Antioxidant therapy in acute, chronic and post-endoscopic retrograde cholangiopancreatography pancreatitis: An updated systematic review and meta-analysis

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Abstract

AIM: To investigate the efficacy and adverse effects of antioxidant therapy in acute pancreatitis (AP), chronic pancreatitis (CP) and post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP).

METHODS: PubMed, Scopus, Google Scholar, Cochrane library database, and Evidence-based medicine/clinical trials published before August 2014 were searched. Clinical and laboratory outcomes of randomized trials of antioxidant therapy in patients with AP, CP and PEP were included. The methodological quality of the trials was assessed by the Jadad score based on the description of randomization, blinding, and dropouts (withdrawals). The results of the studies were pooled and meta-analyzed to provide estimates of the efficacy of antioxidant therapy.

RESULTS: Thirty four trials out of 1069 potentially relevant studies with data for 4898 patients were
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INTRODUCTION

Pancreatitis is an inflammatory metabolic disorder, which is a major cause of physical and socioeconomic loss worldwide[1-3]. Generally, pancreatitis is categorized into two different entities of acute and chronic[4].

Acute pancreatitis (AP) is sudden painful inflammation of the pancreas, basically caused by tissue destruction as a consequence of innate immune-induced epithelial stress pathways[5]. The most common cause of gut-related hospitalization in the United States is AP[6]. Several complicated factors are associated with the development of AP; however, alcohol abuse and ductal obstruction caused by gallstones or bacterial infection are the main factors[7].

Furthermore, pancreatitis remains the most common adverse event of endoscopic retrograde cholangiopancreatography (ERCP). The incidence of post-ERCP pancreatitis (PEP) varies widely, ranging from 1% to 40% in the normal population, to as high as 67% in high-risk patients[7]. While investigations toward preventing or limiting the complications of PEP with pharmacological agents have drawn much attention, these have so far had limited success.

Chronic pancreatitis (CP) is a progressive fibro-inflammatory disorder, representing a continuum from a first inflammatory episode to parenchymal fibrosis and functional insufficiency[8]. While alcohol is the most frequent causative factor in the development of chronic pancreatitis, idiopathic, genetic, and autoimmune factors are considered less frequent causes[9]. CP can eventually give rise to several complications that should be treated accordingly. Principally, the only observable symptom in chronic pancreatitis is pain[10].

Reactive oxidative species (ROS) are inevitable epiphenomenon or the cause of vital processes, particularly aerobic metabolism. When production of ROS exceeds their catabolism in any physiologic and pathologic conditions, oxidant-derived cellular injury can occur which is known as oxidative stress[10,11].

Interestingly, there is ample evidence suggesting that oxidative stress is a common pivotal factor in the pathogenesis of AP, CP and PEP[12]. While an extensive and multilayered antioxidant defense system is present in the human body, dietary intake can play a crucial role in strengthening antioxidant capacity within the blood[13,14]. Thus, it is not surprising that the use of antioxidants have positive effects in pancreatitis.

The question of whether antioxidant supplements might protect against pancreatitis has drawn much attention in recent years, and a meta-analysis has shown some positive effects[15], although the results of randomized trials have been contradictory. The present systematic review with meta-analyses was conducted to critically update the knowledge on the beneficial or harmful effects of antioxidant supplementation in the
management of AP, CP and PEP.

MATERIALS AND METHODS

Data sources
All randomized clinical trials (RCTs) evaluating antioxidants for the treatment of pain, hospitalization, C reactive protein (CRP) and serum amylase in CP, AP and the severity and rate of PEP were included. Data were searched from PubMed, Scopus, Google Scholar, Cochrane library database, and Evidence-based medicine/clinical trials published before August 2014 were searched.

The search terms were as follows: AP, CP, PEP, pancreatic inflammation, antioxidant, vitamin, superoxide dismutase, manganese, glutamine, butylated hydroxyanisole, taurine, glutathione, curcumin, catalase, peroxidase, lutein, xanthophylls, selenium, riboflavin, zinc, carotenoid, cobalamin, retinol, alpha-tocopherol, ascorbic acid, beta-carotene, carotene and all MeSH terms of pharmacologically active antioxidants. The studies were limited to clinical trials and those written in the English language.

