^2 = 0%, 21,758 participants, 114 trials) or serious adverse events (RR 0·93, 95% CI 0·86 to 1·01, P = 0·07, I^2 = 0%, 22,087 participants, 123 trials). Trial Sequential Analyses showed that we had enough information to reject relative risk reductions of more than 10%. Analysing each type of nutrition support separately, enteral nutrition (tube feeding) seemed to reduce all-cause mortality and serious adverse events at maximum follow-up. The remaining types of nutrition support (general nutrition, fortified nutrition,

oral nutrition, and parenteral nutrition) did not seem to have any effects on all-cause mortality or serious adverse events. Only 16 trials assessed quality of life and nutrition support had no effect.

Interpretations

Overall, we found no clinically important beneficial or harmful effects of nutrition support in hospitalised adults at nutritional risk. Enteral nutrition (tube feeding) might be the only single nutrition support intervention that offers benefit to hospitalised patients. Future trials assessing nutrition support interventions ought to be conducted with low risks of systematic errors, low risks of random errors, and include quality of life assessments.

Funding

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Background

The prevalence of malnutrition in patients in Western European hospitals is about 30%.[1,2] Nutrition support is relatively expensive and time consuming. Several reviews have assessed the effects of nutrition support.[3-10] However, these reviews focused on one or a few types of nutrition support which decreases the statistical precision and power and makes it impossible to compare the effects of the different types of nutrition support. Furthermore, none of the reviews searched all relevant databases and took account of both risks of random errors and systematic errors.

This present systematic review summarises the most important findings of our Cochrane systematic review on nutritional support in hospitalised adults considered at nutritional risk.[11,12]

Methods

Search strategy and selection criteria

We have published a protocol with a detailed description of the methods used.[11] Here, we summarise the methodology.

The methodology is based on The Cochrane Handbook for Systematic Reviews of Interventions and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for meta-analyses of interventional studies.[13,14] We used meta-analysis and Trial Sequential Analysis when relevant.[15]

We included eligible randomised clinical trials irrespective of publication type, publication status, publication date, and language. We searched for trials in the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, LILACS, and Science Citation Index Expanded, from conception till February 2016. In addition, we searched: 1) the World Health Organization International Clinical Trials Registry Platform (www.who.int/ictrp); clinicaltrials.gov; Turning Research Into Practice (TRIP); Google Scholar; and BIOSIS; 2) the bibliographies of review articles and already identified trials; 3) conference proceedings from the American Society for Parenteral and Enteral Nutrition and the European Society for Parenteral and Enteral Nutrition meetings; and 4) contacted national nutrition collaborations as well as 10 pharmaceutical companies. The search strategies can be found in our protocol.[11]

Two review authors (JF and EEN) screened the initial searches. The evaluation and data extraction of the identified trials were divided among 16 authors, including four authors fluent in Chinese. Two independent authors evaluated each trial. If the two authors disagreed, a third author (JCJ) resolved the issue.

Two review authors independently assessed the risk of bias of each included trial according to the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions*, and the Cochrane Hepato-Biliary Group Module.[13,16]

We accepted any intervention that the trialists classified as nutrition support, or similar terms, as experimental intervention. This included general nutrition (i.e., dietary advice), fortified nutrition (normal food enriched with extra protein), oral nutrition (protein shakes), enteral nutrition (tube feeding), and parenteral nutrition (feeding through an intravenous catheter).[17] We did not include non-standard nutrition support interventions.[11]

We accepted 'no intervention', placebo, or 'treatment as usual' (as defined by trialists) as control intervention. We classified the control intervention as 'no intervention' if: 1) the control group received no intervention, or 2) if the control group received only a co-intervention that was also planned to be delivered to the experimental group.

We included all types of adult (>18 years of age) participants who were hospitalised when randomised. The participants also had to be at nutritional risk defined by one or more of the following criteria:

- A validated screening tools (e.g., Nutritional Risk Score 2002).[11]
- BMI less than 20·5 kg/m^2, weight loss of at least 5% during the last three months, weight loss of at least 10% during the last six months, or insufficient food intake during the last week.[11]
- Major surgery (e.g., open abdominal surgery), stroke, intensive care, severe infection, or frail elderly patients with pulmonary diseases or cancer. These patient groups are known to be at nutritional risk.[11]
- Nutritionally at risk due to surrogate biomarkers (e.g., low albumin).[11]
- Characterised by the trialists at nutritional risk, or similar terms.[11]

We excluded pregnant or lactating women and participants receiving dialysis.[11] We did not consider ethnicity in our analyses.

