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Original article

Glutamine dipeptide-supplemented parenteral nutrition improves the clinical outcomes of critically ill patients: A systematic evaluation of randomised controlled trials

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SUMMARY

Background & aims: Early randomised controlled trials (RCTs) testing whether parenteral nutrition regimens that include glutamine dipeptides improves the outcomes of critically ill patients demonstrated convincingly that this regimen associates with reduced mortality, infections, and hospital stays. However, several new RCTs on the same question challenged this. To resolve this controversy, the present meta-analysis was performed. Stringent eligibility criteria were used to select only those RCTs that tested the outcomes of critically ill adult patients without hepatic and/or renal failure who were haemodynamically and metabolically stabilised and who were administered glutamine dipeptide strictly according to current clinical guidelines (*via* the parenteral route at 0.3–0.5 g/kg/day; max. 30% of the prescribed nitrogen supply) in combination with adequate nutrition.

Methods: The literature research (PubMed, Embase, Cochrane Central Register of Controlled Trials) searched for English and German articles that had been published in peer-review journals (last entry March 31, 2015) and reported the results of RCTs in critically ill adult patients (major surgery, trauma, infection, or organ failure) who received parenteral glutamine dipeptide as part of an isoenergetic and isonitrogenous nutrition therapy. The following data were extracted: infectious complications, lengths of stay (LOS) in the hospital and intensive care unit (ICU), duration of mechanical ventilation, days on inotropic support, and ICU and hospital mortality rates. The selection of and data extraction from studies were performed by two independent reviewers.

Results: Fifteen RCTs (16 publications) fulfilled all selection criteria. They involved 842 critically ill patients. None had renal and/or hepatic failure. The average study quality (*Jadad* score: 3.8 points) was well above the predefined cut-off of 3.0. Common effect estimates indicated that parenteral glutamine dipeptide supplementation significantly reduced infectious complications (relative risk [RR] = 0.70, 95% CI 0.60, 0.83, $p < 0.0001$), ICU LOS (common mean difference [MD] −1.61 days, 95% CI −3.17, −0.05, $p = 0.04$), hospital LOS (MD −2.30 days, 95% CI −4.14, −0.45, $p = 0.01$), and mechanical ventilation duration (MD −1.56 days, 95% CI −2.88, −0.24, $p = 0.02$). It also lowered the hospital mortality rate by 45% (RR = 0.55, 95% CI 0.32, 0.94, $p = 0.03$) but had no effect on ICU mortality. Visual inspection of funnel plots did not reveal any potential selective reporting of studies.

Conclusions: This meta-analysis clearly confirms that when critically ill patients are supplemented with parenteral glutamine dipeptide according to clinical guidelines as part of a balanced nutrition regimen, it significantly reduces hospital mortality, infectious complication rates, and hospital LOS. The latter two

Abbreviations: Ala, alanine; APACHE, acute physiology and chronic health evaluation; CI, confidence interval; df, degree of freedom; Gln, glutamine; Gly, glycine; LOS, length of stay; MD, common mean difference; N, nitrogen; PN, parenteral nutrition; PRISMA, *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalysis; RCT, randomised controlled trial; RR, risk ratio; RRT, renal replacement therapy; SAPS, simplified acute physiology score; SOI, severity of illness; TPN, total parenteral nutrition.

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effects indicate that glutamine dipeptide supplementation also confers economic benefits in this setting. The present analysis indicates the importance of delivering glutamine dipeptides together with adequate parenteral energy and nitrogen so that the administered glutamine serves as precursor in various biosynthetic pathways rather than simply as a fuel.

1. Introduction

Apart from its role as building block for the endogenous protein synthesis, the amino acid glutamine (Gln) is the transporter nitrogen between organs, regulates amino acid metabolism, serves as metabolic fuel for rapidly proliferating cells, and is a precursor of bioactive metabolites [1–4]. Since Gln can be endogenously synthesized *de novo* and released by protein hydrolysis, it is classified as a dispensable nutrient for healthy humans. However, in severe disease states (*e.g.*, trauma, abdominal major surgery, and burns), the stress-mediated hormonal changes that develop alter Gln metabolism in the whole body [5–9]: as a result, various organs (*e.g.*, gut, liver, and kidneys) and cells (*e.g.*, enterocytes and immunocompetent cells) need more Gln for the necessary synthesis of acute-phase proteins and radical-scavenging metabolites such as glutathione. Since the endogenous capacity of the body to release Gln generally cannot adapt to meet these increased needs, the metabolically stressed body becomes depleted of Gln, as indicated by marked decreases of intracellular Gln in the muscle tissue and, to a lower extent, in plasma [10]. This depletion in turn associates with metabolic impairment such as insufficient protein synthesis; most importantly, it worsens the clinical outcomes of severely ill patients [9–13]. Consequently, Gln is considered to be an indispensable substrate in the hypermetabolic situations that characterize critical illness [4,11–13]. Because of galenic reasons, however, the so-called "standard" amino acid solutions for parenteral nutrition (PN) therapy are free of Gln. Consequently, a total PN regimen administrating even high doses of such a standard amino acid preparation (>1.5 g/kg BW/d) cannot prevent Gln depletion [13].

