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Review

The effects of enteral immunonutrition in upper gastrointestinal surgery: A systematic review and meta-analysis☆

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HIGHLIGHTS

- Perioperative nutritional support is one the important components of enhanced recovery after Surgery (ERAS).
- There is a continued debate as to the effectiveness of immunonutrition in surgical practice.
- In view of inconclusive evidence in this topic, we undertook a comprehensive literature review and analysis to evaluate the effectiveness of immunonutrition in upper gastrointestinal surgery.

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ABSTRACT

Aim: The beneficial of immunonutrition on overall morbidity and mortality remains uncertain. We undertook a systematic review to evaluate the effects of immune-enhancing enteral nutrition (IEN) in upper gastrointestinal (GI) surgery.

Methods: Main electronic databases [MEDLINE via Pubmed, EMBASE, Scopus, Web of Knowledge, Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Library, and clinical trial registry (ClinicalTrial.gov)] were searched for studies reported clinical outcomes comparing standard enteral nutrition (SEN) and immunonutrition (IEN). The systematic review was conducted in accordance with the PRISMA guidelines and meta-analysis was analysed using fixed and random-effects models.

Results: Nineteen RCTs with a total of 2016 patients (1017 IEN and 999 SEN) were included in the final pooled analysis. The ratio of patients underwent oesophagectomy:gastrectomy:pancreatectomy was 2.2:1.2:1.0. IEN, when administered post-operatively, was associated with a significantly lower risk of wound infection (risk ratio (RR) 0.59, 95% confidence interval (CI) 0.40 to 0.88; $p = 0.009$) and shorter length of hospital stay (MD −2.92 days, 95% CI −3.89 to −1.95; $p < 0.00001$). No significant differences in other post-operative morbidities of interest (e.g. anastomotic leak and pulmonary infection) and mortality between the two groups were identified.

Conclusions: Overall, our analysis found that IEN decreases wound infection rates and reduces length of stay. It should be recommended as routine nutritional support as part of the Enhanced Recovery after Surgery (ERAS) programmes for upper GI Surgery.

1. Introduction

Nutritional depletion increases overall morbidity and mortality especially in patients undergoing gastrointestinal (GI) surgery. Malnutrition is not uncommon among these patients and may be due to decreased intake, impaired digestion and absorption of nutrients and increased catabolic states and nutritional requirements. Perioperative nutritional support and optimization reduce malnutrition-associated complications such as wound infection and anastomotic dehiscence and enhance recovery.

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Many studies have been conducted to evaluate the effectiveness of nutrition support in pancreatitis, burns and trauma, and critically ill and septic patients, yield varying results. The evidence of overall improvement with nutritional supplementation in patients undergoing radical curative surgery in upper GI is still lacking. At present, National Institute for Health and Care Excellence (NICE) guideline (*CG32*) has recommended that surgical patients who are malnourished and due to undergo major abdominal surgery should be considered for enteral tube feeding unless contraindicated [1].

Nutritional support can be given orally as well as enterally and parentally. Although enteral feeding following major upper GI surgery is recommended over total parenteral nutrition (TPN) [2], it should not be routinely administered because complications related to enteral tube feeding are common [3]. Parenteral nutrition should be considered when other routes of administration are impractical or not feasible. Scottish Intercollegiate Guidelines Network (SIGN) guideline (*SIGN 77*) recommends that nutritional support should be given based on each patient's nutritional risk and surgical pathology [4]. The Nutritional Risk Score (NRS) endorsed by the European Society for Parenteral and Enteral Nutrition (ESPEN) [5] is commonly being used to predict clinical outcomes and nutritional risk [6].

In more recent times, the use of immunonutrition containing immune-enhancing nutrients such as glutamine, ω-3 fatty acid, arginine and nucleotides to modulate metabolism and immune responses in surgical patients has been proposed. Some studies show positive effects of these therapies and overall reduction in post-operative complications, but not all studies have demonstrated similar clinical benefits [7].

One of the earliest studies, conducted by Daly et al. [8], examines the effect of immunonutrition in adult patients undergo upper GI surgery suggests that IEN significantly reduce infectious complications and length of stay compared to standard enteral feedings. However, subsequently, outcome data from several published prospective, randomised studies have contradictive results. Inconsistency of these results is not clear, but could be attributed to several confounding factors and heterogeneity in patient's demographic, clinical, nutritional or metabolic status of the patient.

