A multicentre, randomised controlled trial comparing the clinical effectiveness and cost-effectiveness of early nutritional support via the parenteral versus the enteral route in critically ill patients (CALORIES)

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Scientific summary

Early nutritional support via the parenteral vs. the enteral route

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Scientific summary

Background

Malnutrition is a common problem in critically ill patients in UK NHS critical care units and early nutritional support is therefore recommended. Evidence is conflicting regarding the optimum route of delivery. Interpretation of meta-analyses of trials comparing delivery via the enteral and parenteral routes in critically ill patients is complicated by small sample size; poor methodological quality; select groups of critically ill patients studied; lack of standardised definitions for outcome measures; and interventions combining more than one element of nutritional support.

The enteral route is the mainstay of nutritional support in critical care but is frequently associated with gastrointestinal intolerance and underfeeding. In contrast, the parenteral route, although more invasive and expensive, is more likely to secure delivery of intended nutrition. The parenteral route has been associated with more risks and complications (e.g. infections) than the enteral route, but recent improvements in the delivery, formulation and monitoring of parenteral nutrition (PN) justify further comparison and evaluation, particularly in the early phase of critical illness. Economic evidence surrounding the optimum route of delivery is largely based on evidence of effectiveness of questionable methodological quality and narrow focus on upfront acquisition costs, and full economic evaluation is lacking.

In view of this, in late 2007 the National Institute for Health Research (NIHR) Health Technology Assessment programme called for a large pragmatic randomised controlled trial to determine the optimal route of delivery of early nutritional support in critically ill adults. The aim of the CALORIES trial was to compare the clinical effectiveness and cost-effectiveness of early nutritional support, delivered via the parenteral route compared with the enteral route, in critically ill patients.

Objectives

The primary objectives of the CALORIES trial were to estimate:

- the effect of early nutritional support via the parenteral compared with the enteral route on all-cause mortality at 30 days, and
- the incremental cost-effectiveness of early nutritional support via the parenteral compared with the enteral route at 1 year.

The secondary objectives of the CALORIES trial were to compare delivery via the parenteral and enteral routes on:

- duration of specific and overall organ support in the critical care unit
- infectious and non-infectious complications in the critical care unit
- duration of critical care unit and acute hospital length of stay
- duration of survival at 90 days and 1 year
- mortality at discharge from the critical care unit and acute hospital
- mortality at 90 days and 1 year
- nutritional and health-related quality of life at 90 days and 1 year
- resource use and costs at 90 days and 1 year, and
- estimated lifetime incremental cost-effectiveness.

Methods

Trial design and governance

The CALORIES trial was a pragmatic, open, multicentre, parallel-group, randomised controlled trial with integrated economic evaluation. It was nested in the Case Mix Programme, the national clinical audit of adult general critical care units in England, Wales and Northern Ireland, co-ordinated by the Intensive Care National Audit & Research Centre (ICNARC). The North West London Research Ethics Committee approved the trial. The NIHR funded the trial, and convened Trial Steering Committee and independent Data Monitoring and Ethics Committee. The trial was sponsored by ICNARC and co-ordinated by the ICNARC Clinical Trials Unit.

Participants: sites and patients

The trial aimed to recruit a representative sample of at least 20 adult, general critical care units from the UK. Inclusion criteria were:

- active participation in the Case Mix Programme
- established protocols for PN and enteral nutrition, reflecting mainstream practice
- pre-existing implementation of bundles as promoted by the NHS to prevent development of bloodstream infection and ventilator-associated pneumonia
- pre-existing prophylaxis protocol for prevention of venous thromboembolism
- pre-existing glycaemic control protocol in line with international guidelines
- agreement to incorporate the CALORIES trial into routine unit practice, including prior agreement from all consultants to adhere to randomisation
- agreement to recruit all eligible patients and to maintain a screening log
- sign up from the clinical director, senior nurse manager, dietitian/clinical nutritionist and pharmacist, and
- identification of a dedicated research nurse.

Patients aged $\geq$ 18 years were eligible if, within 36 hours of their original critical care unit admission, they were an unplanned admission expected to receive nutritional support for $\geq$ 2 days, not planned to be discharged within 3 days from the unit and did not meet any exclusion criteria.

Following informed consent from the patient or agreement from a personal/professional consultee, patients were randomly allocated, 1 : 1, via 24-hour telephone randomisation, to early nutritional support via either the parenteral or enteral route. Allocation was by minimisation with a random component based on site, age, surgical status and malnutrition status (based on clinical judgement).

Treatment groups

Following randomisation, nutritional support was commenced as soon as possible. Blinding to treatment allocation was not possible. As a pragmatic trial, the protocol did not dictate use of specific protocols/products for delivery of nutritional support but ensured that local procedures/practices fell within common boundaries.

