Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery. (Review)

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[Intervention Review]

Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

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ABSTRACT

Background

Post-operative management in gastrointestinal (GI) surgery is becoming well established with 'Enhanced Recovery After Surgery' protocols starting 24 hours prior to surgery with carbohydrate loading and early oral or enteral feeding given to patients the first day following surgery. However, whether or not nutritional intervention should be initiated earlier in the preoperative period remains unclear. Poor pre-operative nutritional status has been linked consistently to an increase in post-operative complications and poorer surgical outcome.

Objectives

To review the literature on preoperative nutritional support in patients undergoing gastrointestinal surgery (GI).

Search methods

The searches were initially run in March 2011 and subsequently updated in February 2012. Databases including all EBM Reviews (Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA and NHSEED) MEDLINE, EMBASE, AMED, British Nursing Index Archive using OvidSP were included and a search was run on each database separately after which duplicates were excluded.

Selection criteria

The inclusion criteria were randomised controlled trials that evaluated pre-operative nutritional support in GI surgical participants using a nutritional formula delivered by a parenteral, enteral or oral route. The primary outcomes included post-operative complications and length of hospital stay.

Data collection and analysis

Two observers screened the abstracts for inclusion in the review and performed data extraction. Bias was assessed for each of the included studies using the bias assessment tables in the Cochrane Software Review Manager (version 5.1, Cochrane Collaboration). The trials were analysed using risk ratios with Mantel-Haenszel in fixed effects methods displayed with heterogeneity. Meta-analyses were undertaken on trials evaluating immune enhancing (IE) nutrition, standard oral supplements, enteral and parenteral nutrition (PN) which were administered pre-operatively.

Study characteristics were summarised in tables. Dichotomous and ratio data were entered into meta-analyses for the primary outcomes. These were then summarised in tables with assumed and corresponding risk with relative effect giving 95% confidence intervals.

Main results

The searches identified 9900 titles and, after excluding duplicates, 6433 titles were initially screened. After the initial title screen, 6266 were excluded. Abstracts were screened for 167 studies and 33 articles were identified as meeting the inclusion criteria, of which 13 were included in the review after an assessment of the complete manuscripts.

Seven trials evaluating IE nutrition were included in the review, of which 6 were combined in a meta-analysis. These studies showed a low to moderate level of heterogeneity and significantly reduced total post-operative complications (risk ratio (RR) 0.67 CI 0.53 to 0.84). Three trials evaluating PN were included in a meta-analysis and a significant reduction in post-operative complications was demonstrated (RR 0.64 95% CI 0.46 to 0.87) with low heterogeneity, in predominantly malnourished participants. Two trials evaluating enteral nutrition (RR 0.79, 95% CI 0.56 to 1.10) and 3 trials evaluating standard oral supplements (RR 1.01 95% CI 0.56 to 1.10) were included, neither of which showed any difference in the primary outcomes.

Authors' conclusions

There have been significant benefits demonstrated with pre-operative administration of IE nutrition in some high quality trials. However, bias was identified which may limit the generalizability of these results to all GI surgical candidates and the data needs to be placed in context with other recent innovations in surgical management (eg-ERAS). Some unwanted effects have also been reported with components of IE nutrition in critical care patients and it is unknown whether there would be detrimental effects by administering IE nutrition to patients who could require critical care support after their surgery. The studies evaluating PN demonstrated that the provision of PN to predominantly malnourished surgical candidates reduced post-operative complications; however, these data may not be applicable to current clinical practice, not least because they have involved a high degree of 'hyperalimentation'. Trials evaluating enteral or oral nutrition were inconclusive and further studies are required to select GI surgical patients for these nutritional interventions.

PLAIN LANGUAGE SUMMARY

Pre-operative Nutrition in Patients Undergoing Surgery on the Digestive System

A large amount of research exists that links a poor level of nourishment (malnutrition) to infections and other complications after surgery on the digestive system. These other complications could include tissue breakdown at the site of surgery, heart failure, blood clots or bleeding. This review looks at literature for providing extra nourishment to patients before an operation on their digestive tract, to determine if this extra nourishment is of any benefit in reducing infections or other complications. This review looked at all methods of providing artificial nourishment to people before surgery. This included giving nourishment directly into the blood stream (parenteral nutrition), a feed given by a device that enables nourishment to be delivered directly into the digestive tract (enteral nutrition) or nutritional supplements that are taken as a drink.

Searches of all relevant databases identified 9990 articles, and after initial screening of all these articles, 167 were selected as being suitable for this review. On reading the summaries of these trials, 33 full articles were obtained, of which 13 fulfilled the inclusion.

Results showed that studies evaluating oral drinks with added nutrients to assist fighting infections ('immune enhancing') given before an operation could reduce total complications from 42% in the control group to 27% in those who received the drinks, while infections were reduced from 27% in the control group to 14% in the group given the drinks. Parenteral nutrition reduced total complications from 45% in the control group to 28% in the group receiving parenteral nutrition. There were no benefits demonstrated for either enteral or standard supplement drinks.

Thus, some benefits have been demonstrated from giving nutritional support to patients before an operation with immune enhancing drinks and with parenteral nutrition. However, studies on parenteral nutrition were over 20 years old and during that time there have been many changes to surgical practice. Quality assessment of studies on PN was generally low. Immune enhancing drinks have only

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Immunonutrition compared with no nutritional support or standard nutrition for preoperative GI surgical patients

Patient or population: preoperative patients undergoing GI surgery
Settings: acute
Intervention: Immunonutrition
Comparison: no nutritional support or standard nutrition

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no nutritional support or standard nutritional support	IE nutrition				
Total complications	**Low risk population**		**RR 0.67** 0.53 to 0.84	548 6	moderate	3 studies of high quality remaining studies had greater degree of bias. Moderate given as overall statement
	42.6 per 100	**28.3 per 100** (22 to 36.6)				
Infectious complications	**Low risk population**		**RR 0.51** 0.35 to 0.73	488 6	moderate	One study did not report infectious complications
	27 per 100	**14.2 per 100** (8.9 to 20.8)				
length of stay number of days	The mean across the control group for length of stay was 15.3 ranged (9.8-25 days)	The mean length of stay in the intervention groups was 13.6 days (range 9-23.8 days)		549 6	moderate	

*The basis for the **assumed risk** is taken from the control group risk across studies is provided in the analysis for each variable. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk Ratio;

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

BACKGROUND

Description of the condition

Pre-operative GI surgical patients who are at risk of malnutrition have an increased rate of mortality, morbidity and length of stay (Correira 2003; Barbosa-Silva 2005; Schiesser 2009). Fourteen percent of patients admitted for elective GI surgery have been found to be at risk of malnutrition, and of these, 40% suffered from post-operative complications, which was significantly greater than for those who were well nourished (Schiesser 2008). Poor nutritional status in preoperative patients has been well documented; it has been observed that 9% of patients undergoing elective GI surgery had a body mass index indicating under-nutrition, 54% had lost weight unintentionally in the six months prior to surgery and 17% had lost more than 10% of their body weight in the same period, which is clinically significant (Fettes 2002).

Malnutrition is a well recognised problem in patients undergoing GI surgery; indeed, a recent UK survey 40% of patients with GI disease were reported to be at risk of malnutrition compared to 28% of all hospital admissions (Russell 2008). It has been demonstrated that poor nutritional status detrimentally affects post-operative outcome in patients undergoing colorectal surgery (Schwegler 2010). Since malnutrition may be detrimental to GI surgical outcomes, strategies aimed at addressing this have been evaluated. In prospective studies that have evaluated nutritional interventions in surgical patients some positive effects have been demonstrated for the use of enteral nutrition (Beier-Holgersen 1996) and for the use of oral sip feeds post-operatively (Keele 1997). In a consensus review of Enhanced Recovery After Surgery (ERAS), it was recommended that patients receive carbohydrate loading 24 hours pre-operatively and nutritional supplements, from the day of surgery, until oral intake is achieved (Lassen 2009). However, In the period prior to hospital admission or more than 24 hours pre-operatively there is a lack of consensus regarding the provision of nutritional support for weight losing patients or those who are malnourished.

Description of the intervention

Nutritional support intervention includes nutritional formulations that are used for medical purposes administered via the oral, enteral or parenteral route. For this review nutritional support intervention refers to mixed formulas containing macro and micronutrients with or without immunomodulating components.

How the intervention might work

The presence of malnutrition can contribute to a poor clinical outcome by affecting body structure, function, physical and psychological health (Stratton 2003). Malnutrition has been shown to be a significant prognostic indicator for post-operative complications (Sungurtekin 2004; Sorensen 2008), which significantly increases length of hospital stay (Leung 2009). Correcting malnutrition pre-operatively in surgical patients to decrease post-operative morbidity and mortality may therefore be beneficial. When nutritional support has been instigated in malnourished patients, positive effects on anthropometry, clinical outcomes, and cost effectiveness have been demonstrated (Smedley 2004; Beier-Holgersen 1996). Benefits from the provision of nutritional intervention have also been demonstrated in well nourished cohorts without any direct effect on nutritional status measurements. This implies that there are physiological benefits to nutrition intervention not necessarily with improvements in anthropometric measurements, which may include improved immune, respiratory and cardiac function, along with improved wound healing and mobility (Akbarshahi 2008; Clark 2000).

Why it is important to do this review

ERAS is becoming increasingly common in the management of patients undergoing GI surgical. ERAS includes recommendations on post-operative nutritional management and feeding with pre-operative carbohydrate loading (Lassen 2009). However, there is no consensus regarding nutritional intervention in the period preceding hospital admission for patients admitted for elective GI surgery.

OBJECTIVES

Primary objective

To evaluate if nutritional support intervention by any route prior to surgery improves clinical outcomes for elective GI surgical patients.

Secondary Objectives

To determine if nutritional support interventions provide any benefit to nutritional intake or nutritional status prior to elective GI surgery.

METHODS

Criteria for considering studies for this review

Types of studies

Published randomised controlled trials, conference abstracts of RCTs where sufficient data can be obtained.

Types of participants

All non- emergency GI surgical patients.

Types of interventions

Nutrition support intervention by any route using any nutritional formulation containing both macro and micronutrients. Studies were included if the nutritional formulation had a carbohydrate, fat and nitrogen source with vitamins and minerals administered over any time (up to 3 months prior to surgery to 24 hours pre-operatively). Studies were included if they had manipulated dietary intake to increase calories and protein. Studies were excluded if they were evaluating a single nutrient or IE agent or any combination of nutritional components that did not meet the inclusion criteria.

Types of outcome measures

Primary outcomes

1. Complications
Infective - including pneumonia, wound infections, abdominal abscess.
Non-infective - including anastomotic leak, wound dehiscence, organ failure or thromboembolism
2. Length of hospital stay

Secondary outcomes

1. Nutritional aspects including weight, anthropometric measurements, hand grip strength and subjective global assessment
2. Quality of life (including patient reported outcomes)
3. Within group and between group changes in macro nutrient (calories and protein/nitrogen) intake
4. Biochemical parameters including albumin, prealbumin and C reactive protein
5. 30 day perioperative mortality
6. Adverse effects from feed and route of feeding
All outcomes will be included up to 3 months post-operatively

Search methods for identification of studies

Electronic searches

RCTs were identified by searching a number of databases including all EBM Reviews (Cochrane DSR, ACP Journal Club, DARE, CCTR, CMR, HTA and NHSEED) MEDLINE, EMBASE, AMED, British Nursing Index Archive using OvidSP to run a search on each database separately then exclude duplicates. Detailed search strategy is shown in Appendix 1. The searches were initially run in March 2011 and subsequently updated in February 2012

Searching other resources

Reference lists of the articles selected were hand searched for the review and we contacted authors of any conference abstracts if further data were required.

Data collection and analysis

Data collection will be undertaken by two reviewers and then with the use of Revman (version 5.1, Cochrane Collaboration) will be displayed in the included and excluded studies section. Data analysis will be performed using the Revman (version 5.1, Cochrane Collaboration).

Selection of studies

Two review authors assessed the title and abstract to determine relevance and eligibility. All papers failing to meet the eligibility criteria were excluded. If there was insufficient information in the title and abstract, then the article was obtained for clarification. The review authors assessed the full text of all the papers and extracted data from those studies meeting the inclusion criteria. We planned to translate any non-English articles before assessment, if needed. A third review author was available to be called upon to resolve any conflicts in study selection.

Data extraction and management

A data collection form was devised that facilitated data collection from the articles. This form allowed eligibility to be assessed by linking the studies directly to the research question. The data extraction form was piloted and modified as required. Two reviewers undertook the process of data extraction independently and any discrepancies were discussed with a third reviewer. The following information was recorded for each trial:-

- Year of publication, country of origin, source of funding and number of participants.
- Details of participants including proportion of malnourished patients (defined by body Mass index less than 20kg/m^2, weight loss greater than 10% in the previous 3-6 months, subjective global assessment or nutrition risk derived from a validated tool).
- Number of participants, age, type of surgery, perioperative management (ERAS or traditional), gender, diagnosis (noting proportion of cancer and non-cancer diagnosis).
- Details of type intervention (nutritional substrate with or without IE agents), route of intervention (oral, enteral or

parenteral) and length of time on intervention, daily volume of nutritional substrate delivered.