Assessment of trial quality
The Jadad score, which indicates the quality of the studies based on their description of randomization, blinding, and dropouts (withdrawals) was used to assess the methodological quality of trials[14]. The quality range scales from 0 to 5 points with a score of 2 or less for a low quality report and a score of at least 3 for a high quality report. The description of this score is as follows: (1) whether randomized (yes = 1 point, no = 0); (2) whether randomization was described appropriately (yes = 1 point, no = 0); (3) double-blind (yes = 1 point, no = 0); (4) was the double-blinding described appropriately (yes = 1 point, no = 0); and (5) whether withdrawals and dropouts were described (yes = 1 point, no = 0). The quality score ranges from 0 to 5 points; a low-quality report score is ≤ 2 and a high-quality report score is at least 3.

Study selection
Data synthesis was conducted by three reviewers who read the title and abstract of the search results separately to eliminate duplicates, reviews, case studies, and uncontrolled trials. The inclusion criteria were that the studies should be clinical trials on the use of an antioxidant for the treatment or prevention of pancreatitis. Outcomes of the studies were not the point of selection and all studies that analyzed the effects of an antioxidant on pancreatitis, from pain reduction to changes in plasma cytokines, were included.

Statistical analysis
Data from selected studies were extracted in the form of 2 × 2 tables by study characteristics. Included studies were weighted by effect size and pooled. Data were analyzed using Statsdirect software version 3.0.146. Relative risk (RR) and 95% confidence intervals (95%CI) were calculated using Mantel-Haenszel, Rothman-Boice (for fixed effects) and DerSimonian-Laird (for random effects) methods. Standardized effect size and 95%CI were calculated using Murow-Oxman (for fixed effects) and Der Simonian-Laird (for random effects) methods. The Cochran Q test was used to test heterogeneity and P < 0.05 was considered significant. In the case of heterogeneity or few included studies, the random effects model was used. Egger and Begg-Mazumdar tests were used to evaluate publication bias indicators in funnel plots.

RESULTS
From the 1069 studies identified through the literature search, 34 randomized controlled trials were identified as eligible (4898 patients; 551 AP, 673 CP and 3674 PEP) (Figure 1). Of these, 12 trials used antioxidant therapy in AP (Table 1)[17-28], 12 trials in CP (Table 2)[28-39] and 11 trials in PEP (Table 3)[40-50].

In these 35 papers, the Jadad score was 5 in 12 papers (34%), 4 in 9 (25%), 3 in 8 (22%), 2 in 5 (14%) and only one study scored 1 (Tables 1-3).

Furthermore, the effects of early discontinuation were minimized by the collection of updates, follow-up and investigated in the analyses.

In each study, patients used antioxidant therapy in order to treat or prevent pancreatitis, although various methods of quantifying outcomes were employed. Tables 1, 2, and 3 detail the characteristics of the trials. In these cases, only the results for length of hospital stay in AP patients, serum CRP in AP patients, pain reduction in CP patients, the incidence and severity of all types of PEP in patients undergoing ERCP, and serum amylase in patients undergoing ERCP were included in the meta-analysis.

Antioxidant therapy in AP
In the context of AP, ten of twelve studies assessed clinical presentations, as outcomes of antioxidant therapy[17,22,24,25,27,28]. One of four studies reported that the mortality rate was reduced following antioxidant therapy[19]. Four of eight studies showed a significantly shorter hospital stay in the treatment groups[17,19,24,25]. In addition, four of eight trials reported a reduction in complications and organ dysfunction[17,19,21,24]. However, one study showed that antioxidant therapy did not alleviate pain in AP[28].

On the other hand, ten of twelve studies assessed laboratory outcomes, as outcomes of antioxidant therapy[17,18,20-26,28]. Three of five studies showed a significant increase in serum free radical activity and a significant increase in serum antioxidant levels[17,24,28].
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1069 potentially relevant articles from electronic search

93 excluded because of duplication
897 reports excluded on the basis of title and abstract

79 reports retrieved

45 reports excluded upon full text search

34 eligible controlled clinical trials included in the systematic review and meta-analyses

Figure 1 Flow diagram of study selection.

