Outcome and cost-effectiveness of perioperative enteral immunonutrition in patients undergoing elective upper gastrointestinal tract surgery: a prospective randomized study


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Perioperative (5 days preoperatively and 10 days postoperatively) oral immunonutrition was compared to an isoenergetic control diet in patients with upper gastrointestinal tract malignant neoplasms.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged between 18 and 80 years who were eligible for elective upper gastrointestinal surgery for histologically documented malignant tumours of the upper gastrointestinal tract. The exclusion criteria for the study were extensively described in the paper and included: presence of endocrine and metabolic disorders; known allergic diseases; haemorrhagic diathesis; sepsis; preexisting severe chronic disease, including kidney or liver failure; congestive heart failure; received immunosuppressive therapy in the last three months before the trial; drug abuse; emergency surgery; inadequate preoperative preparation; use of medications known to affect eicosanoid metabolism during the last two weeks before the trial. Inadequate preoperative preparation was not defined.

Setting
The study was based in secondary care in Germany.

Dates to which data relate
Effectiveness and resource use data were collected between April 1994 and August 1997. The price year was 1998.

Source of effectiveness data
Effectiveness data were derived from a single study.

Link between effectiveness and cost data
Prospective costing was undertaken on the same patient sample as that used in the effectiveness study.

Study sample
The authors did not report any power calculations to determine the sample size required to detect statistically significant differences. The initial study sample comprised 178 consecutive patients scheduled for elective gastrointestinal surgery.
(89 patients per group). The surgical group was appropriate for the research question and study population specified. The characteristics of patients who were excluded from the initial study sample or who refused to participate in the trial were not reported. The authors did not report the reasons for the exclusion criteria used or whether these criteria were appropriate for the research question. Of this sample, 154 completed the study and were included in the final analysis: 78 patients in the immunonutrition group and 76 in the control group. Twenty-four patients (n=11 immunonutrition group and n=13 control group) were excluded for lack of compliance with the preoperative supplement, intolerance of postoperative feed, withdrawal of consent, inadvertent removal of jejunostomy or protocol violation.

**Study design**
The study was a multi-centre (five study sites) prospective randomised controlled trial (RCT). The method of randomisation was not reported. Patients were followed-up until they were discharged from the care of the hospital. The initial study sample comprised 178, and 154 were included in the final analysis. The authors did not report any blinding method for assessment of outcomes.

**Analysis of effectiveness**
The analysis of the clinical study was based on treatment completers only. The primary health outcomes (defined a priori) measured were:

- Infectious complications after postoperative day 3;
- Infectious complications after postoperative day 5.

Postoperative complications were defined as septic, wound, pulmonary, or urinary complications. The definitions of complications were based on the criteria established by the Centers for Disease Control and Prevention and on the definitions proposed by the American College of Chest Physicians and the Society of Critical Care Medicine at a Consensus Conference in 1991. The immunonutrition and control groups were comparable in terms of age range, preoperative diagnosis, operative procedures, mean percentage of usual body weight, mean operative duration and number of patients who received perioperative transfusions. No adjustments were made for confounding factors. A secondary outcome was hospital length of stay.

**Effectiveness results**
Of the 154 patients who completed the study a total of 28 (18%) had postoperative complications.

The proportion of people with infectious complications after postoperative day 3 were 9% (7/78) in the immunonutrition group and 21% (16/76) in the control group, (p=0.04).

The proportion of people with infectious complications after postoperative day 5 were 6% (5/78) in the immunonutrition group and 12% (9/76) in the control group, (p=0.19).

Fewer patients in the immunonutrition group (13%) experienced postoperative complications than in the control group (24%), (p<0.08). However, this difference was not statistically significant at the 5% level used by the authors to indicate a statistical difference. The types of postoperative complications were listed in detail. No dropouts due to gastrointestinal tract intolerance occurred.

**Clinical conclusions**
The authors concluded that the perioperative administration of an enteral immunonutrition significantly decreased the early occurrence of postoperative infections after major upper gastrointestinal tract surgery.

