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Meta-analyses

Antioxidant therapy for patients with chronic pancreatitis: A systematic review and meta-analysis

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SUMMARY

Background & aims: Chronic pancreatitis is a progressive, inflammatory disease of pancreas characterized by significant abdominal pain, malabsorption, and diabetes mellitus. Antioxidant therapy has been proposed as an effective treatment for painful chronic pancreatitis. We performed a meta-analysis of trials in which antioxidant therapy was compared with placebo in chronic pancreatitis.
Methods: We searched six databases to identify relevant trials. Results are expressed as risk ratio (RR) or standardized mean difference (SMD) with accompanying 95% confidence intervals (CI). The meta-analysis was performed with the fixed-effects model or random-effects model according to heterogeneity.
Results: Eight studies including 573 patients met the inclusion criteria. A meta-analysis of these studies revealed that the intervention of antioxidants was associated with a significant increase in patients with pain relief (RR, 2.15; 95% CI, 1.72–2.69; $P < 0.00001$), and a significant decrease in patients' need for analgesics (RR, 0.56; 95% CI, 0.40–0.78; $P = 0.0006$). For pain score, antioxidants improved pain tolerance in chronic pancreatitis patients (SMD: −0.41; 95% CI: −0.83 to −0.10; $P = 0.0005$). Additionally, antioxidants may cause some adverse reactions (RR, 4.22; 95% CI: 2.17–8.20; $P < 0.0001$).
Conclusions: Based on current evidence, oxidative stress may play an important role in the pathophysiology of chronic pancreatitis, and administration of antioxidants to patients with painful chronic pancreatitis is effective in relieving pain. Antioxidant supplements may be advocated as one medical therapy for chronic pancreatitis patients with low antioxidant capacity in their blood.

1. Background

Chronic pancreatitis (CP) is not a common disease and there are few reports providing population statistics for chronic pancreatitis. In Europe, approximately 6–7 per 100,000 population suffer from CP [1]. Similar prevalences of CP have been reported in other regions [2–4], but high prevalence is reported in Asian countries, especially in Japan and India [5].

Although there are many aetiologies of CP, the most common in adults in Western societies is chronic alcohol abuse. Recently, the overall prevalence of CP has increased worldwide, probably due to rising alcohol consumption coupled with improving diagnostic techniques with better diagnostic accuracy, such as endoscopic retrograde pancreatography (ERP), endoscopic ultrasonography (EUS), and magnetic resonance cholangiopancreatography (MRCP) [6].

Based on the aetiology and pathogenesis of CP, the TIGAR-O classification was proposed by Etemad and Whitcomb in 2001 [7], an acronym for "toxic-metabolic, idiopathic, genetic, autoimmune, recurrent severe, and obstructive." Furthermore, an advancement of the TIGAR-O system was presented by Stevens and colleagues, based on these various aetiologies [8].

Although many aetiologies of CP are known, the pathogenic mechanism(s) of CP have remained elusive. One of the best known hypotheses regarding the pathophysiology of CP is oxidative stress, proposed by Braganza et al. [9], which is believed to be due to overactivity of mixed-function oxidases. There are many clinical and experimental findings supporting the oxidative stress hypothesis, including the depletion of circulating antioxidant factors and their precursors [10], along with increases in markers of oxidative injury in blood samples taken from clinical chronic pancreatitis patients [11,12], increased free radical activity compared with healthy

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controls [13], up-regulation of oxidative stress-response genes during pancreatitis [14], and intravital microscopy finding of short-lived oxidative bursts in the pancreatic intra-acinar [15].

Based on these findings, antioxidant supplementation has been suggested as a potentially useful treatment for CP. Furthermore, many studies have reported benefits of antioxidant supplementation in terms of anti-inflammatory effects and reduced risks of cancer and various other diseases [16–18]. Administration of antioxidants, consisting of vitamin C, vitamin E, β-carotene, selenium, and methionine, have shown favourable outcomes in both pain relief and quality of life in CP patients in many clinical studies [19–21]. Recently, Siriwardena and colleagues conducted a randomized controlled trial (RCT), which seems to deny any positive effect of antioxidants [22]. Also, adverse reactions, like allergies, general malaise, headache, nausea, vomiting, dyspepsia, and abdominal pain, were reported in the RCT.

Thus, whether antioxidants therapy is useful and should be prescribed for pain relief to patients with CP is still controversial. Here, to assess the effectiveness and potential side effects of antioxidants for the treatment of CP, we performed a meta-analysis of randomised controlled trials.