- Details of primary and secondary outcomes.

Assessment of risk of bias in included studies

We rated the quality of each trial in the following areas; random sequence generation, allocation concealment, blinding, complete outcome data, selective outcome reporting and other sources of bias using the Cochrane Collaboration's tool New Reference.

Measures of treatment effect

The estimates of effect of an intervention were expressed as risk ratios together with 95% confidence intervals.

Unit of analysis issues

For dichotomous outcomes, estimates of effect of an intervention was expressed as risk ratios together with 95% confidence intervals. Continuous outcomes were expressed using mean differences and standard deviations to summarise the data for each group.

Dealing with missing data

Authors were contacted for abstracts and missing data where possible.

Assessment of heterogeneity

Clinical heterogeneity was assessed by examining the type of participants, interventions and outcomes in each study. Meta-analyses were only conducted if there were studies reporting similar comparisons for the outcome measures.

Assessment of reporting biases

Funnel plots were to be used to evaluate publication bias if appropriate.

Data synthesis

Meta-analyses were only conducted on studies reporting similar comparisons for the same outcome measures.

Subgroup analysis and investigation of heterogeneity

Sub group analyses were to be undertaken on studies including malnourished participants, participants with cancer and without cancer, elective versus semi-elective surgery, those that state the use of an ERAS protocol and route of feeding if data allowed. The studies included did not facilitate these sub group analyses.

Sensitivity analysis

Planned sensitivity analyses were to be undertaken to examine the difference in the quality of the studies and to examine the difference in studies conducted before and after 1990. This date was used because there have been advances in artificial feeding since 1990, including changes in technology, line care, feeding tubes and the type and amount of enteral and parenteral nutrition delivered Braunschweig 2001. Sensitivity analysis was also planned on studies that used an ERAS protocol, if appropriate. The studies included did not facilitate this.

RESULTS

Description of studies

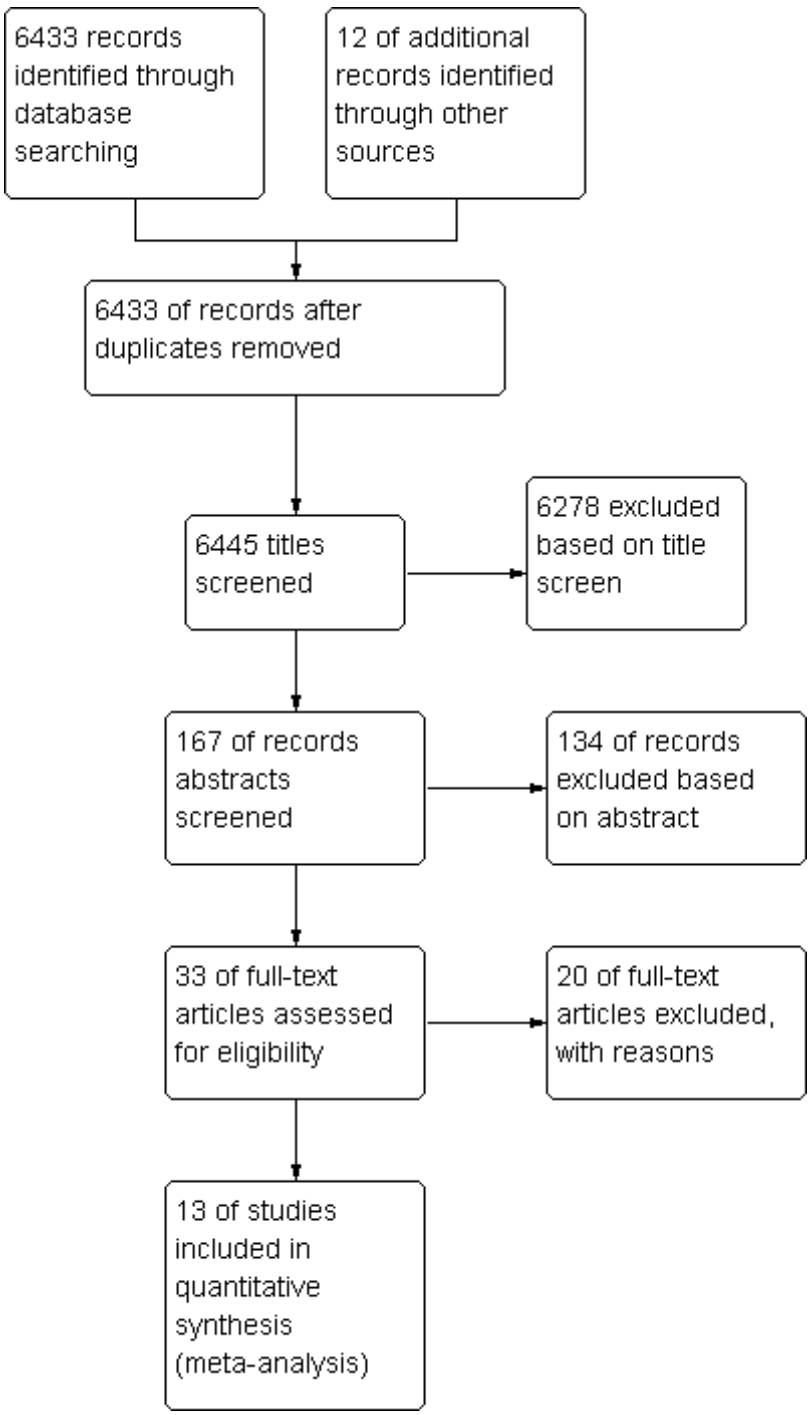
See: Characteristics of included studies; Characteristics of excluded studies.

See characteristics of included studies and characteristics of excluded studies. The searches were initially run in March 2011 and subsequently updated in February 2012. There were 13 randomised controlled trials identified from the literature searches that were included in the final analyses.

Results of the search

The results of the search are shown in Figure 1.

Figure 1. summary of literature review



Included studies

From the included studies, three evaluated pre-operative PN Muller 1982, Von Meyenfeldt 1992 and Smith 1988, two included data on pre-operative standard enteral nutrition, Von Meyenfeldt 1992 and Gunerhan 2009, seven evaluated pre-operative IE nutrition Braga 2002a, Gianotti 2002, McCarter 1998, Okamoto 2009, Gunerhan 2009 ,Xu 2006; Braga 2002b and three evaluated pre-operative standard oral supplements Smedley 2004, Burden 2011 and MacFie 2000.

Braga 2002a included a comparison of pre-operative standard oral nutritional supplements compared to no nutrition, although the data were dichotomous thus not included in the meta-analysis. Smedley 2004 and MacFie 2000 reported data as counts of complications and Burden 2011 had data (unpublished) in the same format to allow an analysis to be undertaken. Gunerhan 2009 published data as counts in the cohort so was not included in the meta-analysis for IE nutrition as the majority of trials published dichotomous variables. In studies that included multiple comparisons which fell into two of the above categories, the data have been included in the appropriate analyses if possible (Braga 2002a, Von Meyenfeldt 1992).

There were a total of 1192 participants included in the analyses of the trials whose data were relevant to pre-operative nutritional support. There were 260 participants included in trials of PN, 120 participants included trials of enteral nutrition, 549 included in trials on IE nutrition and 263 participants included in trials for standard oral nutritional supplements.

Data were collected on methodology, location of surgery, types of participants, details of nutritional substrates, administration and outcomes from each study. Additional unpublished data were obtained from one study Burden 2011 to allow analysis with other trials (data were obtained on the primary outcome as counts or rates within the group, as data were published as dichotomous variables). The dates of included studies ranged from 1982-2011; a PN study was the earliest to be published on this topic Muller 1982. Mandatory for this review was that trials published data on pre-operative nutritional support where the post-operative management was similar in each group. The 13 trials included all published data on pre-operative nutrition compared with: either the absence of nutrition or an alternative nutritional formula. From the trials included, ten included data on participants with a malignant pathology. In one trial, 66% of participants had a malignancy pathology Smedley 2004 and details of pathology were not reported in two studies MacFie 2000, Smith 1988. Two trials included participants who had colorectal surgery Braga 2002a, Burden 2011, one reported participants who had gastric surgery Okamoto 2009, and three reported lower GI surgery Smedley 2004, Von Meyenfeldt 1992, Xu 2006. Patients undergoing either upper and lower GI surgery were included by Muller 1982, Smith 1988, Gianotti 2002, Gunerhan 2009, Braga 2002b and MacFie 2000.

Nutritional status of participants was reported in ten of the trials, four included malnourished patients Smith 1988, Von Meyenfeldt 1992, Gunerhan 2009,Braga 2002b. Between 30-60% of participants were malnourished in three trials Muller 1982, Burden 2011,Smedley 2004 and less than 25% of participants were malnourished in three further trials Braga 2002a, MacFie 2000, McCarter 1998. One trial excluded malnourished patients Gianotti 2002 and the remaining trials did not report nutritional status Xu 2006, Okamoto 2009. Interestingly, all trials used different methods to assess nutritional status Table 1 .

All the PN trials administered nutrition for 10 days pre-operatively and volumes administered exceeded current recommendations for macro-nutrients Muller 1982 Smith 1988, Von Meyenfeldt 1992. In the seven trials on IE nutrition, 1000mls of the substrate was administered for five days in two trials Braga 2002a and Gianotti 2002 for seven days in five trials McCarter 1998, Okamoto 2009, Xu 2006, Gunerhan 2009,Braga 2002b 750mls of IE nutrition was administer in trials by Okamoto 2009, McCarter 1998 and volume was individually determined in trials by Xu 2006 and Gunerhan 2009. The same IE supplement was used in six trials with additional arginine (12.5g/L), omega 3 (3.3g/L) and RNA (1.2g/L):- the remaining trial used a IE substrate containing 3.4g/L of omega 3 and 26.5g/L of arginine McCarter 1998. In the oral supplement trials that evaluated standard formulas, two trials administered 400mls of supplement daily Burden 2011 and MacFie 2000 and in one trial participants were advised to take drinks ad libitum Smedley 2004; all these trials used the same supplement and all were conducted in the UK. The mean energy value consumed from supplements was 542 and 507 kilocalories in Smedley 2004 and MacFie 2000 respectively. Two trials compared enteral nutrition pre-operatively with no artificial nutritional support Von Meyenfeldt 1992 and Gunerhan 2009.

All trials included post-operative complications as an outcome, although the definition applied to complications varied considerably. In some trials, post-operative complications were defined as infectious and non infectious complications Braga 2002a, Gianotti 2002, Burden 2011 and Smedley 2004. Other trials outlined definitions used for complications in the publication Muller 1982, Smith 1988, Von Meyenfeldt 1992 and Okamoto 2009. Definitions for complications were not included in the remaining trials MacFie 2000, Gunerhan 2009, McCarter 1998 and Xu 2006. Biochemistry (albumin, transferrin or prealbumin) were recorded in seven trials Muller 1982, Smith 1988, Von Meyenfeldt 1992,Braga 2002b,Gunerhan 2009, Okamoto 2009 and MacFie 2000. Other outcomes included in the trial are listed in Table 2. All adverse events reported in the trials are given in Table 3.

Excluded studies

Twenty studies did not meet the inclusion criteria and the details of these are given in the table of excluded studies section. From the trials identified it was determined that 13 fitted our inclusion criteria (see table of included studies).

Risk of bias in included studies

Allocation

Sequence generation was described well in six of the included trials Braga 2002a,Braga 2002b Burden 2011, Gianotti 2002, Smedley 2004 and Smith 1988, allocation concealment was described in Burden 2011, Smedley 2004 and Smith 1988. The method of sequence generation and allocation concealment was not reported in the other included trials.

Blinding

Blinding was only undertaken in two of the trials Braga 2002a and McCarter 1998. In some instances it would be difficult to blind the intervention especially where parenteral was compared with enteral nutrition. The remaining studies did not report any blinding of the researchers or the participants taking part, thus introducing a high risk of bias.

Incomplete outcome data

A number of trials reported a high risk or unclear risk of attrition bias including Burden 2011, Gunerhan 2009, MacFie 2000, McCarter 1998, Muller 1982; Smedley 2004 . This was primarily due to participants being recruited who did not then have elective surgery and therefore were not included in the analysis. Nutritional intervention is a supportive therapy, so if participants do not then undergo surgery, postoperative complications can clearly not be evaluated. Post randomisation exclusions occurred in four trials for this reason Burden 2011, Smedley 2004 Muller 1982 and MacFie 2000. In four trials, participants were excluded for other reasons including GI bleeding, emergency surgery to relieve obstruction, uncontrolled blood sugar levels, minimum oral intake of the intervention, no diagnosis of a malignancy and some participants were excluded if they received postoperative enteral or parenteral nutrition Gunerhan 2009, Muller 1982, McCarter 1998, Smedley 2004.

Selective reporting

All of the trials included in the review reported at least one of the primary outcomes listed in the methodology section of this review.

