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Review article

Antioxidants as a treatment for acute pancreatitis: A meta-analysis

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ABSTRACT

Objective: To assess the efficacy of antioxidants in acute (AP) pancreatitis.
Methods: We searched PubMed, Embase and the Cochrane library for all randomized controlled trials (RCT) involving administration of antioxidants in the therapy of AP until February 2012. AP studies were pooled to analyze the effect of antioxidants on hospital stay, mortality, and complications. Subgroup analyses were performed on the use of the antioxidant glutamine.
Results: In total, eleven RCTs were included. Among patients with AP, antioxidant therapy resulted in a borderline significant reduction in hospital stay (mean difference −1.74; 95%CI −3.56 to 0.08), a significant decrease in complications (RR 0.66; 95%CI 0.46–0.95) and a non-significant decrease in mortality rate (RR 0.66; 95%CI 0.30–1.46). Subgroup analyses showed that glutamine significantly reduced complications (RR 0.51; 95%CI 0.34–0.78) and mortality rate (RR 0.33; 95%CI 0.13–0.85).
Conclusion: The present meta-analysis shows a possible benefit of glutamine supplementation in patients with acute pancreatitis. However, large randomized trials are needed to confirm these observations.

Introduction

Acute pancreatitis (AP) is an acute inflammatory condition of the pancreas, characterized by abdominal pain and elevated levels of amylase and lipase and is in the Western world most commonly caused by gallstones. The incidence of AP has been reported to range from 4.9 to 35 per 100,000 persons and the mortality rate is approximately 10 percent, with even higher rates among patients with severe AP [1]. The current treatment protocol includes nil per mouth, intravenous fluids, pain management and correction of electrolyte and metabolic abnormalities [2].

Previous studies have indicated that AP is associated with oxidative stress, seemingly independent of the etiology of the pancreatitis [3–6]. A number of experimental studies in animal models of AP have shown that antioxidant compounds are depleted and lipid peroxidation is increased [7] and have suggested a beneficial effect of antioxidant treatment of AP [8–10]. These findings suggest that administering antioxidants in addition to conventional therapy of AP may counteract the inflammatory processes in the pancreas, thereby improving recovery. However, human clinical trials performed so far have remained inconclusive about the positive effects of antioxidants in the treatment of AP [5].

An antioxidant of particular interest is glutamine, which is synthesized in various cells including skeletal, muscle, lungs and brain, and is the most abundant nonessential amino acid in the plasma and intracellular amino-acid pool [11]. It is known to exert a positive effect on immune function in a variety of disorders [12]. It attenuates the pro-inflammatory cytokine release and is considered to be essential for the growth and function of immune cells [5,13]. In animal models of acute pancreatitis, glutamine has been proven to stabilize intestinal barriers and reduce pancreatic infection [14,15]. Human clinical trials have found that in some conditions, such as severe AP, sepsis or major surgery, glutamine depletion occurs, possibly because of inadequate endogenous glutamine production [16]. In addition, they showed that depleted glutamine is an independent predictive factor for a poor outcome in critical illness. Moreover, they showed that correction of glutamine levels improved survival and shortened duration of enteroparalysis resulting in reducing the duration of vital-organ dysfunction [17], a reduction of the rate of infectious complications [18,19] and a shorter length of hospital stay [19]. The greatest benefit was found in surgical patients being treated with high dose glutamine [20].

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Presumably, this enhancing effect of glutamine and other antioxidants can be used to optimize the current conservative treatment strategy. Several clinical trials have been performed to investigate the effect of antioxidants in pancreatitis. However, as most of these studies included small populations and investigated different types of antioxidants, a clear picture on the efficacy of antioxidants in AP is currently lacking.

We therefore aimed to perform a meta-analysis on the efficacy of antioxidants as complementary therapy in AP, focusing on their effect on hospital stay, complication and mortality rate.

Materials and methods

Search method

We searched PubMed, Embase and the Cochrane library for all relevant studies investigating antioxidant treatment of AP, until February 2014. Search terms included pancreatitis or pancreatic inflammation combined with all substance names for pharmacologically active antioxidants plus all MeSH terms for frequently applied antioxidants (see appendix for the full search). In addition, the reference lists of relevant articles were scanned for additional trials. Clinicaltrials.gov was searched for ongoing trials.