The benefits of immunonutrition have been addressed in recent meta-analyses, all of which have concluded that enteral immunonutrition reduces perioperative complications and shortens hospital stay compared to standard enteral nutrition, but does not affect mortality [9,10]. Although these data would seem compelling, however, the population involved was a mixture of patients undergoing upper and lower gastrointestinal surgery for cancer. Based on the previous literature review, it seems logical that reduction in infectious complication would have an indirect effect on duration of hospitalisation. The mechanisms by which enteral nutrition decreases infectious complications are unknown. However, preservation of gut immune function and reduction of inflammation have been proposed [11,12].

To date, study designs of most published systematic reviews and meta-analyses [9,10,13,14] examining the effects of immunonutrition in GI surgery are heterogeneous (i.e. mixture of study population between upper GI and lower GI surgery, inclusion of parenteral nutrition, and nutritional status). A recent review published by Mabvuure et al. [15], comparing enteral immunonutrition versus standard enteral nutrition for patients undergoing oesophagogastric resection for cancer, suggested that there is not enough evidence to recommend routine immunonutrition in all patients undergoing oesophageal or gastric resection for cancer. This study was not a systematic review and meta-analysis.

Controversy remains as to whether or not enteral immunonutrition (IEN) supplementation of selective amino acids and/or fatty acids confers any additional clinical benefit and could improve outcomes of these patients post-operatively as compared to standard enteral nutrition (SEN).

The aim of this systematic review and meta-analysis is to determine and evaluate the effects of enteral immunonutrition in patients undergoing upper GI surgery, to provide recommendations based on a higher level of evidence and to update our current knowledge on this topic.

2. Material and methods

2.1. Search strategy

The systematic review and meta-analysis was performed in accordance with the PRISMA guidelines [16]. This review was registered with the International Prospective Register of Systematic Review (**PROSPERO**) (Registration No. **CRD42014010458**). Main electronic databases MEDLINE via PubMed (1966 to current), EMBASE (via OVID) (1980 to current), Scopus (1995 to current), Web of Science (ISI Web of Knowledge) (1900 to current), Cochrane Central Register of Controlled Trials (CENTRAL) and the Cochrane Library, and clinical trial registries (ClinicalTrial.gov and WHO International Clinical Trials Registry Platform (ICTRP)) were searched for studies reporting outcomes of immunonutrition in upper GI surgery using following search terms or key words. Key words – *'immunonutrition'; 'enteral'; 'gastrointestinal surgery'; 'glutamine'; 'omega-3'; 'fish oil'; 'fatty acid'; 'gastrectomy'; 'oesophagectomy'; 'pancreatectomy'; 'nutrition'; 'complication'*.

These terms were searched using Boolean operators (AND and OR) and appropriate Medical Subject Headings (MeSH) terms were combined in the search builder. A truncation symbol (e.g. adding superscript asterisk * at the end of a word) was used wherever appropriate. Searches were not restricted by publication year, publication status or language. Relevant conference abstracts and proceedings presented at the American Surgical Association, Association of Surgeons of Great Britain and Ireland, Annual Conference of American College of Surgeons were hand-searched. A manual search was also conducted for reference lists in the included studies.

2.2. Study selection and data extraction

Eligible studies were included provided they met the following inclusion criteria:

(1) Randomised controlled trial (RCT);
(2) Patient undergoing upper GI surgery
(3) With reported outcomes comparing enteral immunonutrition (exclude parenteral) and standard nutritional supplementation

We excluded following studies: non-RCT (case series, case-control study, and cohort study), narrative or expert reviews, and animal studies or trials. Article reference lists were scrutinised for relevant articles independently by two authors (CSW and EHA). Study design and level of evidence of all identified studies were categorised according to the Oxford Centre for Evidence-Based Medicine (CEBM) levels of evidence [17].

2.3. Quality assessment

The Jadad scale was used to evaluate the methodological quality of the published randomised control trial [18]. Three main items were scored (randomisation, double blinding, and withdrawals and dropouts). Scores range from 0 (poorest) to 5 (best). Bias risk was evaluated as per Cochrane methodology [19]. Briefly, Cochrane