Other potential sources of bias

Although some trials predominantly included participants with malignant pathology, they excluded patients who had received pre-operative chemotherapy, radiotherapy or immuno suppressive treatment Gianotti 2002, McCarter 1998; Gunerhan 2009 Braga 2002b. This will introduce external bias and thus affect the generalizability of the results.

Only a few trials specifically enrolled malnourished patients Braga 2002b,Gunerhan 2009,Von Meyenfeldt 1992,Smith 1988 and the majority of participants included in the trials reviewed were well nourished. Thus participants who would be most likely to benefit from nutritional support were not included in the majority of existing research. Perioperative surgical management has changed over the last decade with the advent of ERAS along with technological advances in the delivery, assessment and formulation of nutritional substrates, all of which may introduce temporal bias into the body of evidence. The risk of bias summary is given in Figure 2 and judgements about each risk of bias item presented as percentages across all included studies is shown in Figure 3.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

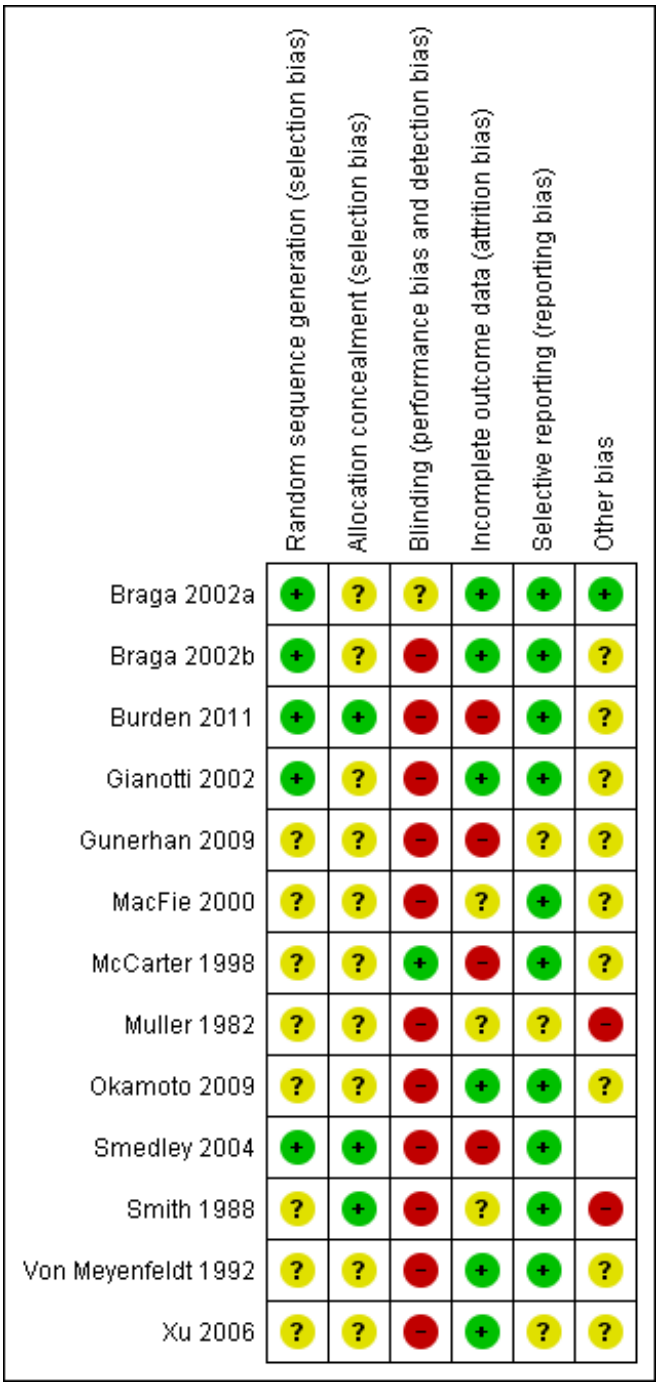
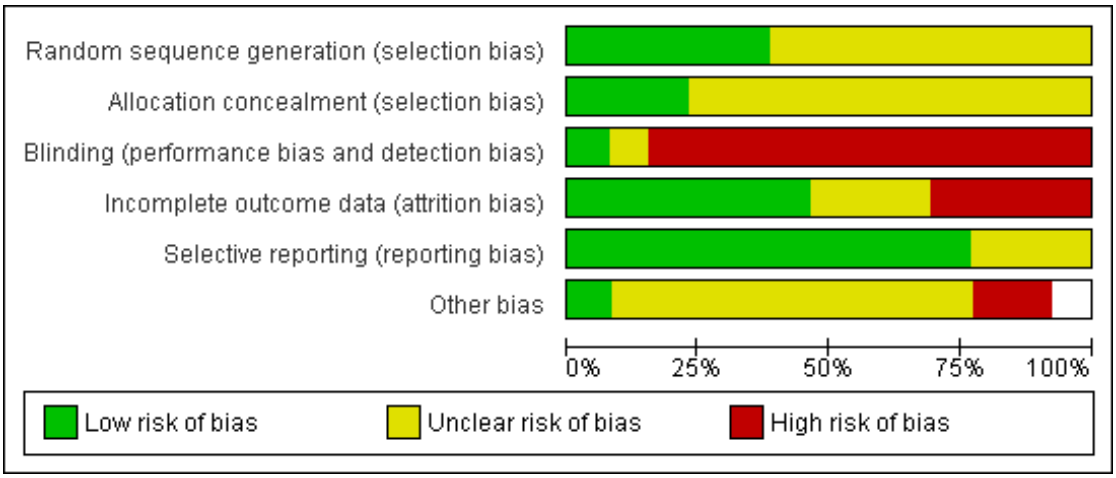


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Effects of interventions

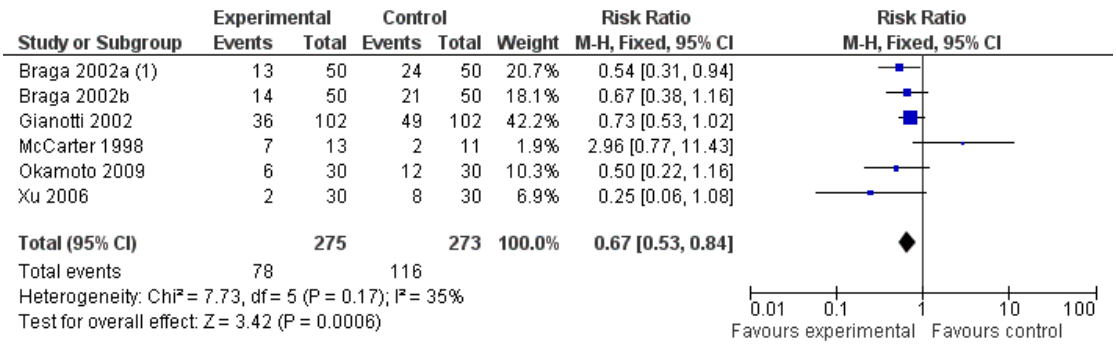
See: **Summary of findings for the main comparison**; **Summary of findings 2**; **Summary of findings 3**; **Summary of findings 4**

The analysis of the studies has been divided into IE nutrition trials, parenteral nutrition, enteral nutrition and oral standard nutritional formulas. The analysis for IE nutrition included non-infectious complications, infectious complications and length of hospital stay.The analysis compared all the IE pre-operative trials with no nutritional support or standard nutritional support and then looked at trials comparing IE nutrition with no nutrition, and then IE nutrition with standard nutritional support.

Immune-enhancing nutrition

There were seven trials Braga 2002a, Braga 2002b,Gianotti 2002, Gunerhan 2009, McCarter 1998, Okamoto 2009, Xu 2006 comparing IE nutrition to either no nutritional support or standard nutritional support, of which six Braga 2002a,Braga 2002b Gianotti 2002, McCarter 1998, Xu 2006; Okamoto 2009 were included in the mets analysis involving 548 participants Figure 4. Dichotomous data were analysed using risk ratios with Mantel-Haenszel in a fixed effects method. Absolute risk of a complication ranged from 42.6% (116/273) in the control group and 28.3% (78/275) in the intervention group and heterogeneity between the studies was low to moderate (Chi^2 =7.73, P=0.17) Analysis 1.1 . The relative effect was 0.67 (CI 0.53 to 0.84) for total complications.

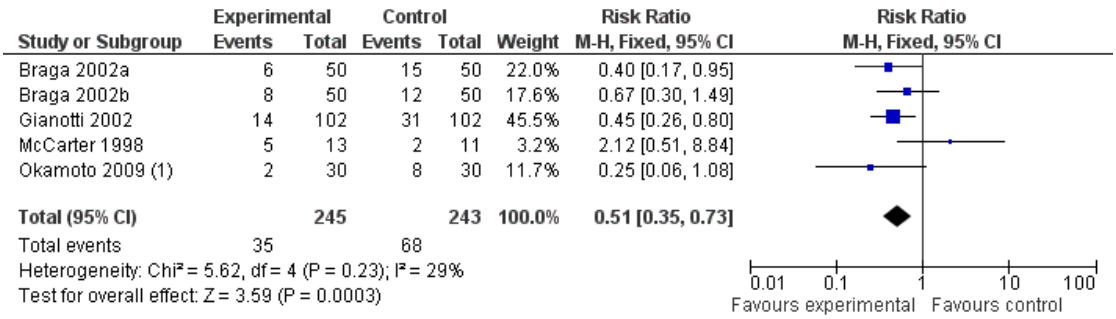
Figure 4. Forest plot of comparison: 1 All IE nutrition compared to no nutrition or standard nutrition, outcome: 1.1 Total complications.



(1) Data comparing immune enhancing nutrition to no nutrition is used in the first instance.

Five trials (including 488 participants) reported infectious complications Figure 5 Analysis 1.2. The absolute risk for infectious complications ranged from 27% (68/243) in the control group to 14.2% in the intervention group (35/245) and the relative risk was 0.51(CI 0.35 to 0.73). The heterogeneity between these studies represented a moderate risk (Chi^2 =5.2.162, P=0.23).

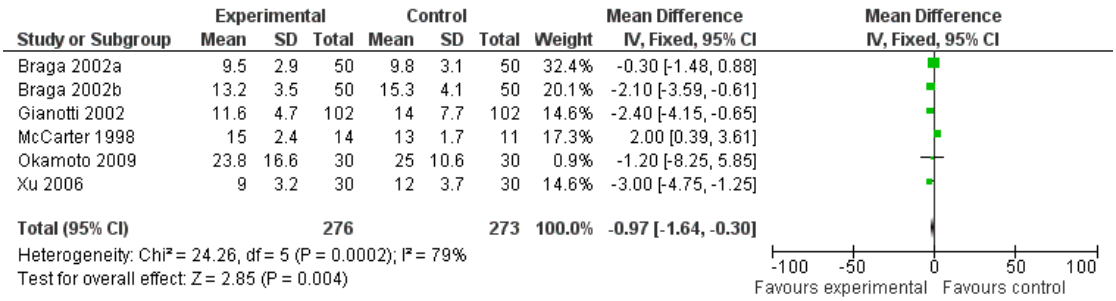
Figure 5. Forest plot of comparison: 1 All IE nutrition compared to control or standard nutrition, outcome: 1.2 Infectious complications.



(1) Xu- not included as infections given as counts not a dichotomous variable

Six trials (549 participants) reported the mean length of stay Figure 6, Analysis 1.3 for all trials reporting this outcome for IE nutrition was15.3 (9.8-25) days in the control group and 13.6 (9-23.8) days in the intervention group an difference was -0.97 (CI -1.64 to -0.30) and heterogeneity for this outcome was (Chi^2 =24.26, P= 0.0002) which represents a low level of heterogeneity.

Figure 6. Forest plot of comparison: 1 All IE nutrition compared to control or standard nutrition, outcome: 1.3 length of stay.



Immune-enhancing nutrition was then compared to standard nutritional supportFigure 7 Analysis 2.1 , Figure 8, Analysis 2.2 Figure 9 Analysis 2.3 and no nutritional support Figure 10 Analysis 3.1, Figure 11 Analysis 3.2, Figure 12 Analysis 3.3.

Figure 7. Forest plot of comparison: 2 Preoperative IE nutrition compared to standard nutrition, outcome: 2.1 Total complications.

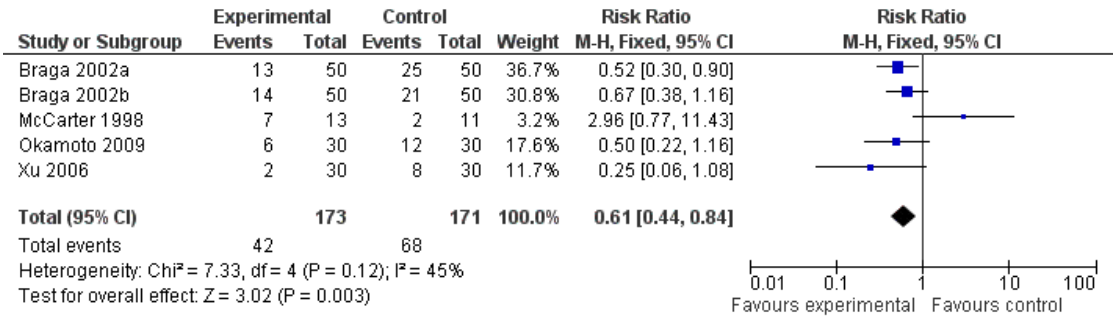


Figure 8. Forest plot of comparison: 2 Preoperative IE nutrition compared to standard nutrition, outcome: 2.2 Infectious complications.