2. Methods

2.1. Literature search

Two independent reviewers (DKZ, XFC) searched PubMed, EMBASE, The Cochrane Library, CPCI-S (Conference Proceedings Citation Index-Science), ICTRP (International Clinical Trials Registry Platform), and CSCD (Chinese Science Citation Database) to identify relevant RCTs published before March 2014. The following key words were used in the search strategy: chronic pancreatitis, alcoholic pancreatitis, hereditary pancreatitis, idiopathic pancreatitis, recurrent pancreatitis, tropical pancreatitis, antioxidants, free radical scavengers, and oxidation-reduction, filtered by Humans and Randomised Controlled Trial. Diverse anti-oxidative substances, such as vitamin C, vitamin E, allopurinol, β-carotene, selenium, and methionine, were also considered in the search strategy. The search strategy was adapted for each database as necessary. There were no restrictions regarding language, publication status, or type of publication. References from relevant articles were checked for further studies.

2.2. Eligibility criteria

Both reviewers independently scanned the titles, abstracts, and full text articles to determine whether the articles met the selection criteria: (a) study design: randomised controlled trial (RCT) was best choice, but some well-designed non-RCT studies were also taken into account, (b) participants: chronic pancreatitis patients diagnosed by appropriate clinical evidence (CT and/or ERCP or MRCP), (c) comparison intervention: any single or compound antioxidants compared with placebo or no intervention, (d) outcome measure: pain relief, analgesic use, quality of life, and adverse effects. Cross-over clinical trials of high quality were also included in this review.

2.3. Data extraction and outcome measure

Two authors independently extracted data (first author, year of publication, number of patients, patient characteristics, study design, follow-up period, regimen of antioxidant supplementation) using a prespecified data extraction form. All discrepancies were double-checked. Disagreements between the reviewers were resolved by discussion, and if agreement could not be reached, a third reviewer was consulted.

Both pain relief status, assessed by various pain scores, and free-of-pain patient numbers were considered as the primary outcomes of interest in the included studies. Secondary outcomes included quality of life measured by various quality-of-life tests, requirement for oral/parenteral analgesics, and any adverse effects caused by the antioxidants. Antioxidant status change in peripheral blood was also taken into account if reported in the studies.

2.4. Assessment of risk of bias

Assessing risk of bias in included studies was based on the Cochrane Handbook for Systematic Review of Interventions [23]. There were six sections of risk of bias assessment: sequence allocation, allocation concealment, blinding, incomplete data outcome, selective outcome reporting, and other sources of bias. Each section was judged according to the appropriate definitions of “high risk” and “low risk”, whereas a judgement of “unclear risk” was made when there was no evidence of high or low risk in the selected studies.

2.5. Statistical analyses

The meta-analysis of extracted data was conducted using Cochrane Review Manager 5.2.6. (http://ims.cochrane.org/revman). A fixed-effects model or random-effects model was used, depending on the absence or presence of heterogeneity. To include as many trials in the meta-analysis as possible, even when not all information was reported, means and standard deviations were estimated based on medians, ranges, and sample sizes [24]. Because several pain outcomes (e.g., patient-assessed pain) were assessed on different scales across the studies, SMD was used instead of weighted mean differences (WMD) as a measure of effect size. The risk ratio (RR) with 95% CI was introduced in other outcome measures, like number of patients with pain relief or adverse effects. Statistical heterogeneity was tested using the Q test (χ^2) and reported with the I^2 statistic. Higher values of I^2 indicate higher heterogeneity. Sensitivity analyses were performed to determine the effect of outliers (by excluding every single study) and low quality studies. Potential publication bias was assessed using visual examination of the funnel plot (plots of effect estimates against their standard errors; SEs).

3. Results

3.1. Characteristics of the studies included

There were 157 studies identified by an initial database search. After adjusting for duplicates, 121 studies remained. Of these studies, 106 studies were removed on the basis of inclusion criteria after reviewing the titles and abstracts. For the remaining 15 studies, the full texts were obtained and examined in more detail. One study was excluded due to comparison of oral cholecalciferol versus ultraviolet radiation applied in CP [25]. Another five studies were excluded due to insufficient data [25–29], although we contacted the corresponding authors for missing information. Additionally, we excluded another study because of the complex ingredients of pentoxifylline and solcoseryl [30]. We did not exclude a 5-day trial because of its comprehensive report [20], although the antioxidant treatment was combined with intramuscular pethidine hydrochloride.

Finally, eight studies met the inclusion criteria and were included in the analysis [19–22,31–34] through our search strategy (Fig. 1), with a total of 573 patients. Risk of bias is shown in Fig. 2 based on the review authors' judgements. The main characteristics of these studies are presented in Table 1. All these patients were

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