Data analyses

Our primary outcomes were all-cause mortality, proportion of participants with one or more serious adverse event,[18] and quality of life.[11]

Our secondary outcomes were time to death, proportion of participants with morbidity, body mass index, weight, hand-grip strength, and six-minute walking distance.[11]

We assessed all outcomes at the end of the trial intervention period (primary time point) and at maximum follow-up.

We performed the analyses using Review Manager 5, STATA 14, and Trial Sequential Analysis.[15,19,20] We used visual inspection of forest plots to look for signs of statistical heterogeneity. We also assessed the presence of statistical heterogeneity using the Chi^2 test with significance set at P value <0·10 and measured the quantities of heterogeneity using the I^2 statistic.[21,22] We used a funnel plot to assess reporting bias if 10 or more trials were included in the analysis.

To assess the potential impact of the missing data for dichotomous outcomes, we performed 'best-worst-case' scenario and 'worst-best-case' scenario sensitivity analyses.[23]

We planned to base our primary conclusions on the results of the primary outcomes assessed at the end of intervention with low risk of bias. We considered the results of our primary outcomes at high risk of bias, results of secondary outcomes, results of outcomes at maximum follow-up, sensitivity analyses, and subgroup analyses as hypothesis generating analyses.[24]

We used three primary outcomes and, therefore, we considered a P value of 0·025 or less as statistically significant.[24] We used an eight-step procedure to assess if the thresholds for statistical and clinical significance were crossed.[24]

Traditional meta-analysis runs the risk of random errors due to sparse data and repetitive testing of accumulating data when updating reviews. Therefore, we performed Trial Sequential Analysis [15,25]

on the outcomes in order to calculate the required information size and assess the cumulative Z-curve's breach of the relevant trial sequential monitoring boundary.[26-31] Hereby, we wished to control the risks of type I errors and type II errors.

For dichotomous outcomes, we estimated the required information size based on the proportion of participants with an event in the control group, a relative risk reduction (RRR) of 20%, an alpha of 2·5%, a beta of 20%, and the diversity suggested by the trials in the meta-analysis. For continuous outcomes, we estimated the required information size based on the standard deviation (SD) observed in the control group of trials at low risk of bias, a minimal relevant difference of 50% of this SD, an alpha of 2·5%, a beta of 20%, and the diversity suggested by the trials in the meta-analysis. Zero events were handled in all Trial Sequential Analyses by replacing them with 0·001.

We planned to perform a large number of subgroup analyses (please consult our published protocol for a detailed description).[11]

We used the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system to assess the quality of the body of evidence associated with each of the primary outcomes in our review constructing 'Summary of findings' tables using GRADE software.[11, 32]

Role of funding

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. JF had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified a total of 126,614 potentially relevant records. 820 full text articles were assessed for eligibility. Of these, we excluded 480 references according to our inclusion and exclusion criteria. We were not able to obtain 34 records, mostly records from China.

A total of 306 publications reporting results of 252 trials were included. Eight of these trials were ongoing trials. Accordingly, 244 trials randomising 28,619 participants could be included (**Figure 1**).

Based on the information that we collected from the published reports and information from trial authors, all 244 trials were considered at high risk of bias. Please see online appendix for risk of bias table (**Supplementary Table 1** in the online appendix).

The number of participants in each trial ranged from 8 to 4640. The mean age was 64·2 years. The mean proportion of women was 43·6%. We included participants from 20 medical specialties (**Table 1**). Two trials accounted for 1/3 of all included participants.[33,34] We did not account for etnicity.

We included 86 trials where the experimental group received parenteral nutrition, 80 trials with enteral nutrition, 55 with oral nutrition support, 12 with a mixed experimental intervention (e.g., a combination of oral nutrition and parenteral nutrition), 9 trials with general nutrition support, and 2 trials with fortified food. 203 trials had an intervention that lasted 3 days or more and 25 trials had an intervention that lasted 2 days or less. 16 trials had an unknown duration. Most intervention periods were until hospital discharge, but in the 79 trials reporting a specific intervention length, the mean in-hospital intervention length was 10·4 days (range 1 to 32 days).