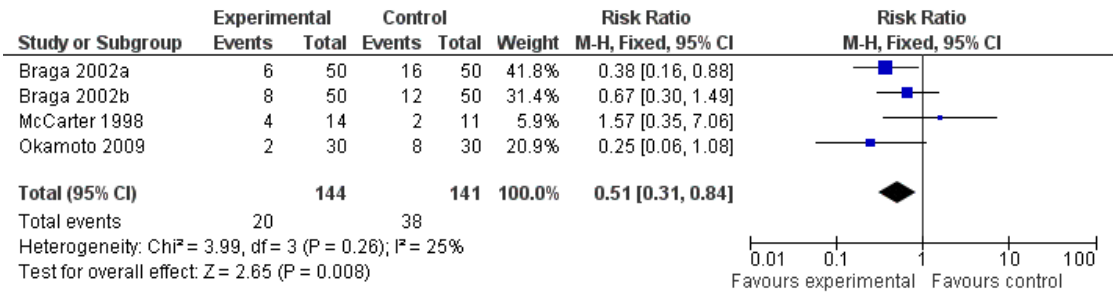


Figure 9. Forest plot of comparison: 2 Preoperative IE nutrition compared to standard nutrition, outcome: 2.3 Length of stay.

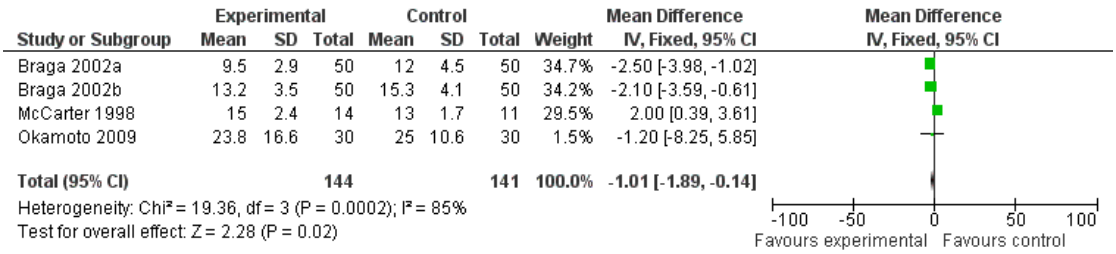


Figure 10. Forest plot of comparison: 3 Preoperative IE nutrition compared to no nutrition, outcome: 3.1 Total complications.

Figure 11. Forest plot of comparison: 3 Preoperative IE nutrition compared to no nutrition, outcome: 3.2 Infectious complications.

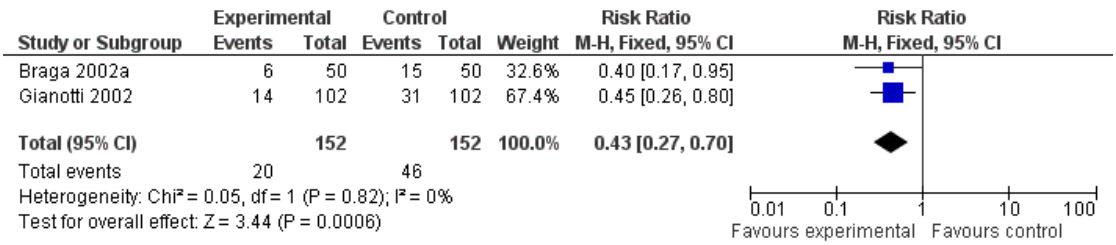
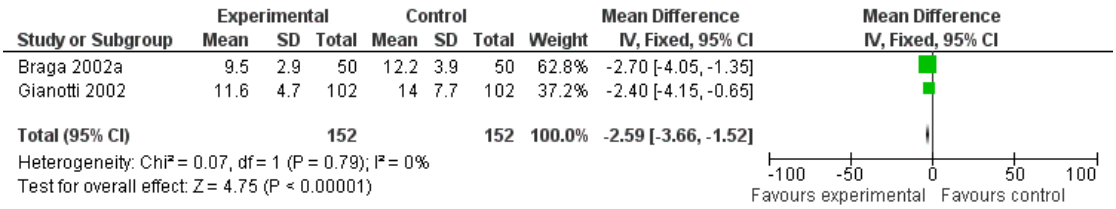


Figure 12. Forest plot of comparison: 3 Preoperative IE nutrition compared to no nutrition, outcome: 3.3 Length of stay.



Standard oral nutritional support

Pre-operative oral nutritional support was compared to no nutritional support or dietary advice Burden 2011, Smedley 2004 and MacFie 2000, which included non-infectious complications and infectious complication reporting on 263 and 250 participants, respectively. Count data were analysed using risk ratios with Mantel-Haenszel in a fixed effects method. The absolute risk for non-infectious complications in the control group was 45.2% (62/137); in the intervention group 52.65% (60/126) and the relative effect was 1.06 (CI 0.82 to 1.36). For this outcome, heterogeneity was Chi^2 =13.1, P=0.001, representing a high level of heterogeneity Figure 13 Analysis 4.1. For infectious complications the absolute risk was 43.5% (57/131) in the control group and 47.4% (56/119) in the intervention group. The relative effect was 1.09 (CI 0.83 to 1.42) and the heterogeneity was Chi^2 =12.5, P=0.002 thus representing a high level of heterogeneity Figure 14 Analysis 4.2. Length of stay is shown in Figure 15 Analysis 4.3.

Figure 13. Forest plot of comparison: 4 Preoperative standard oral nutrition compared to no nutrition, outcome: 4.1 Total complications.

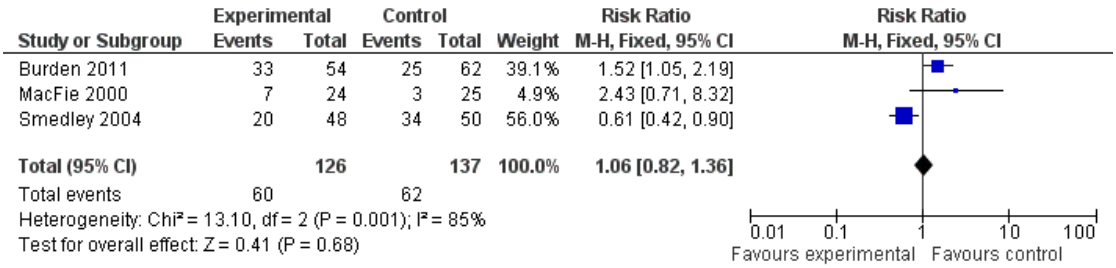


Figure 14. Forest plot of comparison: 4 Preoperative standard oral nutrition compared to no nutrition, outcome: 4.2 Infectious complications.

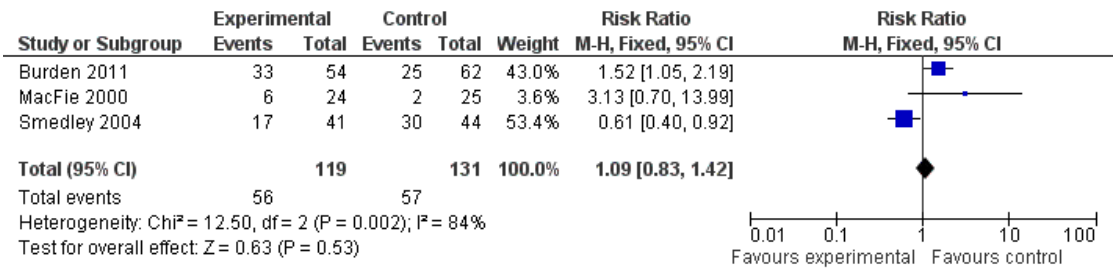
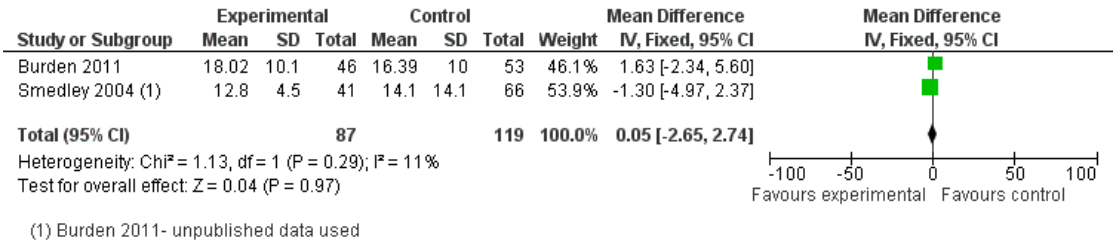


Figure 15. Forest plot of comparison: 4 Preoperative standard oral nutrition compared to no nutrition, outcome: 4.3 Length of stay.



(1) Burden 2011- unpublished data used

Enteral Nutrtional support

Two trials that evaluated enteral nutrition compared to no artificial nutritional support Von Meyenfeldt 1992 and Gunerhan 2009; these trials included 120 participants who were all malnourished. Nutritional status was assessed using subjective global assessment Gunerhan 2009 and nutritional index Von Meyenfeldt 1992. However, both trials were rated as having a high risk of bias. Count data were analysed using risk ratios with Mantel-Haenszel in a fixed effect method. The absolute risk for total complications was 42% (35/59) in the control group and 40.7% (28/66) in the intervention groups and the relative effect was 0.79 (CI 0.56 to1.10). Heterogeneity for this outcome in the two trials was low (Chi^2 =0.25, P=0.62) Figure 16 Analysis 5.1. For infectious complications, the absolute risk in the control and intervention group was the same at 45% for the control (based on 29/59) and for the intervention group (based on 30/66). The relative effect was 1 (CI 0.69 to 1.44) and, again, heterogeneity for the two trials for this outcome was low (Chi^2 =0.84, P=0.36)Figure 17 Analysis 5.2.

Figure 16. Forest plot of comparison: 5 Preoperative enteral nutrition compared to no nutrition, outcome: 5.1 Total complications.

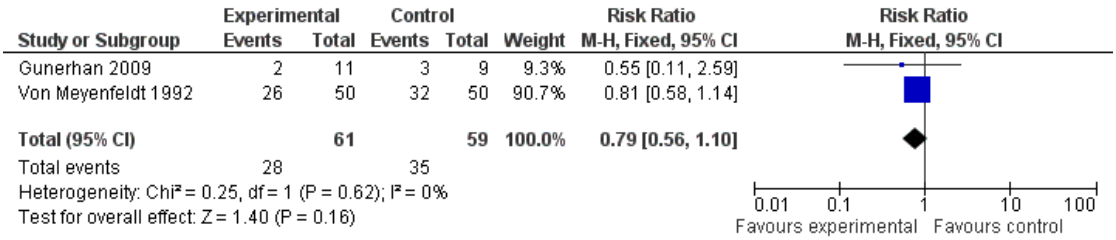
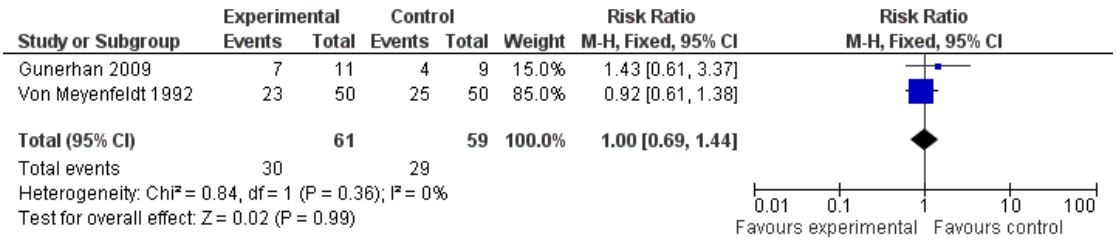


Figure 17. Forest plot of comparison: 5 Preoperative enteral nutrition compared to no nutrition, outcome: 5.2 Infectious complications.



Parenteral nutritional support

Parenteral nutrition was given preoperatively in three trials Smith 1988, Von Meyenfeldt 1992 and Muller 1982, including 260 participants with non-infectious complications reported as an outcome and 226 participants reported for infectious complications. Count data were analysed using risk ratios with Mantel-Haenszel in a fixed effects method. Absolute risk for non-infectious complication was 45.2 (57/126) for the control group and 28.9 (38/134) for the intervention group. Relative effect was 0.64 (CI 0.46 to 0.87) for non-infectious complications Figure 18 Analysis 6.1 and 0.94 (CI 0.80 to 1.10) for infectious complications Figure 19 Analysis 6.2. Heterogeneity between the three studies for total complications was low (Chi^2 =1.16, P=0.56) and for infectious complications was high (Chi^2 =18.56, P=0.0001). The trials evaluating PN pre-operatively were assessed as having a high risk of bias as these trials were all over 20 years old and clinical practices have now altered with improved delivery techniques, nutrient solutions, assessment and patient management.