**Measure of benefits used in the economic analysis**
The measure of benefit used in the economic analysis was effectiveness, defined as the percentage of complication-free patients.
Direct costs
The direct medical costs for the hospital included in the analysis were the costs of clinical nutrition and the costs of treating postoperative complications during the hospital stay. The authors reported the number and costs of complications separately for each of the study groups. They did not report the resources used to manage the complications separately. The authors gave a comprehensive list of the quantities of nutrients taken by each group. The average intake per person was multiplied by the price per litre for the preoperative and postoperative stages. The price data used for study diets was not reported. The cost of postoperative complications included: operative interventions and anaesthetic procedures; complication-related physician consultations and services; artificial respiration, nutritional support and dialysis; radiography and ultrasonography; physical therapy; antibiotics and other complication-related medications. The authors reported that prolonged hospital length of stay and days in the intensive care unit were not included because these resources could not be unambiguously attributed to postoperative complications.

The estimation of the quantities of resource use for the management of complications was based on patients’ medical records. The estimation of the costs for diagnostic and therapeutic services was based on the German hospital association tariff and pharmaceuticals. Devices and material costs were based on hospital buying prices. The time horizon was from admission to the surgical unit to discharge from the care of the hospital. Discounting was not carried out because of the short time frame of the study (less than one year). Resource use data were collected between April 1994 and August 1997. The price year was 1998. The study reported average costs.

Statistical analysis of costs
The authors compared differences between the groups in the mean length of stay and costs of complications using the t-test and a 5% level of significance.

Indirect Costs
Indirect costs were not included in the analysis because they were not appropriate for the chosen study perspective.

Currency
German marks (DM). The conversion rate from DM to US$ was DM1.00 to US$0.5967 at the end of December 1998.

Sensitivity analysis
No sensitivity analysis was carried out.

Estimated benefits used in the economic analysis
The percentage of complication-free patients in the immunonutrition group was 87.2% and 76.3% in the control group.

Cost results
There was no statistical difference in the mean length of stay between the immunonutrition group (22.2 days, SD 4.1) and the control group (25.8 days, SD 3.8, p=0.09).

The cost per patient for nutrition was DM347 for the immunonutrition group and DM49 in the control group.

The cost per patient of treating postoperative complications was DM964 for the immunonutrition group and DM2,688 in the control group, (p=0.14).

The total cost per patient was DM1,311 for the immunonutrition group and DM2,737 in the control group.

The immunonutrition group was less expensive than the control group (net saving of DM1,426).
**Synthesis of costs and benefits**

The authors did not report an incremental cost-effectiveness ratio. The immunonutrition group was associated with net savings and a net benefit, and so was dominant compared to the control. Incremental cost-effectiveness ratios were not appropriate in this case.

**Authors’ conclusions**

The authors concluded that oral immunonutrition reduced hospital length of stay and costs for treating complications when compared to an isoenergetic control diet. In addition, the cost-effectiveness of immunonutrition was better than the isoenergetic control diet.

**CRD COMMENTARY - Selection of comparators**

The authors clearly reported why they chose to study the impact of oral immunonutrition in patients with upper gastrointestinal tract malignant neoplasms who were eligible for surgery, but did not report the rationale for the selection of isoenergetic diet as the relevant alternative. The authors did not report whether alternative methods were available to reduce the number of postoperative complications. The authors did not report whether diet supplements or other methods to reduce postoperative complications were routinely used. If standard practice does not include interventions such as diet supplements to reduce postoperative complications, the relative cost-effectiveness of immunonutrition found in this study may be an over-estimate. You, as a user of this database, should consider whether the comparator used in this study is relevant to practice in your own setting.