Early nutritional support was delivered via either the parenteral or enteral route for 5 days (intervention period) unless the patient transitioned to exclusive oral feeding or was discharged from the critical care unit before this. Patients were able to start oral feeding, if clinically indicated, during the 5 days.

For patients who were randomised to the parenteral route, a central venous catheter, with a dedicated lumen, was inserted and positioned in accordance with NHS guidelines. Patients received a standard parenteral feed, obtained from the unit's usual supplier, and used within the licence indication, which contained 1365–2540 total kcal/bag and 7.2–16.0 g nitrogen/bag. Enteral 'trickle feeding' ('trophic feeding') was not permitted for the 5-day intervention period.

For patients randomised to the enteral route, a nasogastric or nasojejunal tube was inserted and positioned in accordance with UK National Patient Safety Agency guidelines. Patients received a standard enteral feed, obtained from the unit's usual supplier, and used within the licence indication, which contained 1365–2540 total kcal/day and 7.2–16.0 g nitrogen/day.

In both groups, unit staff aimed to feed patients to a target of 25 kcal/kg/day (based on actual body weight) within 48–72 hours.

Data sources

A secure, dedicated data entry system enabled trial data to be entered by staff at units. Eligibility, baseline, intervention, physiology and location of care data to hospital discharge were collected by sites. Following linkage with the Health and Social Care Information Centre Data Linkage and Extract Service to confirm mortality, a Health Services Questionnaire and a EuroQol 5-dimension (5-level version) questionnaire (EQ-5D-5L) were sent to patients at 90 days and 1 year. Linkage to the Case Mix Programme Database provided information on subsequent admission(s) to adult general critical care following discharge from acute hospital.

Analysis principles

All analyses were by intention to treat, following a pre-specified statistical analysis plan. A *p*-value of 0.05 was considered statistically significant. All tests were two-sided, with no adjustment for multiple comparisons. A sensitivity approach was taken when clinical effectiveness primary outcome data were missing. Missing data for the cost-effectiveness analysis and for baseline data for adjusted analysis of clinical outcomes were handled by multiple imputation using chained equations.

Outcome measures

The primary clinical effectiveness outcome was all-cause mortality at 30 days following randomisation and the primary cost-effectiveness outcome was the incremental net benefit (INB) gained at 1 year following randomisation, at a willingness-to-pay of £20,000 per quality-adjusted life-year (QALY).

Secondary outcomes were:

- number of days alive and free from organ support up to 30 days
- new confirmed or strongly suspected infectious complications and non-infectious complications in the critical care unit
- duration of critical care unit and acute hospital length of stay
- duration of survival at 90 days and 1 year
- all-cause mortality at discharge from the critical care unit and acute hospital
- all-cause mortality at 90 days and 1 year
- nutritional and health-related quality of life at 90 days and 1 year
- resource use and costs at 90 days and 1 year, and
- estimated lifetime incremental cost-effectiveness.

Secondary analyses of primary outcomes included:

- adjusted analyses – adjusted for age, ICNARC Physiology Score, surgical status, degree of malnutrition and a site-level random effect
- subgroup analyses to test for an interaction of treatment effect with pre-specified subgroups (age, degree of malnutrition, acute severity of illness, mechanical ventilation, presence of cancer and time from critical care unit admission to commencement of nutritional support)
- sensitivity analyses for missing data in the primary outcome, and
- adherence-adjusted analyses, using a structural mean model with an instrumental variable of allocated treatment.

A full cost-effectiveness analysis was undertaken to assess which route of delivery was most cost-effective. The cost-effectiveness analysis was reported for three time periods: to 90 days; to 1 year; and lifetime. For each time period, the analysis took a health and personal health services perspective, using information on health-related quality of life at 90 days and 1 year, combined with information on vital status to report QALYs, valued using the National Institute for Health and Care Excellence recommended threshold of willingness-to-pay for a QALY gain (£20,000). The main assumptions were subjected to extensive sensitivity analyses.

Results

Sites and patients

Overall, 11,108 patients were screened at 34 sites, with 2400 enrolled between 17 June 2011 and 2 March 2014. Twelve patients requested complete withdrawal, resulting in 2388 for initial analysis (1191 parenteral, 1197 enteral). Five patients were lost to follow-up before 30 days, resulting in 2383 for analysis of the primary outcome (1188 parenteral, 1195 enteral). Groups were well matched at baseline.

Adherence to protocol

Adherence to delivery of nutritional support during the intervention period was high. Ninety-seven per cent of patients received nutritional support via the assigned route. Any non-adherence to the protocol was reported for 150 (12.6%) patients in the parenteral group and 127 (10.6%) patients in the enteral group.