Figure 18. Forest plot of comparison: 6 Preoperative PN compared to no nutrition, outcome: 6.2 Infectious complications.

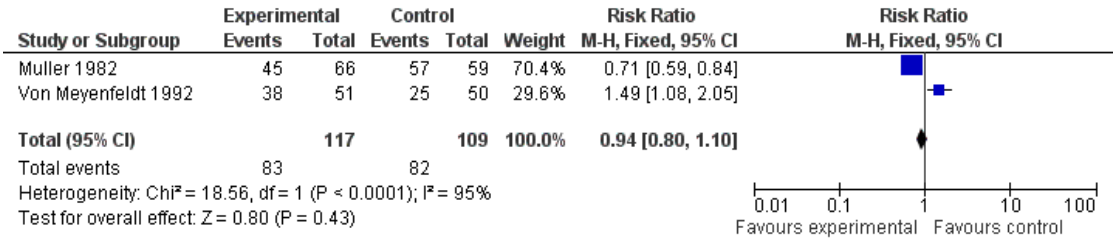
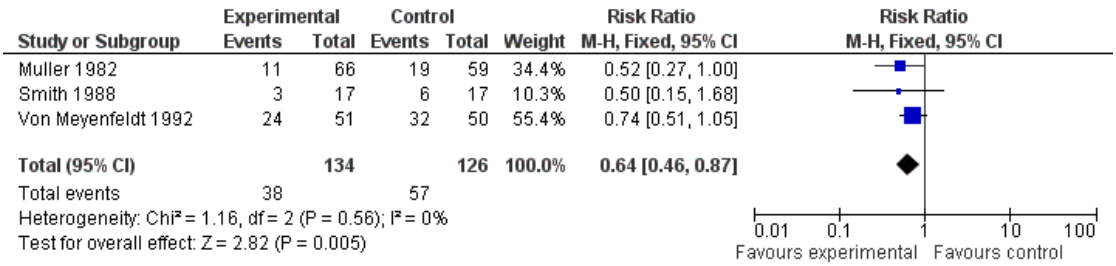


Figure 19. Forest plot of comparison: 6 Preoperative PN compared to no nutrition, outcome: 6.1 Major complications.



Other outcomes

The length of follow up in the trials for post-operative complications was only reported in one of the trials Gianotti 2002. Nutritional status parameters including anthropometry, handgrip strength or biochemistry were monitored in Muller 1982, .Smith 1988 Gianotti 2002 Okamoto 2009; Xu 2006; Smedley 2004 MacFie 2000 Nutritional intake was reported in trials that evaluated oral supplements MacFie 2000, Smedley 2004, Burden 2011 and quality of life was only reported in two trials Smedley 2004 and MacFie 2000.

Funnel plots were not undertaken on any of the comparisons in the review as the number of trials in each of the analyses was too small to determine risk of publication bias.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Stanadard oral nutritional supplements compared with no nutritional support or dietary advice for pre-operative GI surgical patients

Patient or population: Patients undergoing GI surgery
Settings: acute
Intervention: oral nutritional supplements
Comparison: no nutritional support or dietary advice

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No nutritional support	Oral nutritional supplements				
Total complications	Medium risk population		**RR 1.17** (0.54 to 2.55)	263 3	**moderate**	
	45.2 per 100	**52.6 per 100** (24.3 to 114)				
Infectious complications	Medium risk population		**RR 1.09** (0.83 to 1.42)	250 3	**moderate**	
	43.5 per 100	**47.4 per 1000** (35.8 to 61.7)				
length of hospital stay	The mean length of hospital stay ranged across control groups from 15.4 (range 12.8-18.0) days.	The mean length of hospital stay in the intervention groups was 15.2 (range 14.1 - 16.3) days.		206 2	**moderate**	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; [other abbreviations, e.g.. OR, etc]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

PN compared with no nutrition in preoperative GI surgical patients

Patient or population: GI surgical patients
Settings: acute
Intervention: pre-operative parenteral
Comparison: no nutritional support

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	No nutritional support	PN				
Total complications	High risk population		**RR 0.64** (0.46 to 0.87)	260 3	low	
	45.2 per 100	**28.9 per 100** (20.7 to 39.3)				
Infectious complications	High risk population		**RR 0.94** (0.80 to 1.10)	226 2	low	
	75.2 per 100	**70.6 per 100** (60 to 82.7)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; [other abbreviations, e.g.. OR, etc]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[Preoperative enteral nutrition compared with no nutrition in GI patients

Patient or population: preoperative GI patients
Settings: acute
Intervention: preoperative enteral nutrition
Comparison: no artificial nutrition

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	no artificial nutritional support	enteral nutrition				
total complications	**42 per 100**	**40.7 per 100** (23.5 to 46.2)	**0.97** (0.56 to 1.10)	120	low	Nutritional was delivered 150% of energy requirements in the largest study and no adverse effects noted in one of the studies from feed or route
Infectious complications	**45 per 100**	**45 per 100** (3.1 to 64)	**1.00** (0.69 to 1.44)	120	low	Nutritional was delivered 150% of energy requirements in the largest study and no adverse effects noted in one of the studies from feed or route

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk Ratio; [other abbreviations, e.g.. OR, etc]

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

DISCUSSION

Summary of main results

Thirteen studies that met the inclusion criteria and these were of varying quality. This quality assessment is important to place the current evidence into the context of today's clinical practice. The predominant outcomes in these trials concentrated on post-operative complications and all the trials included either total or infectious complications (or both). A small number of trials reported on nutritional status measurements or dietary intake. The majority of the trials concentrated on malignant pathologies in well nourished patients.

The early trials investigated PN and, given current recommendations for the provision of nutritional support, would not necessarily be applicable to clinical practice today. In some trials, the volume of nutrition provided exceeded current guidelines and not all participants had a non-functioning GI tract or other relevant indication for PN according to current practice guidance National Institute 2006. In two out of three PN trials, participants receiving PN were malnourished and over half of participants were malnourished in the third trial. The administration of nutritional support favoured the intervention for the major complications, but favoured controls for infectious complications. This could possibly be attributed to over feeding and PN catheter infections which could have contributed to the number of participants experiencing an infectious event. Homogeneity between the trials evaluating PN was good.

There were only two trials which incorporated data on enteral nutrition in the preoperative period. The results on enteral nutrition were inconclusive. The trials had a high degree of homogeneity, albeit were assessed at a high risk or unclear risk of bias.

The results of the IE nutrition trials indicated a beneficial effect, but they required interpretation in view of exclusion criteria and patient selection. These trials could also be subject to temporal bias as there have been advances in surgical practice due to ERAS initiatives which affect surgical outcome and directly influence post-operative complication rates. The purpose of IE nutrition is to improve immune function and not to provide nutritional support. The trials did not state whether they had been undertaken in hospitals where ERAS protocols were in place. In addition, these results need to be considered in light of adverse reactions identified with arginine Suchner 2002 and omega 3 fatty acids Rice 2011 in critical care patient populations.

The trials on standard oral supplements which were carried out on predominantly well nourished participants, demonstrated no benefit.

Overall completeness and applicability of evidence

The evidence presented is applicable for the current management of GI surgical participants with regard to IE nutrition and standard supplements. The evaluation of PN is only of academic relevance and included for completeness due to temporal modifications in indications, assessment, prescribing and monitoring of intravenous nutritional support.

Quality of the evidence

The quality of the evidence is variable with some high quality trials included and others with a high risk of bias.

Potential biases in the review process

S Burden was one of the reviews and is also an author on an included study.

Agreements and disagreements with other studies or reviews

A previous review incorporating IE nutrition in the preoperative period Cerantola 2011 concurs with the results presented in this review demonstrating that pre-operative IE nutrition reduced overall post-operative complications including non-infectious and infectious complications.

AUTHORS' CONCLUSIONS

Implications for practice

The results from pre-operative IE nutrition has favoured the intervention compare to control for non-infectious and infectious complications in predominantly well nourished surgical candidates and, in the absence of serious co-morbidities. Pre-operative IE showed inconclusive effects on length of stay. Immune-nutrition has not been evaluated in conjunction with ERAS programmes and has demonstrated no benefit in improving nutritional status in weight losing or malnourished surgical candidates in the pre-operative period. It is note worthy that surgical candidates who are at the highest risk of incurring post-operative complications have been excluded from the majority of research on IE nutrition.

The data relating to pre-operative oral supplements and enteral nutrition are inconclusive. Pre-opperative PN had a positive effect on total complications but not on infectious complications in predominantly malnourished participants.

Implications for research

This review highlights the lack of research utilising standard oral supplementation for pre-operative nutritional support in malnourished patients under going GI surgery. The changing clinical environment has lead to the wide scale implementation of ERAS protocols for peri-operative management of surgical patients, thus future research would need to evaluate pre-operative regimens

in conjunction with ERAS protocols. Immune-enhancing nutritional formulations require further evaluation with regard to the individual active components of the IE substrates. This will enable informed clinical decisions to be made with increased confidence in the use of IE nutrition in GI surgical candidates.

ACKNOWLEDGEMENTS

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by year of study]*

MacFie 2000

Methods	Randomised controlled trial
Participants	100 participants recruited requiring major GI surgery Mean age range in groups 63-68 years Male:female 46:54
Interventions	Group 1-pre and postoperative supplements Group 2-preoperative supplements Group 3-postoperative supplements Group 4-no supplements
Outcomes	weight change, total and septic complications, mortality, albumin,mid arm muscle circumference, hand grip strength and energy intake
Notes	Outcome defined by Copeland 1991

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	no information given
Allocation concealment (selection bias)	Unclear risk	no information given
Blinding (performance bias and detection bias) All outcomes	High risk	no blinding of oral supplements
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	12 patients excluded from the analysis as they did not go on to have surgery
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Some groups merged after surgery allowing for some confusion in interpretation of results

Muller 1982

Methods	Randomised controlled trial
Participants	160 patients approached, 125 included with carcinoma of the oesophagus, stomach, colon, rectum or pancreas Mean age range in groups 58-59 years Male: female 77:48
Interventions	Intervention group - PN for 10 days Control group - regular hospital diet
Outcomes	Infectious and non infectious complications, mortality, serum protein levels, immunological status
Notes	Patients considered malnourished if they had incurred a weight loss of more than 5kg in the previous 3 months prior to admission, serum albumin was below 3.5g/dl and the response to five skin tests were negative

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details given
Allocation concealment (selection bias)	Unclear risk	No details given
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not all patients included in the trial were in the analysis, two patients did not have malignant disease and the remaining patients did not go on to have surgery
Selective reporting (reporting bias)	Unclear risk	All outcomes were reported
Other bias	High risk	Clinically lacks applicability as current recommendations outline PN should only be administered in patients who cannot meet their nutritional requirements via oral or enteral route. Amount of nutrition administered was quite high compared to current practices

Smith 1988

Methods	Randomised controlled trial
Participants	34 Patients undergoing major GIl surgery including upper GI surgery and colorectal surgery with a prognostic nutritional index score of > 30% Mean age range in groups 67-68 years Male:female 27:7
Interventions	10 Days preoperative PN
Outcomes	Hand grip strength, infective and non-infective complications categorised as minor and major. Outline of definitions for complications was pre defined in article
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Randomly ordered cards in sealed envelopes opened after the prognostic nutrition index was obtained. Does not describe an audit trail for sealed envelopes
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	All patients included in the results
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	High risk	Clinically lacks applicability as current recommendations outline PN should only be administered in patients who cannot meet their nutritional requirements via oral or enteral routes. Amount of nutrition administered was high compared to current practices

Von Meyenfeldt 1992

Methods	Randomised controlled trial
Participants	200 patients with histologically proven gastric or colorectal cancer requiring surgery less than 80 years old and nutritionally depleted using albumin, total lymphocyte counts and percentage ideal body weight. These were used to calculate nutritional index Mean age range in groups 61-67 years Male: females 126:74

Von Meyenfeldt 1992 (*Continued*)

Interventions	Group 1 -preoperative parenteral nutrition (n=51) Group 2 - preoperative enteral nutrition via nasogastric tube or by mouth (n=50) Group 3 - no nutrition (n=50) Group 4- non depleted group not randomised (n=49)
Outcomes	Complications defined in manuscript
Notes	Enterial nutrition used was Precitene or Isotein.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded, however would be difficult to blind the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients randomised were included
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Clinically lacks applicability as current recommendations outline parenteral nutrition should only be administered in patients who cannot meet their nutritional requirements via oral or enteral route. Amout of nutrition administered was quite high compared to current practices

McCarter 1998

Methods	Randomised controlled trial
Participants	38 patients were approached and 38 included undergoing major surgery of the oesophagus, stomach or pancreas for cancer were included Mean age ranges from 62-66 years Male:female 21:17
Interventions	Group 1-Standard nutritional supplement Group 2-Standard supplement with added arginine Group 3-Standard supplement with added arginine and omega 3 fatty acids
Outcomes	Infectous and non infectious complications, length of stay, mortality

McCarter 1998 (*Continued*)