We included 122 trials with 'treatment as usual' as the control intervention, 107 trials with ‘no intervention’, and 15 trials with placebo as intervention.

A list of the experimental and control interventions according to medical specialty can be seen in **Table 1**.

114 out of 244 trials with a total of 21,758 participants reported mortality at end of intervention. Random-effects meta-analysis showed no statistically significant effect of nutrition support on risk of all-cause mortality at end of intervention (RR 0·94, 95% CI 0·86 to 1·03, P = 0·16, I^2 = 0%, 21,758 participants, 114 trials, very low quality of evidence, **Figure 2**). Trial Sequential Analysis showed that the acquired information was large enough to rule out that nutrition support reduced the relative risk of all-cause mortality by more than 10% (**Figure 3**).

127 out of 244 trials with a total of 23,170 participants reported all-cause mortality at maximum follow-up. Random-effects meta-analysis showed no statistically significant effect of nutrition support on risk of all-cause mortality at maximum follow-up (RR 0·93, 95% CI 0·88 to 0·99, P = 0·03, I^2 = 0%, 23,170 participants, 127 trials, very low quality of evidence). Trial Sequential Analysis showed that the acquired information was large enough to rule out that nutrition support reduced the relative risk of all-cause mortality by more than 9%.

123 out of 244 trials with a total of 22,087 participants reported serious adverse events at end of intervention. Random effects meta-analysis showed no statistically significant effect of nutrition support on risk of serious adverse events at the end of intervention (RR 0·93, 95% CI 0·86 to 1·01, P = 0·07, I^2 = 0%, 22,087 participants, 123 trials, very low quality of evidence, **Figure 4**). Trial Sequential Analysis showed that the acquired information was large enough to rule out that nutrition support reduced the relative risk of serious adverse events by more than 10% (**Figure 5**). An overview of the different types of serious adverse events can be seen in the online appendix (**Supplementary table 2 and 3**).

137 out of 244 trials with a total of 23,413 participants reported serious adverse events at maximum follow-up. Random-effects meta-analysis showed a statistically significant effect of nutrition support on risk of serious adverse events at maximum follow-up (RR 0·91, 95% CI 0·85 to 0·97, P = 0·004, I^2 = 3%, 23,413 participants, 137 trials, very low quality of evidence). However, the Trial Sequential Analysis showed we had enough information to rule out a relative risk reduction of 10% or more on risk of serious adverse events.

When assessing each specific type of nutrition support (general nutrition, fortified nutrition, oral nutrition, or parenteral nutrition) separately, only enteral nutrition (tube feeding) showed a significant result. Random-effects meta-analyses showed that enteral nutrition seemed to reduce the risk of all-cause mortality at maximum follow-up (RR 0·84, 95% CI 0·75 to 0·95, P = 0·005, I^2 = 0%, 4212 participants, 41 trials, very low quality of evidence) and of serious adverse events at both end of intervention (RR 0·85, 95% CI 0·74 to 0·98, P = 0·03, I^2 = 0%, 3935 participants, 42 trials, very low quality of evidence) and at maximum follow-up (RR 0·82, 95% CI 0·73 to 0·91, P = 0·0002, I^2 = 0%, 4425 participants, 48 trials, very low quality of evidence). Trial Sequential Analyses only confirmed that enteral nutrition seemed to decrease the risk of all-cause mortality and serious adverse events with 20% at maximum follow-up (the Z-curves crossed the boundaries for benefit). All other meta-analyses of each specific nutrition support intervention (general nutrition, fortified nutrition, oral nutrition, or parenteral nutrition) did not show any significant results when analysed separately.

Test for subgroup differences comparing trials where participants were at nutritional risk according to a specific condition showed a statistically significant difference at maximum follow-up (subgroup difference P = 0·03). When each type of participants was analysed separately, only major surgery participants and stroke participants showed a significant meta-analysis result at maximum

follow-up. Trial Sequential Analyses of both types of participants showed that we had enough information to rule out that nutrition support reduced the risk of serious adverse events with 20% or more.