**Validity of estimate of measure of effectiveness**

This study was a multi-centre randomised controlled trial, which was appropriate for the study question. The authors applied a number of exclusion criteria. This means that the study sample may have been healthier and/or better able to tolerate the intervention. This may mean that the results over-estimated the tolerance of patients to the interventions. However, it is not clear what the impact would be on the comparison of postoperative complications. For example a healthier study sample may be at lower risk of postoperative complications, which could under-estimate the effectiveness of the interventions in the study population. Alternatively, the diet supplements may be more effective in preventing infection in a study sample healthier than the study population, which could over-estimate effectiveness. The characteristics of the study population and of those patients not included in the study sample were not reported in detail, so it is not possible to judge the applicability of the results to the study population.

The study groups were comparable at baseline. The analysis only included those patients who consumed 3000ml of the study diet preoperatively, which may bias the results if there were differences in withdrawal rates or reasons for withdrawal between the groups. The authors reported that 24 patients were withdrawn (11 immunonutrition and 13 control) but did not report the numbers by reason for withdrawal. The two groups (immunonutrition and control) only showed a statistically significant difference for the number of infectious complications after postoperative day 3. There was no difference between the groups for the other primary and reported measures of effectiveness. However, no power calculations were reported for this study and it may have been underpowered to detect a statistical difference between the two groups in terms of effectiveness.

**Validity of estimate of measure of benefit**

The authors use the percentage of complication-free patients as the measure of benefit in this study. They reported the type of complications experienced by the patients but they did not weight this measure by the severity of different complications. It was not clear if the severity of complications experienced in the immunonutrition and control group were similar. The percentage of complication free patients included complications in the index admission only. The long term effects on patient outcome in terms of morbidity and mortality following discharge were not included.

**Validity of estimate of costs**

The authors clearly described the types of costs included in the study, but did not include the cost of prolonged length of stay and extra days in the intensive care unit due to measurement problems. They suggested that the higher rate of
complications in the control group meant that the results represented conservative estimations of the reduction in complication-related costs. This is valid if the severity of complications in the control group is similar to or worse than the severity of those in the immunonutrition group and the study diets directly influence the length of stay of the patient. The length of stay between the immunonutrition group and control group was not statistically different. This may have been due to a number of reasons, including the need for postoperative care per se, the organisation of hospital care, or fewer but more severe complications in the immunonutrition group. The costs of care (e.g. primary care or informal care) required following discharge from the hospital were not included. As with the costs of intensive care or prolonged hospital stay, it was not clear what the impact of this exclusion would be. The authors did not report resource use and costs separately.

The authors measured resource use for the patients included in the trial. Statistical analysis was used to compare length of inpatient stay and the costs of complications. The authors did not report the use of statistical analysis or sensitivity analysis to test the robustness of other resource or cost variables. The authors did not report power calculations to assess whether the sample size was sufficient to detect statistically significant differences in resource and cost variables or total cost. The use of discounting was not reported, but would not have been appropriate given the short time frame of the study. The price data were based on hospital association tariffs (inpatient stay) and prices paid by the hospital. The authors did not report whether the tariffs were charges or were based on actual resource cost.

**Other issues**
The authors compared the results of the study with other published evaluations of postoperative and perioperative immunonutrition to prevent postoperative infectious complications and concluded that the effectiveness and cost result of the study were consistent with those found in other evaluations. The authors did not discuss whether the results are generalisable to other settings or populations. The exclusion criteria suggest that the study sample may have been healthier than the study population. The authors did not discuss the implications of this in the comments section. The authors did not justify the choice of comparator and, as a user of this database, you therefore need to consider whether the study sample and comparator represent current practice in your own setting.

The authors presented average cost-effectiveness ratios (CERs) for analyses where there were both net saving and gains in health benefits. In this case CERs were not required as the intervention dominated the control group. Furthermore, CERs are not the appropriate method of synthesising costs and benefits in an economic evaluation: the correct approach is to report incremental cost-effectiveness ratios (ICERs).

**Implications of the study**
The authors suggested that the use of perioperative immunonutrition decreased the early occurrence of postoperative infections and reduced the treatment costs of the complications after major upper gastrointestinal tract surgery. This was consistent with the clinical results of one previous study of perioperative immunonutrition and the cost results of evaluations of early postoperative immunonutrition. No recommendations for future research were made.

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