| Ref.               | Drug/supplements                      | Study design                     | Jadad score | Participants | Treatment (intervention) | Outcome (results)                  | Adverse effects/events |
|--------------------|--------------------------------------|----------------------------------|-------------|--------------|--------------------------|-------------------------------------|------------------------|
| Bansal et al[18], 2011 | Combined antioxidant (vitamin A, vitamin C, vitamin E) | Single-center, prospective randomized, open-label with blinded endpoint | 4           | 39 patients with severe AP | 19 patients; combined antioxidants: 1000 mg vitamin C in 100 mL normal saline, 200 mg vitamin E oral, and 1000 IU vitamin A intramuscularly; per day; for 14 d | Multi-organ dysfunction; Length of hospital stay | Serum GSH↑ Serum SOD↓ |
| Sateesh et al[17], 2009 | Combined antioxidant (vitamin C, N-acetyl cysteine, antoxyl forte) | Randomized; placebo-controlled | 3           | 53 patients with AP | 23 patients; combined antioxidants: 500 mg vitamin C, 200 mg 8 hourly N-acetyl cysteine and 1 capsule hourly antoxyl forte; per day; for 7 d | Length of hospital stay and complications ↓ | Serum MDA↑ TBARS↓ SOD↓ |
| Xue et al[19], 2008 | Glutamine                             | Randomized;                       | 1           | 80 patients with severe AP | 38 patients; 100 mL/d of 20% AGD intravenous infusion; for 10 d; starting on the day 1 (Early treatment) | Infection rate ↓ Operation rate ↓ Mortality ↓ Hospitalization ↓ Duration of ARDS ↓ Renal failure ↓ Acute hepatitis ↓ Encephalopathy ↓ Enteroparalysis ↓ | TAC ↓ Vitamin C↑ |

Table 1 Controlled clinical trials of antioxidants in patients with acute pancreatitis
| Study                  | Intervention                                                                 | Design                          | Study Population | Control Population | Outcomes                                                                 | Comparison                                                                 |
|-----------------------|------------------------------------------------------------------------------|---------------------------------|------------------|-------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Fuentes-Orozco et al.  | Glutamine                                                                     | Randomized; double blind; controlled | 44 patients with AP | 22 patients; 0.4 g/kg per day of L-alanyl-L-Glutamine in standard TPN; 10 d | Duration of shock ↓ 15 d APACHE II core ↓ Infectious morbidity ↓ Hospital stay day ↓ Mortality ↓ Serum IL10 ↑ Serum IL-6 ↓ CRP ↓ Ig A ↑ Protein ↑ Albumin ↑ Leucocyte ↓ |
| Sahin et al. 2007     | Glutamine enriched total parenteral nutrition (TPN)                          | Randomized; double blind; placebo-controlled | 40 patients with AP | 20 patients; 0.3 g/kg per day glutamine; for 7-15 d | 20 patients; placebo Duration of shock ↓ APACHE II core ↓ Infectious morbidity ↓ Hospital stay day ↓ Mortality ↓ Complication rates ↓ Total lymphocyte ↑ Nitrogen balance was (+) in treated group vs (−) in control group |
| Siriwardena et al. 2008| Combined antioxidant (N-acetylcysteine, selenium, vitamin C)                  | Randomized; double blind; placebo-controlled | 43 patients with severe AP | 22 patients; N-acetylcysteine, selenium and vitamin C; for 7d | 21 patients; placebo Organ dysfunction ↓ APACHE-II Hospitalization ↑ All case mortality ↑ CRP ↑ CAPAP ↓ Serum lipase ↓ Amylase activities↓ CRP ↓ Serum vitamin C ↓ Serum selenium ↓ GSH/GSSG ratio ↓ CRP² |
| Pearce CB et al. 2006  | Glutamine, arginine, tributyrin and antioxidants                              | Randomized; double blind; placebo-controlled | 31 patients with severe AP | 15 patients; glutamine, arginine, tributyrin and antioxidants; for 3 d; If patients required further feeding the study was continued up to 15 d | 16 patients; placebo isocaloric isonitrogenous control feed was undertaken Organ dysfunction ↓ APACHE-II Hospitalization ↑ All case mortality ↑ CRP ↑ CAPAP ↓ Serum lipase ↓ Amylase activities↓ CRP ↓ Serum vitamin C ↓ Serum selenium ↓ GSH/GSSG ratio ↓ CRP² |
| Du et al. 2003         | Vitamin C                                                                     | Randomized; controlled           | 84 patients with AP | 44 patients; 1g/d; for 5 d | Hospitalization ↓ Deterioration of disease ↓ Improvement of disease ↑ Cure rate ↑ Hypernatremia ↑ Plasma vitamin C ↑ Plasma liperoxidase ↑ Plasma vitamin E ↑ Plasma β-carotene ↑ Whole blood glutathione ↑ Activity of erythrocyte superoxide dismutase ↑ Erythrocyte catalase ↑ |
| Ockenga et al. 2002    | Glutamine                                                                     | Randomized; double blind; controlled | 28 patients with AP | Standard TPN which contains 0.3 g/kg per day L-alanine-L-glutamine; at least 1 wk | Hospitalization ↓ Duration of TPN ↓ Cost of TPN ↑ Cholinesterase ↑ Albumin ↑ |