Only 16 out of 244 trials reported quality of life. Few trials used similar quality of life questionnaires and only data from EuroQoL utility score and SF-36 could be meta-analysed. The meta-analysis of EuroQoL utility score and SF-36 did not show any statistically significant difference between the compared groups.

68 trials with a total of 5445 participants reported weight at end of intervention. Random-effects meta-analysis showed that nutrition support versus control seemed to significantly increase weight at the end of intervention using (MD 1·32 kg, 95% CI 0·65 to 2·00, P = 0·0001, I^2 = 98%, 5445 participants, 68 trials, very low quality of evidence).

The amount of data for the remaining secondary outcomes were sparse. The details of the analyses are given in the online appendix '**Supplementary results - secondary outcomes**'.

Our main results are summarised in the '**Table 2 - Summary of findings table**'.

Discussion

We included 244 trials randomising a total of 28,619 participants. As expected, the trials included a heterogeneous group of participants, the settings varied, and the experimental and control interventions differed. All trials were at high risk of bias and the evidence for all outcomes was of very low quality according to GRADE. We saw no or only limited clinical effects of nutrition support when analysed as one intervention on all-cause mortality, serious adverse events, and quality of life. When assessing each specific type of nutrition support separately, enteral nutrition

(tube feeding) showed a statistically significant result, but risks of bias questions the validity of this result.

Our review has numerous strengths. We used predefined high quality methods and our literature searches were extensive. We included more participants than previous reviews, giving us increased power and precision to detect any significant differences between the nutritional intervention and control groups. [3-10] As anticipated, the included trials were clinically heterogeneous. The limited signs of statistical heterogeneity including limited subgroup differences support the decision to conduct the overall meta-analysis of all types of nutrition support.

Our review also has several limitations. The primary limitation is that all the included trials were at high risk of bias. Hence, there is a great risk that our results overestimate benefit and underestimate harms. Our estimations of information sizes showed that most of the subgroup analyses were underpowered, i.e., we were not able to confirm or reject our anticipated intervention effects. We also included many subgroup analyses increasing the risk of a type I error.

Our review has several clinical implications. When all types of nutrition support were pooled in one analysis versus control, most meta-analyses neither showed significant difference on risk of death nor on risk of serious adverse events and none could be confirmed in a Trial Sequential Analysis for our prespecified relative risk reduction. This overall meta-analysis result might guide hospital clinicians who are in doubt whether to implement nutrition support interventions across specialities in nutritionally at risk patients compared to standard care (typically a standard hospital diet providing 1800-2000 kcal per day). Our results suggest that enteral nutrition may reduce the risk of all-cause mortality and serious adverse events at maximum follow-up. However, it must be noted that these results were at high risk of bias such as incomplete outcome data bias, lack of blinding, publication bias, and other types of bias. Many subgroups were inadequately powered to show if

nutrition support has a beneficial or harmful effect. As such, our meta-analyses do not with certainty reject that a specific nutrition support intervention for specific patient populations does have beneficial or harmful effects.

Our subgroup analyses and Trial Sequential Analyses suggest that future trials may assess the effects of enteral nutrition across different patient populations. Such trials ought to be designed and reported according to the SPIRIT and CONSORT guidelines. Furthermore, such trials should be conducted with low risk of systematic error and low risk of random errors, and assess quality of life. They should also be powered to detect a RRR of under 11% on all-cause mortality and serious adverse events.

Contributors

JF drafted the protocol, extracted data, coordinated the review, conceived the review, designed the review, interpreted the data providing a methodological view and revised the review; EEN drafted the protocol, extracted data, drafted the review, interpreted the data providing a methodological view and revised the review; SKK, KHE, MSR, KZ, MD, LL, SH, XY, NL, WX, PB, AG, and SS extracted data and commented on the review; JL revised the protocol and extracted data; CG revised the protocol, interpreted the data providing a methodological and clinical view, commented on, and revised the review; JCJ revised the protocol, analysed the data, interpreted the data providing a methodological and clinical view, commented on, and revised the review.

Declaration of interest

All authors declare no conflict of interest.

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