Delivery of care by treatment group

The median times to initiation of nutritional support were within 24 hours of critical care unit admission (parenteral 23.5 hours, enteral 21.8 hours). The mean daily caloric intake during the intervention period was higher in patients who were assigned to the parenteral (21.3 kcal/kg/day) than in those assigned to the enteral (18.5 kcal/kg/day) route. In the majority of patients, the targeted delivery of 25 kcal/kg/day was not achieved irrespective of route. The mean total protein was similar in the two groups (parenteral 0.7 g/kg/day, enteral 0.6 g/kg/day).

Primary outcome: clinical effectiveness

At 30 days, 393 (33.1%) patients in the parenteral group had died compared with 409 (34.2%) patients in the enteral group, corresponding to an absolute risk reduction of 1.15 percentage points [95% confidence interval (CI) −2.65 to 4.94; $p = 0.57$] and a relative risk of 0.97 (95% CI 0.86 to 1.08). This difference remained non-significant after adjustment for baseline characteristics (odds ratio 0.95, 95% CI 0.79 to 1.13; $p = 0.55$).

Secondary outcomes: clinical effectiveness

The proportions of patients in the parenteral group who experienced episodes of hypoglycaemia ($p = 0.006$) and vomiting ($p < 0.001$) were significantly lower than for patients in the enteral group. There were no significant differences between groups for any of the 15 other secondary outcomes.

Subgroup and secondary analyses

There was no statistically significant interaction between the effect of treatment group on 30-day mortality and any of the pre-specified subgroups. Sensitivity analyses for missing data and adherence-adjusted analyses were consistent with the primary analysis.

Cost-effectiveness analysis

At 90 days, the parenteral group had higher mean total costs per patient compared with the enteral group (£24,458 vs. £23,164). Health state profiles on the EQ-5D-5L were similar and resulted in similar mean EQ-5D-5L utility scores for survivors (parenteral 0.655, enteral 0.654) and QALYs (parenteral 0.051, enteral 0.050). The INB for the parenteral route compared with the enteral route was negative at −£1263 (95% CI −£2952 to £426).

At 1 year, the mean total costs per patient were £28,354 for the parenteral group and £26,775 for the enteral group. The mean EQ-5D-5L utility scores were similar between groups (parenteral group 0.684, enteral group 0.683). At 1 year, a slightly higher proportion of patients in the parenteral group were alive but the difference was not statistically significant and the 1-year QALYs were similar (parenteral group 0.348, enteral group 0.335). The INB for the parenteral group compared with the enteral group was negative at −£1320 (95% CI −£3709 to £1069). At 1 year, the probability that early nutritional support via the parenteral route is more cost-effective than via the enteral route – given the data – is < 20% at the £20,000 willingness-to-pay threshold. When extrapolated to the lifetime, INB was positive (£440) but with a wide 95% CI that included zero (−£3586 to £4466). The estimated INBs were similar across all scenarios considered in the sensitivity analyses.

Conclusions

Among adults with an unplanned critical care unit admission, for whom early nutritional support could be provided through either route (parenteral or enteral), there was no significant difference in mortality at 30 days according to route of delivery. In addition, there was no significant interaction on the basis of age, degree of malnutrition, severity of illness, or timing of the initiation of nutritional support. The enteral route was associated with significantly more episodes of hypoglycaemia and vomiting, but there were no significant differences between groups in the duration of organ support, infectious complications, critical care unit or hospital length of stay, or duration of survival up to 1 year. The energy target of 25 kcal/kg/day was not reached in a majority of patients in each group.

Providing nutritional support to critically ill adult patients via the parenteral route compared with the enteral route is unlikely to be cost-effective. At 1 year, on average, early nutritional support via the parenteral route had higher intervention and morbidity costs, similar QALYs and a negative INB than the enteral route. Cost-effectiveness results for the pre-specified subgroups were similar to the overall results, and sensitivity analyses indicated that the conclusions were robust to alternative assumptions to those in the base-case analysis. The lifetime analysis indicated that early nutritional support via the parenteral route had higher mean lifetime QALY at higher additional mean costs, leading to a positive INB.

Implications for health care

The results of the CALORIES trial support the continuation of current, widespread practice in NHS critical care units of delivering early nutritional support via the enteral route as both clinically effective and cost-effective. However, they also challenge concerns about possible harm from delivering early nutritional support via the parenteral route when such delivery is clinically indicated.

Recommendations for research

Recommendation 1

Evaluation of the longer-term outcomes for patients in the CALORIES trial should be extended beyond 1 year.

Recommendation 2

Following evaluation of the route for delivery of early nutritional support (CALORIES), a study utilising rigorous consensus methods is required to establish future priorities for research on optimal nutritional support for all/groups of critically ill patients.

Trial registration

This trial is registered as ISRCTN17386141.

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