Inclusion criteria

We included all randomized controlled trials evaluating antioxidants and scrutinized for (1) patients with AP, (2) use of antioxidant supplements compared with placebo or no treatment, and (3) studies written in the English and Dutch language only. Animal studies were excluded. In addition, if more than one paper of a trial was found, we included the paper with most complete data. The selection of eligible studies was performed by two independent reviewers (SMJ, MN and/or HABP) who independently evaluated all studies. Discrepancies were resolved by discussion until a consensus was reached.

Data extraction and management

Data collection was conducted independently using data extraction forms developed by the Cochrane Library. If information was not available in the published trial, we contacted authors of the publication in order to obtain missing data. From each trial, the following information was extracted: first author, year of publication, trial design, number of patients randomized, patient characteristics (age, gender), severity of pancreatitis, etiology of pancreatitis, type of intervention used (type and dose of antioxidant, duration of intervention, route of admission), type of control group, and outcome (duration of hospital stay, mortality rate and systemic complication rate).

Quality of included studies

We used the Jadad score to evaluate the quality of included trials which is a validated method to assess trials based on appropriate randomization, blinding and description of study withdrawals or dropouts [21]. In addition, we evaluated whether baseline characteristics between studies were comparable.

Statistical analysis

We performed a meta-analysis on outcome parameters that were available in at least 3 studies. These included hospital stay, mortality and complications in AP patients. Data on hospital stay, mortality and complications were pooled. Dichotomous data were expressed as risk ratios (RR) with 95% confidence intervals (CI). Continuous scales were expressed as mean difference (MD) with 95% CI. The I^2 test was used to test for heterogeneity. Subgroup analyses were performed for the antioxidant glutamine only, administration route and severity of pancreatitis. Funnel plot graphs were created to give an indication of the likelihood of publication bias. Analyses were performed with Review Manager 5.1.

Results

Results of the search

Our search strategy identified 3299 studies in PubMed and 3775 studies in Embase. The Cochrane library did not contain studies on antioxidants and pancreatitis (Fig. s1). After removing duplicates, a total of 4286 publications remained for selection based on title and abstract. A total of 4260 studies were excluded because they were performed in animals (n = 1239), were not performed as an RCT or did not investigate the efficacy of antioxidants in patients with pancreatitis (n = 3009) or were not available in the English or Dutch language (n = 12). After reading the full text of the 26 remaining papers, another eight studies were excluded, as they did not contain variables that were comparable. Seven more studies were excluded as they focused on the efficacy of antioxidants in patients with chronic rather than acute pancreatitis. Finally, a total of 11 studies investigating the efficacy of antioxidants in patients with AP were included in this meta-analysis (Fig. s1). Q3

Description of the studies

Study characteristics are shown in Table 1 for AP. All included RCTs were published between 1990 and February 2014, with a mean age of 39–68 years. Most studies included severe pancreatitis only. Outcomes that were evaluated in the studies on AP were hospital stay, complications and mortality rate (Table 2). The effect of antioxidants on hospital stay, complications and mortality rate was assessed in 469 patients. The Jadad score of 11 studies on AP is shown in Table 3. Most studies achieved high quality scores (Jadad $\geq$ 4). Four studies had a score of 3 and one study had a score of 2. Funnel plots did not show publication bias (data not presented).

Hospital stay, complication rate, and mortality

Hospital stay was evaluated in 7 studies investigating the effect of antioxidants on AP. There was a borderline significant reducing effect (MD −1.74; 95%CI 3.56–0.08; I^2 = 22%) of antioxidants on hospital stay (Fig. 1) [11,22–27].

Systemic complication rate was evaluated in 7 studies investigating the effect of antioxidants on AP. We observed a significant decrease in number of patients with complications when they were treated with antioxidants (RR 0.66; 95%CI 0.46–0.95; I^2 = 14%) (Fig. 2) [11,22,24–28].

Mortality was evaluated in all 11 studies on AP. We found a non-significant positive effect of antioxidants on mortality in patients with AP (RR 0.66; 95%CI 0.30–1.46; I^2 = 21%) (Fig. 3) [11,16,22–30].

Subgroup analysis on glutamine, severity and route of administration and AP

Glutamine was investigated in 5 studies, with 3 studies assessing hospital stay [11,22,25], 4 assessing complications [11,22,25,28] and all 5 studies assessing mortality rates [11,16,22,25,28]. The effect of glutamine on hospital stay was non-significant (MD −1.72;

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