Beginning in the 1980s, randomised controlled trials (RCTs) were performed to evaluate whether parenteral supplementation with nutritive amounts of a Gln source (about 10–12 g/day) would prevent or reduce the Gln depletion in various PN-requiring patient groups and improve their outcomes. These RCTs were mainly single centre trials and the supplemented Gln source was either free Gln (bed-side preparation due to its limited chemical stability) or stable Gln dipeptides in ready-to-use solutions [14–16]. Consistent with the working hypotheses of these early RCTs, Gln supplementation ameliorated the disease-specific Gln depletion compared to standard treatment. This in turn improved various functions (*e.g.*, maintenance of gut barrier function and gut-associated lymphoid tissue) and strengthened the biochemical pathways needed to fight the disease-associated metabolic stress (*e.g.*, the cellular synthesis of short-life proteins). Most importantly, it reduced mortality and morbidity rates and the length of hospital stay (LOS) [17–19]. These RCTs led to changes in international guidelines, which then started to recommend that parenteral delivery of Gln dipeptides should be part of the nutritional care in critical illness [20,21].

Within the last decade, several single and multi-centre RCTs that tested the usefulness of Gln-supplemented PN in various patient groups and following various designs have been performed. Recently, three meta-analyses have been initiated with obviously lacking consistency and only partly supporting the earlier recommendation for Gln use in critically ill patients [22–24]. These discrepancies may reflect some weaknesses in the meta-analysis criteria that determined study inclusion. Most importantly, these meta-analyses included the RCTs that used free Gln. This is problematic because most of these studies did not indicate the "true" Gln content in the solutions before administration. Moreover, free Gln and Gln dipeptides may differ in terms of their kinetics, which in turn may influence the degree of Gln uptake by the target sites. Thus, studies that used free Gln may not be equivalent to those that employed Gln dipeptide; meta-analyses should consider these RCTs separately. In addition, two of the three recent meta-analyses, namely, those by Bollhalder et al. [23] and Tao [24], included both critically ill and post-surgery patients in their cohorts. However, these patient groups vary markedly in terms of clinical outcomes, especially mortality and morbidity rates, and thus may not be directly comparable. This suggests that RCTs that employed mixtures of these patient groups to evaluate the effect of Gln supplementation on these outcome variables may suffer from bias.

These shortcomings encouraged us to perform the present meta-analysis which focused specifically and stringently on only those RCTs that examined the outcomes of critically ill adult patients without hepatic and/or renal failure who were haemodynamically and metabolically stabilised and who were administered glutamine dipeptide strictly according to current clinical guidelines (*i.e.*, *via* the parenteral route at 0.3–0.5 g/kg/day; max. 30% of the prescribed nitrogen supply) in combination with adequate nutrition. The control group received isoenergetic and isonitrogenous supplements without Gln dipeptide supplementation.

2. Methods

This meta-analysis was performed and reported according to the PRISMA (*P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalysis) guideline [25].

2.1. Identification of potentially eligible studies

The systematic literature search (PubMed, Embase, and the Cochrane Central Register of Controlled Trials) sought to identify all eligible English and German articles that had ever been published in peer-review journals (last entry March 31, 2015). The following search terms were used. At least one of the terms in each of the following four lists had to be present in the title and/or abstract of the article: (1) 'randomized', 'randomised', 'clinical trial', 'clinical study', (2) 'critical ill', 'critically ill', 'critical illness', 'critical care', 'intensive care', 'intensive care units', 'surgery', 'traumatic injury', 'infection', 'organ failure', 'trauma', 'ICU', (3) 'nutrition', 'nutritional support', 'supplementation', 'parenteral nutrition', 'parenteral nutrition solution', 'supplemental parenteral', 'total parenteral', 'parenteral', 'intravenous', 'i.v.', 'iv', (4) 'glutamine/glutamin', 'GLN', 'GLN dipeptide', 'glutamine dipeptide/glutamin-dipeptid', 'alanyl-glutamine', 'Ala-Gln', 'glycyl-glutamine', 'Gly-Gln'. In addition, the reference lists of 33 review articles identified during the literature search were checked to ensure complete identification of eligible articles.

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