Notes	Excluded patients who had received chemotherapy or radiotherapy No definitions used for complications	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	13 patients excluded from the analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Exclusion criteria - Evidence of active infection, renal failure, hepatic failure, human immunodeficiency virus, history of immunosuppressive therapy, uncontrolled diabetes and pregnancy

Gianotti 2002

Methods	Randomised controlled trial
Participants	517 patients assessed 305 patients with histologically proven neoplasm of the GI tract and planned major elective surgery Mean age range in groups 62-63 years Male:female 166:139
Interventions	Group 1-IEN 5 days preoperatively of a supplemented liquid diet n=102 Group 2-IEN 5 days preoperatively of a supplemented liquid diet and postoperatively jejunal feeding with the same formula before starting within 12 hours after surgery n=101 Group 3-No artificial nutrition before or after surgery n=102
Outcomes	Postoperative complications recorded up to 30 days by a member of surgical staff not directly involved in the study
Notes	IEN- IE nutrition with arginine and omega 3 fatty acids (Oral Impact Norvartis. Bern Switzerland) All patients with weight loss $\geq$ 10% of their previous weight in the previous 6 months Excluded patients who had received neoadjuvant chemoradiotherapy

Gianotti 2002 (*Continued*)

	Post operative complications defined by Bozzetti 2001i 2001

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Individual random numbers
Allocation concealment (selection bias)	Unclear risk	No details given on the process
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding. However, surgical staff not involved in the trial applied the definitions for complications
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients enrolled were included in the results
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Extensive exclusion criteria limit generalizability of the results. Exclusion criteria were weight loss 10% (with respect to usual body weight) in the past 6 months, age younger than 18 years, hepatic dysfunction (Child-Pugh class B), respiratory dysfunction (arterial PaO2 70 torr), renal dysfunction (serum creatinine level 3 mg/dL, haemodialysis), cardiac dysfunction (New York Heart Class 3), Karnofsky score 60, pregnancy, ongoing infections, and immune disorder (neoadjuvant radiochemotherapy, circulating neutrophils 2.0 109/L)

Braga 2002b

Methods	Randomised controlled trial
Participants	150 participants randomised undergoing elective surgery for GI malignance
Interventions	Goup 1- Standard enteral formula postoperatively Group 2- IE formula 7 days preoperatively and standard enteral formula postoperatively Group 3 - IE nutrition postoperatively
Outcomes	postoperative complications and length of stay
Notes	Extensive exclusion criteria Respiratory tract dysfunction (arterial PaO2 70 mm Hg) Cardiac dysfunction (New York Heart Class 3, stroke history) Karnofsky score 60 Hepatic dysfunction (Child-Pugh score 2, portal hypertension)

Braga 2002b (*Continued*)

	Ongoing infection Renal dysfunction (serum creatinine level 3 mg/dL [265 mol/L], haemodialysis) Immune disorder (neoadjuvant radiochemotherapy, neutrophil level 2000/IL, hypoimmunoglobulinemia) Pregnancy Age 18 Y oral impact (Novartis Consumer Health, Bern, Switzerland) Definitions for complications given in the paper

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	computer generated
Allocation concealment (selection bias)	Unclear risk	Not detailed in method
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention to treat analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	Extensive exclusion criteria 196 approached 46 patients were excluded

Braga 2002a

Methods	Randomised controlled studies
Participants	233 patients were approached of whom 200 patients were included with colorectal neoplasm Histologically proven colorectal cancer who were candidates for elective curative surgery Male:females 118:82 Mean age range in groups was 60.5-63 years
Interventions	Group 1- n=50, 1 litre of IEN 5 days before surgery and continued after surgery for by jejunal feeding Group 2- n=50, 1 litre of IEN orally before surgery of IEN Group 3- n=50, 1 litre of isonitrogenous and isoenergetic diet pre-operatively Group 4- n=50, conventional diet did not receive any artificial diet before or after surgery

Braga 2002a (*Continued*)

Outcomes	Infectious complications, non infectious complications, anastomotic leak, antibiotic therapy and length of stay. Patients followed up for complications for 30 days after surgery
Notes	IEN- immune enhancing nutrition with arginine and omega 3 fatty acids (Oral Impact Norvartis. Bern Switzerland) 10% of participants had a weight loss >10% in the previous 6 months Outcomes were defined Bozzetti 2001 2001 and were recorded by a member of surgical staff independent from the study

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation was by a computer generated list.
Allocation concealment (selection bias)	Unclear risk	No mention of concealment of randomisation sequencing
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Interventions were blinded where it was possible to do.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in the study were included in the intention to treat analysis
Selective reporting (reporting bias)	Low risk	All outcomes measured were reported in the results.
Other bias	Low risk	well conducted study

Smedley 2004

Methods	Randomised controlled trial
Participants	532 were approached of whom 179 patients undergoing lower GI surgery were included Mean age range in groups 55-63 years Male:females 100:79
Interventions	Group 1- Supplements were given preoperatively for a minimum of 7 days Group 2- Supplements given pre and postoperatively up to 4 weeks after discharge from hospital Group 3-Supplements given postoperatively up to 4 weeks after discharge from hospital Group 4- No artificial nutrition administered
Outcomes	Major and minor complications using definitions by Buzby 1988. Anthropometric measurements, nutritional intake, quality of life, length of stay, health service costs

Smedley 2004 (*Continued*)

Notes	Encouraged to drink supplements ad libitum Supplement was Fortisip (Nutricia, Wageningen, The Netherlands)	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Sealed envelopes stratified according to nutritional status
Allocation concealment (selection bias)	Low risk	Used sealed envelopes
Blinding (performance bias and detection bias) All outcomes	High risk	Unblinded
Incomplete outcome data (attrition bias) All outcomes	High risk	27 patients were withdrawn from the study this was at the patients request, surgery cancelled, enteral or PN was started
Selective reporting (reporting bias)	Low risk	No difference in quality of life mentioned. However no data reported

Xu 2006

Methods	Randomised controlled trial	
Participants	60 participants colorectal and gastric carcinoma Age range in groups 57-60 years Male:female 36:24	
Interventions	IE nutrition or standard enteral nutrition	
Outcomes	complications infectious and total recorded by surgical staff not involved in the study	
Notes		
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given

Xu 2006 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	No information
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients included in the analysis
Selective reporting (reporting bias)	Unclear risk	All outcomes reported
Other bias	Unclear risk	Exclusion criteria included those with any of the following conditions: pulmonary, cardiovascular, renal or hepatic disease; history of recent immunosuppressive therapy (including preoperative radiochemotherapy) or immunological diseases; ongoing infection; emergency operation; or preoperative evidence of widespread metastatic disease.

Gunerhan 2009

Methods	Randomised controlled trial
Participants	56 patients with GI tumours were included in the study Mean age range in groups 61-64.5 years Male:female 25:17
Interventions	Group 1 - IE nutrition n=16 Group 2 - Normal nutrition n=13 Group 3 - Standard enteral feed n=13
Outcomes	CRP, prealbumin, nitrogen balance, infection rates and duration of hospital stay
Notes	IE nutrition = Impact Standard enteral feed = Fresubin

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information given
Allocation concealment (selection bias)	Unclear risk	No information given
Blinding (performance bias and detection bias) All outcomes	High risk	Not blinded

Gunerhan 2009 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	14 patients excluded from the analysis due to GI bleeding, emergency surgery to relieve an obstruction, and uncontrolled blood sugars
Selective reporting (reporting bias)	Unclear risk	All outcomes reported
Other bias	Unclear risk	Extensive excluded criteria - Excluded patients with diabetes mellitus, renal and/or hepatic failure, and active infection were excluded, as were the patients with a history of immunosuppressive drug use or clinical signs of vitamin or trace element deficiency

Okamoto 2009

Methods	Randomised controlled trial
Participants	60 patients entered into the trial with gastric carcinoma Male:female 42:18 Age range 41-90 years
Interventions	Intervention group was given 750mls of IEN for 7 days Control received an isoenergetic standard formula for 7 days
Outcomes	Infectious and non infectious complications, immunological and nutritional measurements. Length of hospital stay
Notes	IEN -IE nutrition with arginine and omega 3 fatty acids (Oral Impact, Ajinomoto Pharma Co Ltd Japan) Excluded abdominal radiotherapy and pre operative chemotherapy Definition of complications outlined by authors

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	block randomisation
Allocation concealment (selection bias)	Unclear risk	no information given
Blinding (performance bias and detection bias) All outcomes	High risk	Standard drink given as a control, no details given regarding the similarity in appearance or taste described
Incomplete outcome data (attrition bias) All outcomes	Low risk	All patients who were included in the trial were analysed.

Okamoto 2009 (*Continued*)

Selective reporting (reporting bias)	Low risk	All outcomes reported
Other bias	Unclear risk	The exclusion criteria included those with any of the following conditions: an unresectable neoplasm, previous abdominal radiotherapy, preoperative chemotherapy, pulmonary, cardiovascular, renal or hepatic disease, history of recent immunosuppressive therapy (including preoperative radiochemotherapy) or immunological diseases, ongoing infection, emergency operation, or preoperative evidence of widespread metastatic disease, or stenotic lesions

Burden 2011

Methods	Unblinded randomisation trial
Participants	226 were assessed for eligibility of whom 125 were enrolled Subjective global assessment B and C indicating moderate to high risk of malnutrition 45% of participants Mean age range in groups 64.5-65.3 years Male:females 72:44
Interventions	Intervention group received 400ml of oral supplement and dietary advice n=59 control group received dietary advice n=66
Outcomes	Infectious and non infectious complications, antibiotics, nutritional intake using 24 hour unstructured dietary recall hospital anxiety and depression score, Karnofsky performance index Complications recorded up to 3 months post surgery.
Notes	Oral supplement was Fortisip Nutricia Ltd, Uk Dietary advice was to increase energy and protein participants were given written information Two sets of published definitions were applied to postoperative complications Buzby et al 1988 Ayliiffe et al 1993

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Block randomisation
Allocation concealment (selection bias)	Low risk	Sequentially numbered brown opaque envelopes were used

Burden 2011 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	High risk	No blinding was undertaken
Incomplete outcome data (attrition bias) All outcomes	High risk	There were patients who did not go on to have surgery and these were not included in the analysis
Selective reporting (reporting bias)	Low risk	All outcomes were reported
Other bias	Unclear risk	Imbalance at baseline more weight losing patients in intervention group. However, did not effect outcome on adjusted analysis

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bozzetti 2001	Post-operative administration of feed.
Braga 1999	Peri-operative administration of feed.
Finco 2007	Perio-perative comparator study.
Gianotti 1999	Does not report outcomes specified in review protocol.
Giger 2007	Pre-operative nutrition administered with postoperative nutritional support
Heatley 1979	Quasi randomised according to odd and even year of birth.
Hendry 2008	Not randomly allocated.
Horie 2006	Sequentially enrolled not randomised.
Klek 2011	Peri-opertive comparator study.
Lim 1981	Peri-operative data only.
Lin 1997	Did not include outcomes specified in the protocol.
Mueller 1982	Did not include a lipid source in the peripheral parenteral nutrition administered
Ozkan 2002	Peri-operative administration of feed comparing pre and post-operative administration no data on pre-operative administration only

(*Continued*)

Rombeau 1982	Not randomised
Ryan 2009	Peri-operative administration of feed comparing pre and post-operative administration no data on pre-operative administration only
Sakurai 2007	Peri-operative administration of feed comparing pre and post-operative administration no data on pre-operative administration only
Senkal 1999	Peri-operative administration of feed comparing pre and post-operative administration no data on pre-operative administration only
Senkal 2005	Did not include outcomes specified in the protocol.
Sodergren 2010	Post-operative feeding only.
Takeuchi 2007	Peri-operative administration of feed comparing pre and post-operative administration no data on pre-operative administration only

DATA AND ANALYSES

Comparison 1. All immune enhancing nutrition trials compared to no nutrition or standard nutrition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total complications	6	548	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.53, 0.84]
2 Infectious complications	5	488	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.35, 0.73]
3 length of stay	6	549	Mean Difference (IV, Fixed, 95% CI)	-0.97 [-1.64, -0.30]

Comparison 2. Preoperative immune enhancing nutrition compared to standard nutrition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total complications	5	344	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.44, 0.84]
2 Infectious complications	4	285	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.31, 0.84]
3 Length of stay	4	285	Mean Difference (IV, Fixed, 95% CI)	-1.01 [-1.89, -0.14]

Comparison 3. Preoperative immune enhancing nutrition compared to no nutrition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total complications	2	304	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.51, 0.89]
2 Infectious complications	2	304	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.27, 0.70]
3 Length of stay	2	304	Mean Difference (IV, Fixed, 95% CI)	-2.59 [-3.66, -1.52]

Comparison 4. Preoperative standard oral nutrition compared to no nutrition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total complications	3	263	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.82, 1.36]
2 Infectious complications	3	250	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.83, 1.42]
3 Length of stay	2	206	Mean Difference (IV, Fixed, 95% CI)	0.05 [-2.65, 2.74]

Comparison 5. Preoperative enteral nutrition compared to no nutrition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Total complications	2	120	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.56, 1.10]
2 Infectious complications	2	120	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.69, 1.44]

Comparison 6. Preoperative parenteral nutrition compared to no nutrition

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Major complications	3	260	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.46, 0.87]
2 Infectious complications	2	226	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.80, 1.10]

Analysis 1.1. Comparison 1 All immune enhancing nutrition trials compared to no nutrition or standard nutrition, Outcome 1 Total complications.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 1 All immune enhancing nutrition trials compared to no nutrition or standard nutrition

Outcome: 1 Total complications

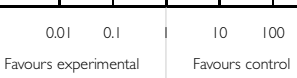
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Braga 2002a (1)	13/50	24/50		20.7 %	0.54 [0.31, 0.94]
Braga 2002b	14/50	21/50		18.1 %	0.67 [0.38, 1.16]
Gianotti 2002	36/102	49/102		42.2 %	0.73 [0.53, 1.02]
McCarter 1998	7/13	2/11		1.9 %	2.96 [0.77, 11.43]
Okamoto 2009	6/30	12/30		10.3 %	0.50 [0.22, 1.16]
Xu 2006	2/30	8/30		6.9 %	0.25 [0.06, 1.08]
Total (95% CI)	**275**	**273**		**100.0 %**	**0.67 [0.53, 0.84]**

Total events: 78 (Experimental), 116 (Control)

Heterogeneity: Chi^2 = 7.73, df = 5 (P = 0.17); I^2 =35%

Test for overall effect: Z = 3.42 (P = 0.00063)

Test for subgroup differences: Not applicable



(1) Data comparing immune enhancing nutrition to no nutrition is used in the first instance.

