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Meta-analyses

Efficacy of arginine-enriched enteral formulas in the reduction of surgical complications in head and neck cancer: A systematic review and meta-analysis☆

Alfonso Vidal-Casariego*, Alicia Calleja-Fernández, Rocío Villar-Taibo, Georgios Kyriakos, María D. Ballesteros-Pomar

Clinical Nutrition and Dietetics Unit, Department of Endocrinology and Nutrition, Complejo Asistencial Universitario de León, Altos de Nava SN, 24008 León, Spain

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SUMMARY

Introduction: Arginine improves healing and modulates inflammation and the immune response. A systematic review and meta-analysis were conducted to assess whether arginine-enriched enteral formulas reduce complications (fistulas, wound infections, other infections) and hospital length of stay (LoS) in patients undergoing surgery for head and neck cancer.

Methods: Medline, CENTRAL, and Trip Database were searched using the search strategy "Head and Neck Neoplasms" AND "Enteral Nutrition" AND "Arginine" OR "Immunonutrition". Inclusion criteria comprised: type of study (RCT), language (English, Spanish), outcomes (complications of surgery, LoS), and methodological quality (Jadad scale). The odds ratio (OR) and confidence intervals (95% CI) were calculated using the Mantel–Haenszel method, and the mean difference (MD) with the random effects method. Heterogeneity was assessed using Cochran's *Q*.

Results: Six studies were included, with 397 patients receiving peri/postoperative enteral nutrition with different doses of arginine (6.25–18.7 g/L). Enteral formulas containing arginine were associated with a reduction in fistulas [OR = 0.36 (95% CI 0.14–0.95), $p = 0.039$; $Q = 3.93$, $p = 0.269$], and LoS [MD = −6.8 (95% CI −12.6 to −0.9) days, $p = 0.023$; $Q = 2.44$, $p = 0.486$]. There were no reductions in wound infections [OR = 1.04 (95% CI 0.49–2.17), $p = 0.925$; $Q = 1.60$, $p = 0.809$] or other infections [OR = 0.79 (95% CI 0.48–1.31); $p = 0.369$; $Q = 7.94$, $p = 0.094$]. Arginine administration did not increase the occurrence of diarrhoea [OR = 1.80 (95% CI 0.50–6.52), $p = 0.375$; $Q = 0.16$, $p = 0.691$].

Conclusions: The administration of arginine-enriched enteral nutrition led to a significant reduction in fistulas and hospital stay in patients undergoing surgery for head and neck cancer.

1. Introduction

Beyond their purely nutritious function, some nutrients have been associated with pharmacologic-like effects. These immunonutrients comprise a wide range of molecules including fats (e.g. n-3 fatty acids), amino acids (e.g. arginine, glutamine), vitamins (e.g. vitamin E), and other substances (e.g. nucleotides, antioxidants), which can be administered either by the enteral or parenteral route. Arginine is a conditionally essential amino acid that serves as a substrate for the synthesis of nitric oxide, promotes collagen formation, stimulates growth hormone production, and regulates immune function by means of its action on T-lymphocytes [1]. These characteristics suggest that arginine could enhance wound healing and reduce infection, especially in situations that compromise immune function, such as surgery or critical illness.

Arginine-enriched enteral nutrition has been widely tested in the perioperative period. Three meta-analyses have assessed the efficacy of immunomodulating nutrition in trials that included patients with gastrointestinal cancer. They consistently found a beneficial effect on the postoperative infection rate and length of stay [2–4], Most of the included studies used enteral formulas that contained several immunonutrients (e.g. n-3 fatty acids,

Non-standard abbreviations: LOS, length of stay; RCT, randomized controlled trial; OR, Odds ratio; MD, mean difference; RD, risk difference.

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* Corresponding author. Tel.: +34 987237400x43044; fax: +34 987240503.
E-mail addresses: avcyo@hotmail.com, avcyo@mixmail.com (A. Vidal-Casariego).

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nucleotides, arginine, glutamine), and therefore it is difficult to determine which single nutrient or mixture was responsible of the improvement of outcomes [5].