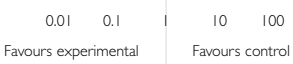
Analysis 1.2. Comparison 1 All immune enhancing nutrition trials compared to no nutrition or standard nutrition, Outcome 2 Infectious complications.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 1 All immune enhancing nutrition trials compared to no nutrition or standard nutrition

Outcome: 2 Infectious complications

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Braga 2002a	6/50	15/50		22.0 %	0.40 [0.17, 0.95]
Braga 2002b	8/50	12/50		17.6 %	0.67 [0.30, 1.49]
Gianotti 2002	14/102	31/102		45.5 %	0.45 [0.26, 0.80]
McCarter 1998	5/13	2/11		3.2 %	2.12 [0.51, 8.84]
Okamoto 2009 (1)	2/30	8/30		11.7 %	0.25 [0.06, 1.08]
Total (95% CI)	**245**	**243**		**100.0 %**	**0.51 [0.35, 0.73]**
Total events: 35 (Experimental), 68 (Control)					
Heterogeneity: Chi^2 = 5.62, df = 4 (P = 0.23); I^2 =29%					
Test for overall effect: Z = 3.59 (P = 0.00033)					
Test for subgroup differences: Not applicable					



(1) Xu- not included as infections given as counts not a dichotomous variable

Analysis 1.3. Comparison 1 All immune enhancing nutrition trials compared to no nutrition or standard nutrition, Outcome 3 length of stay.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 1 All immune enhancing nutrition trials compared to no nutrition or standard nutrition

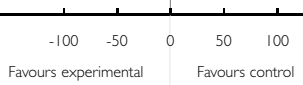
Outcome: 3 length of stay

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Braga 2002a	50	9.5 (2.9)	50	9.8 (3.1)		32.4 %	-0.30 [-1.48, 0.88]
Braga 2002b	50	13.2 (3.5)	50	15.3 (4.1)		20.1 %	-2.10 [-3.59, -0.61]
Gianotti 2002	102	11.6 (4.7)	102	14 (7.7)		14.6 %	-2.40 [-4.15, -0.65]
McCarter 1998	14	15 (2.4)	11	13 (1.7)		17.3 %	2.00 [0.39, 3.61]
Okamoto 2009	30	23.8 (16.6)	30	25 (10.6)		0.9 %	-1.20 [-8.25, 5.85]
Xu 2006	30	9 (3.2)	30	12 (3.7)		14.6 %	-3.00 [-4.75, -1.25]
Total (95% CI)	**276**		**273**			**100.0 %**	**-0.97 [-1.64, -0.30]**

Heterogeneity: Chi^2 = 24.26, df = 5 (P = 0.00019); I^2 =79%

Test for overall effect: Z = 2.85 (P = 0.0044)

Test for subgroup differences: Not applicable



Analysis 2.1. Comparison 2 Preoperative immune enhancing nutrition compared to standard nutrition, Outcome 1 Total complications.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 2 Preoperative immune enhancing nutrition compared to standard nutrition

Outcome: 1 Total complications

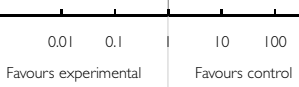
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Braga 2002a	13/50	25/50		36.7 %	0.52 [0.30, 0.90]
Braga 2002b	14/50	21/50		30.8 %	0.67 [0.38, 1.16]
McCarter 1998	7/13	2/11		3.2 %	2.96 [0.77, 11.43]
Okamoto 2009	6/30	12/30		17.6 %	0.50 [0.22, 1.16]
Xu 2006	2/30	8/30		11.7 %	0.25 [0.06, 1.08]
Total (95% CI)	**173**	**171**		**100.0 %**	**0.61 [0.44, 0.84]**

Total events: 42 (Experimental), 68 (Control)

Heterogeneity: Chi^2 = 7.33, df = 4 (P = 0.12); I^2 =45%

Test for overall effect: Z = 3.02 (P = 0.0025)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Preoperative immune enhancing nutrition compared to standard nutrition, Outcome 2 Infectious complications.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 2 Preoperative immune enhancing nutrition compared to standard nutrition

Outcome: 2 Infectious complications

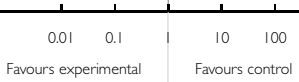
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Braga 2002a	6/50	16/50		41.8 %	0.38 [0.16, 0.88]
Braga 2002b	8/50	12/50		31.4 %	0.67 [0.30, 1.49]
McCarter 1998	4/14	2/11		5.9 %	1.57 [0.35, 7.06]
Okamoto 2009	2/30	8/30		20.9 %	0.25 [0.06, 1.08]
Total (95% CI)	**144**	**141**		**100.0 %**	**0.51 [0.31, 0.84]**

Total events: 20 (Experimental), 38 (Control)

Heterogeneity: Chi^2 = 3.99, df = 3 (P = 0.26); I^2 =25%

Test for overall effect: Z = 2.65 (P = 0.0079)

Test for subgroup differences: Not applicable



Analysis 2.3. Comparison 2 Preoperative immune enhancing nutrition compared to standard nutrition, Outcome 3 Length of stay.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 2 Preoperative immune enhancing nutrition compared to standard nutrition

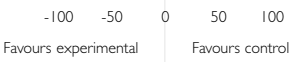
Outcome: 3 Length of stay

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Braga 2002a	50	9.5 (2.9)	50	12 (4.5)		34.7 %	-2.50 [-3.98, -1.02]
Braga 2002b	50	13.2 (3.5)	50	15.3 (4.1)		34.2 %	-2.10 [-3.59, -0.61]
McCarter 1998	14	15 (2.4)	11	13 (1.7)		29.5 %	2.00 [0.39, 3.61]
Okamoto 2009	30	23.8 (16.6)	30	25 (10.6)		1.5 %	-1.20 [-8.25, 5.85]
Total (95% CI)	**144**		**141**			**100.0 %**	**-1.01 [-1.89, -0.14]**

Heterogeneity: Chi^2 = 19.36, df = 3 (P = 0.00023); I^2 =85%

Test for overall effect: Z = 2.28 (P = 0.023)

Test for subgroup differences: Not applicable



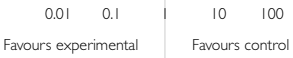
Analysis 3.1. Comparison 3 Preoperative immune enhancing nutrition compared to no nutrition, Outcome 1 Total complications.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 3 Preoperative immune enhancing nutrition compared to no nutrition

Outcome: 1 Total complications

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Braga 2002a	13/50	24/50		32.9 %	0.54 [0.31, 0.94]
Gianotti 2002	36/102	49/102		67.1 %	0.73 [0.53, 1.02]
Total (95% CI)	**152**	**152**		**100.0 %**	**0.67 [0.51, 0.89]**
Total events: 49 (Experimental), 73 (Control)					
Heterogeneity: Chi^2 = 0.87, df = 1 (P = 0.35); I^2 =0.0%					
Test for overall effect: Z = 2.75 (P = 0.0059)					
Test for subgroup differences: Not applicable					



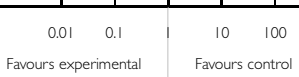
Analysis 3.2. Comparison 3 Preoperative immune enhancing nutrition compared to no nutrition, Outcome 2 Infectious complications.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 3 Preoperative immune enhancing nutrition compared to no nutrition

Outcome: 2 Infectious complications

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Braga 2002a	6/50	15/50		32.6 %	0.40 [0.17, 0.95]
Gianotti 2002	14/102	31/102		67.4 %	0.45 [0.26, 0.80]
Total (95% CI)	**152**	**152**		**100.0 %**	**0.43 [0.27, 0.70]**
Total events: 20 (Experimental), 46 (Control)					
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 3.44 (P = 0.00058)					
Test for subgroup differences: Not applicable					



Analysis 3.3. Comparison 3 Preoperative immune enhancing nutrition compared to no nutrition, Outcome 3 Length of stay.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 3 Preoperative immune enhancing nutrition compared to no nutrition

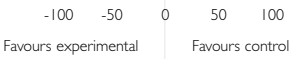
Outcome: 3 Length of stay

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Braga 2002a	50	9.5 (2.9)	50	12.2 (3.9)		62.8 %	-2.70 [-4.05, -1.35]
Gianotti 2002	102	11.6 (4.7)	102	14 (7.7)		37.2 %	-2.40 [-4.15, -0.65]
Total (95% CI)	**152**		**152**			**100.0 %**	**-2.59 [-3.66, -1.52]**

Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%

Test for overall effect: Z = 4.75 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 4.1. Comparison 4 Preoperative standard oral nutrition compared to no nutrition, Outcome 1 Total complications.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 4 Preoperative standard oral nutrition compared to no nutrition

Outcome: 1 Total complications

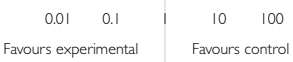
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Burden 2011	33/54	25/62		39.1 %	1.52 [1.05, 2.19]
MacFie 2000	7/24	3/25		4.9 %	2.43 [0.71, 8.32]
Smedley 2004	20/48	34/50		56.0 %	0.61 [0.42, 0.90]
Total (95% CI)	**126**	**137**		**100.0 %**	**1.06 [0.82, 1.36]**

Total events: 60 (Experimental), 62 (Control)

Heterogeneity: Chi^2 = 13.10, df = 2 (P = 0.001); I^2 =85%

Test for overall effect: Z = 0.41 (P = 0.68)

Test for subgroup differences: Not applicable



Analysis 4.2. Comparison 4 Preoperative standard oral nutrition compared to no nutrition, Outcome 2 Infectious complications.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 4 Preoperative standard oral nutrition compared to no nutrition

Outcome: 2 Infectious complications

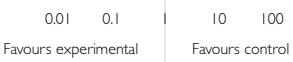
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Burden 2011	33/54	25/62		43.0 %	1.52 [1.05, 2.19]
MacFie 2000	6/24	2/25		3.6 %	3.13 [0.70, 13.99]
Smedley 2004	17/41	30/44		53.4 %	0.61 [0.40, 0.92]
Total (95% CI)	**119**	**131**		**100.0 %**	**1.09 [0.83, 1.42]**

Total events: 56 (Experimental), 57 (Control)

Heterogeneity: Chi^2 = 12.50, df = 2 (P = 0.002); I^2 =84%

Test for overall effect: Z = 0.63 (P = 0.53)

Test for subgroup differences: Not applicable



Analysis 4.3. Comparison 4 Preoperative standard oral nutrition compared to no nutrition, Outcome 3 Length of stay.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 4 Preoperative standard oral nutrition compared to no nutrition

Outcome: 3 Length of stay

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Burden 2011	46	18.02 (10.1)	53	16.39 (10)		46.1 %	1.63 [-2.34, 5.60]
Smedley 2004 (1)	41	12.8 (4.5)	66	14.1 (14.1)		53.9 %	-1.30 [-4.97, 2.37]
Total (95% CI)	**87**		**119**			**100.0 %**	**0.05 [-2.65, 2.74]**

Heterogeneity: Chi² = 1.13, df = 1 (P = 0.29); I² =11%

Test for overall effect: Z = 0.04 (P = 0.97)

Test for subgroup differences: Not applicable

(1) Burden 2011- unpublished data used

Analysis 5.1. Comparison 5 Preoperative enteral nutrition compared to no nutrition, Outcome 1 Total complications.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 5 Preoperative enteral nutrition compared to no nutrition

Outcome: 1 Total complications

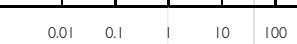
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunerhan 2009	2/11	3/9		9.3 %	0.55 [0.11, 2.59]
Von Meyenfeldt 1992	26/50	32/50		90.7 %	0.81 [0.58, 1.14]
Total (95% CI)	**61**	**59**		**100.0 %**	**0.79 [0.56, 1.10]**