Malnutrition can be found in more than 50% of patients with head and neck cancer, and has a multifactorial aetiology that includes mechanical difficulties for oral intake, the tumour-induced inflammatory response, poor dietary habits, and the adverse effects of surgery, chemotherapy and radiotherapy [6]. A poor nutritional status has been associated with the occurrence of major postoperative complications and shorter survival [7,8]. Some studies have demonstrated that perioperative arginine-based immunonutrition diets may modulate the inflammatory response and immunologic status after surgery in head and neck cancer patients, but undoubtedly the main purpose of this kind of nutritional intervention is the prevention of surgical complications [9–11]. A previous meta-analysis of ten studies found a significant reduction of 3.5 days in hospital stay associated with the administration of immunonutrition, but not an improvement in postoperative fistulas [12]. Since the publication of this meta-analysis, new trials have been released.

A systematic review and meta-analysis were performed to test the current evidence about the effects of arginine-enriched enteral formulas in the surgical outcomes of head and neck cancer patients.

2. Methods

The systematic review and meta-analysis were conducted following the principles of the PRISMA declaration [13].

2.1. Search strategy

A bibliographic search was performed in Medline (PubMed), Trip Database, and Central (Cochrane Library) databases, using the following terms: “Head and Neck Neoplasms”, “Head and Neck Cancer”, “Enteral Nutrition”, “Tube Feeding”, “Arginine”, and “Immunonutrition”, in combination with the Boolean operators “AND”, “OR”.

2.2. Inclusion criteria

The eligibility criteria for including studies in the review were the type of assay (randomized, double-blinded, controlled studies), patients (head and neck cancer treated with surgery), species (humans), and language (English, Spanish).

2.3. Exclusion criteria

Non-randomized studies, trials that compared two enteral formulas with immunonutrients, trials that used immunonutrition not based on arginine, studies in which study outcomes were not measured (e.g. studies measuring inflammatory response to surgery) or studies that did not fulfil the inclusion criteria were excluded.

2.4. Type of intervention

Arginine-based immunonutrition compared with an isocaloric and isonitrogenous enteral formula, administered either preoperative and postoperatively (pre&post) or only postoperatively.

2.5. Outcomes

The primary outcome was the effect of arginine-enriched enteral formulas on the development of postoperative complications (fistulas, surgical site infections, other infections). Secondary outcomes included the effects of these formulas on hospital length of stay (LoS), mortality, and enteral nutrition-related adverse effects (e.g. diarrhoea).

2.6. Data collection

Data were collected from the selected trials by the authors (ACF, RVT, GK, MDBP) in an independent manner, using a common structured form for this purpose. Collected data included age of participants, sample size, timing of start of intervention (preoperative or postoperative), duration of intervention, formula of enteral nutrition, dose of arginine, study outcomes, and adverse effects. Outcome measures were recorded as mentioned in the publication, either as an intention-to-treat analysis or per protocol.

2.7. Assessment of quality and risk of bias

Each identified study was independently evaluated for inclusion by two reviewers (ACF, RVT, GK, MDBP), who were blinded to the authors, institutions and journal during the selection process. When several papers related to the same study were found, the publication with higher methodological quality was selected. Any disagreement between reviewers was resolved by consensus discussions with the other members of the team.

The identified randomized, controlled trials were considered suitable for revision if they matched the initial inclusion criteria. The adequacy of the selected articles was measured using the Jadad scale, which considers whether the study was randomized (and the method of randomization), blinded (and the method of blindness), and the description of patient losses and drop-outs. A minimum score of three points was necessary for inclusion in this review [14].

2.8. Statistical analysis

The mean and standard deviation of each quantitative variable, and the frequency of the measured qualitative outcomes, were obtained. A meta-analysis was conducted after the aggregation of data using the inverse variance-fixed effect model, which accurately calculates global results when heterogeneity is assumed not to be present. The mean differences (MD) were calculated for quantitative variables and the odds ratio (OR) for qualitative outcomes, with their confidence intervals of 95% (CI 95%). Continuity correction was applied for the calculation of OR when no event for the analysed outcome was found in one of the groups. As an alternative, risk difference (RD) with its confidence interval of 95% was obtained when OR could not be calculated. Heterogeneity, which represents the differences among studies that may prevent the aggregation of results, was evaluated using the Q test. Heterogeneity was considered to be present when $p < 0.05$, and significant differences between interventions were considered when CI 95% did not include the value 0 (for MD) or 1 (for OR). The presence of publication bias was evaluated using the Egger test.

3. Results

3.1. Eligible studies

After the selection process six studies, with a total of 397 patients, were included in the review (Fig. 1) [15–20]. The characteristics of these studies are summarized in Table 1. The immunonutrition group included 210 patients (range 17–82), and the control group 187 patients (range 20–47). Randomization was performed using computerized systems [16,19], randomization

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