Total events: 28 (Experimental), 35 (Control)

Heterogeneity: Chi² = 0.25, df = 1 (P = 0.62); I² =0.0%

Test for overall effect: Z = 1.40 (P = 0.16)

Test for subgroup differences: Not applicable



Analysis 5.2. Comparison 5 Preoperative enteral nutrition compared to no nutrition, Outcome 2 Infectious complications.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 5 Preoperative enteral nutrition compared to no nutrition

Outcome: 2 Infectious complications

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Gunerhan 2009	7/11	4/9		15.0 %	1.43 [0.61, 3.37]
Von Meyenfeldt 1992	23/50	25/50		85.0 %	0.92 [0.61, 1.38]
Total (95% CI)	**61**	**59**		**100.0 %**	**1.00 [0.69, 1.44]**

Total events: 30 (Experimental), 29 (Control)

Heterogeneity: $Chi^2 = 0.84$, df = 1 (P = 0.36); $I^2 = 0.0\%$

Test for overall effect: Z = 0.02 (P = 0.99)

Test for subgroup differences: Not applicable

Analysis 6.1. Comparison 6 Preoperative parenteral nutrition compared to no nutrition, Outcome 1 Major complications.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 6 Preoperative parenteral nutrition compared to no nutrition

Outcome: 1 Major complications

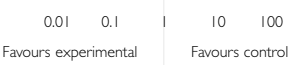
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Muller 1982	11/66	19/59		34.4 %	0.52 [0.27, 1.00]
Smith 1988	3/17	6/17		10.3 %	0.50 [0.15, 1.68]
Von Meyenfeldt 1992	24/51	32/50		55.4 %	0.74 [0.51, 1.05]
Total (95% CI)	**134**	**126**		**100.0 %**	**0.64 [0.46, 0.87]**

Total events: 38 (Experimental), 57 (Control)

Heterogeneity: Chi^2 = 1.16, df = 2 (P = 0.56); I^2 =0.0%

Test for overall effect: Z = 2.82 (P = 0.0048)

Test for subgroup differences: Not applicable

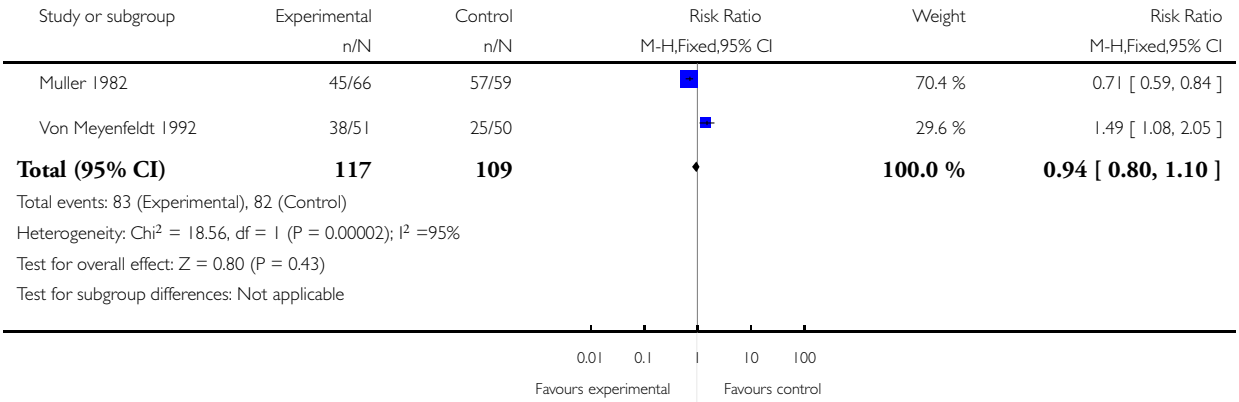


Analysis 6.2. Comparison 6 Preoperative parenteral nutrition compared to no nutrition, Outcome 2 Infectious complications.

Review: Pre-operative Nutrition Support in Patients Undergoing Gastrointestinal Surgery.

Comparison: 6 Preoperative parenteral nutrition compared to no nutrition

Outcome: 2 Infectious complications



ADDITIONAL TABLES

Table 1. Characteristics of the trials included on preoperative feeding

Study & country	Site of surgery	Feed type and volume	Route and duration	undernourished
Muller 1982 Germay	oesophagus stomach colon rectum pancreas	1.5g amino acids/kg 11g glucose/kg	10 days central venous catheter	62% controls 59% active (weight loss >5% in previous 3 months or alb<35d/L)
Smith 1988 Australia	major upper GI colorectal multiple operations	50-60kcals/kg glucose & amino acid 150kcals/1g nitrogen	10 days central venous catheter	all (Prognostic nutritional Index >30%)
Von Meyenfeldt 1992 Netherlands	gastric colorectal	150% basal energy expenditure calculated from Harris & Benedict equation	At least 10 days enteral - nasogastric or oral	all depleted (Nutrition Index)

Table 1. Characteristics of the trials included on preoperative feeding (*Continued*)

Braga 2002a Italy	colorectal	1000mls of IE formula with food ad libitum	5 days oral	12% active 8% control (10% weight loss in previous 6 months)
Braga 2002b Italy	gastric pancreatic colorectal oesophageal	preoperative 1000mls IE nutrition and standard enteral postoperatively	7 days oral preoperatively	weight loss >10% within the previous 6 months
Gianotti 2002 Italy	oesophageal pancreas colorectal	1000mls IE formula	5 days oral	excluded weight losing patients
Gunerhan 2009 Turkey	GI	not reported	7 days	all at risk (subjective global assessment)
McCarther 1998 America	oesophagus stomach pancreas	750mls supplement with added arginine and omega 3 fatty acids	7 days oral	21% active 18% control
Okamoto 2009 Japan	gastric	750mls IE formula	7 days oral	not reported
Xu 2006 China	gastric colorectal	25kcals/kg IE nutrition & oral diet	7 days nasogastric	not reported
Burden 2011 United Kingdom	colorectal	400mls standard supplement between meals 72% managed 400mls 16% managed 200mls	oral	46% at risk using subjective global assessment
Smedley 2004 United Kingdom	lower GI surgery	ad libitum standard supplement in between meals	oral	34% at risk (determined by body mass index & weight loss)
MacFie 2000 United Kingdom	colorectal GI hepatobiliary	minimum of 2 supplements a day & normal diet	oral	17 patients lost >10% weight in previous 6 months

Table 2. Outcomes and postoperative management

Study	complications	mortality	Anthropometry	Biochemisty	Oral nutritional intake	Postoperative management	length of stay
Muller 1982	major infections standardised observation forms used	control-11 active-3 P=<0.05	weight	albumin prealbumin	-	postoperative infusion regimen identical for both groups	not reported
Smith 1988	major minor pre defined classification	control-3 active- 1	weight triceps skin folds	albumin transferrin	-	Received postop nutritional support if surgeon deemed necessary	no significant difference
Von Meyenfeldt 1992	infectious non-infectious defined in manuscript	PN-2 EN-4 control 2	not reported	albumin	not reported	PN continued until oral intake postop Other groups increased amounts of food and fluid as tolerated	postop hospital stay no significant difference. LOS longer preop in treatment groups
Braga 2002a	infective total defined by Bozzotti 2001	active -0 control -1	not reported	not reported	not reported	4 different groups in trial IN preop only, IN periop, standard nutrition periop & control	IN versa no nutrition & IN versa standard P=<0.0005
Braga 2002b	major infections infectious non-infectious defined in manuscript	Group1-2 Group 2-1 Group 3-0	reported at baseline not as an outcome	reported at baseline	not reported	control and preop group given same enteral formula	preop group versa control group P=0.01
Gianotti 2002	infective total defined by Bozzotti	active -1 control -1	weight	not reported	not reported	3 different groups in trial IN preop only, IN periop and control (no nutrition)	preop IN versa control P=0.008

Table 2. Outcomes and postoperative management (*Continued*)

Gunerhan 2009	infectious non infectious	not reported	reported at baseline	CRP prealbumin nitrogen balance	not reported	preop IN preop std nutrition control - no nutrition	no significant difference
McCarther 1998	infectious non infectious complications	group 1 0 group 2 1 group 3 0	not reported	not reported	not reported	1 std supplement 2std plus arginine 3 arginine plus omega 3	no significant difference
Okamoto 2009	infectious non infectious defined in manuscript	not reported	weight loss skin fold thickness arm circumference	prealbumin transferrin	not reported	both groups received postop care	no significant difference
Xu 2006 China	infectious non infectious	not reported	weight between groups	not reported	not reported	both groups fed enterally with a standard formula	significantly shorter P=0.05
Burden 2011	infectious non infectious Buzby 1988 CDC 1993	not reported separately	not reported	not reported	significant difference in energy intake between control and intervention but not for protein	sip feeds given up until surgery	no significant difference
Smedley 2004	minor major Buzby 1988	not reported separately	no significant differences between groups	not reported	sip feeds preop compared to control significant difference 2528 kcals/ 606	4 groups in trial sip feeds preop compared with control	no significant difference
MacFie 2000	total complications septic complications	preop sip feeds 1 control 1	body weight mid arm circumference grip strength no significant difference in groups	albumin	mean 507 kcals in preop period from supplements no significant difference in Kcal intake	4 groups only compared data in preop group and control	no significant difference

Table 3. Adverse effects or complications of feed or route of delivery

Study	GI	Metabolic	Route
Muller 1982	nil	7 instances of elevated liver function tests	4 CVC related
Smith 1988	nil	nil	2 febrile episodes
Von Meyenfeldt 1992	3 in enteral group diarrhoea 3 vomiting 2 gastric retention	nil	1 arterial puncture 1 pneumothorax 4 catheter related sepsis
Braga 2002a	18 abdominal cramping or bloating 9 diarrhoea 3 postoperative vomiting	nil	nasojejunal tube blocked in 5 patients
Braga 2002b	29 cramping and distention 13 diarrhoea 4 vomiting	nil	nil
Gianotti 2002	cramping and distention diarrhoea vomiting	not reported	
Gunerhan 2009	not reported	not reported	not reported
McCarther 1998	cramping bloating distention gas	nil	nil
Okamoto 2009	not reported	not reported	not reported
Xu 2006 China	not reported	not reported	not reported
Burden 2011	4 nausea & vomiting 2 diarrhoea	nil	not appropriate
Smedley 2004	not reported	nil	not appropriate
MacFie 2000	nil in preop group	nil	not appropriate

APPENDICES

Appendix 1. Search strategy

1. exp Preoperative Period/ or exp Preoperative Care/ or preoperative.mp.
2. exp Perioperative Nursing/ or exp Perioperative Care/ or perioperative.mp.
3. 1 or 2
4. exp Food, Formulated/ or exp Nutritional Status/ or exp Dietary Supplements/ or exp Malnutrition/ or exp Enteral Nutrition/ or sip feeds.mp. or exp Nutritional Requirements/
5. Oral supplements.mp.
6. parenteral nutrition.mp. or exp Parenteral Nutrition/
7. exp Parenteral Nutrition/ or exp Enteral Nutrition/ or enteral.mp.
8. jejunostomy.mp. or exp Jejunostomy/
9. exp Enteral Nutrition/ or nasogastric.mp.
10. gastrostomy.mp. or exp Gastrostomy/
11. 4 or 5 or 6 or 7 or 8 or 9 or 10
12. exp Glutamine/ or exp Food, Formulated/ or exp Arginine/ or exp Fatty Acids, Omega-3/ or immunonutrition.mp.
13. Novel substrates.mp.
14. exp Carbohydrates/ or carbohydrate.mp.
15. glucose.mp. or exp Glucose/
16. protein.mp. or exp Proteins/
17. Amino acids.mp. or exp Amino Acids/
18. 12 or 13 or 14 or 15 or 16 or 17
19. exp Esophagectomy/ or gastrointestinal surgery.mp. or exp Gastrectomy/
20. colorectal surgery.mp. or Colorectal Surgery/
21. exp Gastrectomy/ or gastric cancer surgery.mp.
22. exp Esophagectomy/ or oesophageal cancer surgery.mp.
23. pancreatic cancer surgery.mp. or exp Digestive System Surgical Procedures/ or exp Pancreatectomy/ or exp Pancreaticoduodenectomy/
24. 19 or 20 or 21 or 22 or 23
25. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 12 or 13 or 14 or 15 or 16 or 17
26. 3 and 11 and 18 and 24

HISTORY

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CONTRIBUTIONS OF AUTHORS

SB - Written proposal, CT, JH & SL commented on proposal, CT - Assisted with search strategy.

DECLARATIONS OF INTEREST

None to declare

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Internal sources

- No sources of support supplied

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The data derived from the included trials did not allow any sensitivity analyses or sub group analyses.

INDEX TERMS

Medical Subject Headings (MeSH)

*Digestive System Surgical Procedures; Enteral Nutrition [*methods]; Length of Stay; Malnutrition [*therapy]; Parenteral Nutrition [*methods]; Postoperative Complications [*prevention & control]; Preoperative Care [*methods]; Randomized Controlled Trials as Topic

MeSH check words

Humans