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Table 2  Controlled clinical trials of antioxidants in patients with chronic pancreatitis

| Ref. | Drug/supplements | Study design | Jadad score | Participants | Treatment (intervention) | Outcome (results) | Adverse effects/events |
|------|-----------------|--------------|-------------|--------------|--------------------------|--------------------|------------------------|
| Dhingra et al[29], 2013 | Combined antioxidant (organic selenium, vitamin C, \(\beta\) carotene, vitamin E, methionine) | Randomized; placebo-controlled | 3 | 61 patients with CP | 31 patients; 600 Hg of organic selenium, 0.54 g of vitamin C, 9000 IU of \(\beta\) carotene, 270 IU of vitamin E, and 2 g of methionine | 30 patients; placebo | Number of painful days per month ↓; Number of analgesic tablets per month ↓ |
| Shah et al[30], 2013 | Combined antioxidant (vitamin C, vitamin E, \(\beta\) carotene, selenium, methionine) | Randomized; double-blind; placebo-controlled | 5 | 14 patients with CP | 7 patients; Antox tablet: vitamin C, vitamin E, \(\beta\) carotene, selenium, methionine (Pharma Nord, Morpeth, United Kingdom); 6 m | 7 patients; placebo | Opiate usage

No significant difference between groups. ↑: Significant increase as compared with control; ↓: Significant decrease as compared with control; TBARS: Thiobarbituric acid reactive substances; FRAP: Ferric reducing antioxidant power; SOD: Superoxide dismutase; AGD: Alanyl-glutamine dipeptide; CRP: C-reaction protein; MDA: Malondialdehyde; LDH: Lactate dehydrogenase; APACHE II: Acute Physiology and Chronic Health Evaluation II; GSH: Glutathione; TPN: Total parenteral nutrition; AST: Aspartate aminotransferase; ALT: Alanine transaminase; CAPAP: Carboxypeptidase B activation peptide; BUN: Blood urea nitrogen.
| Authors | Interventions | Study Design | No. of Patients (No. of Patients) | Interventions/Results |
|---------|---------------|--------------|----------------------------------|-----------------------|
| Sirwardena et al.<sup>[31]</sup>, 2012 | Combined antioxidant (selenium, d-a-tocopherol acetate, ascorbic acid, L-methionine) | Randomized; double blind; placebo-controlled | 5 | 70 patients with CP, Antox tablet: 38.5 mg selenium Yeast, 113.4 mg d-a-tocopherol acetate, 126.3 mg ascorbic acid, 480 mg L-methionine; per d; for 6 m | Quality of life↑ Average daily pain scores↑ Opiate use↑ Number of hospital admissions↑ Outpatient visits↑ Serum vitamin C↑ Serum vitamin E↑ Serum beta carotene↑ Serum selenium↑ Increased frequency of stool, occasional diarrhea, bad taste, and heartburn with nausea |
| Shah et al.<sup>[32]</sup>, 2010 | Combined antioxidant (vitamin C, vitamin E, β carotene, selenium, methionine) | Randomized; placebo-controlled | 2 | 137 patients with CP, Antox tablet: vitamin C, vitamin E, β carotene, selenium, methionine (Pharma Nord, Morpeth, United Kingdom); at least 6 m | Median visual analogue pain score↑ Cognitive, emotional, social, physical and role function↑ Analgesics and opiate usage↑ |
| Bhardwaj et al.<sup>[33]</sup>, 2009 | Combined antioxidant (organic selenium, vitamin C, β-carotene, α-tocopherol and methionine) | Randomized; double blind; placebo-controlled | 5 | 147 patients with CP, combined antioxidants: 600 μg organic selenium, 0.54 g ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol and 2 g methionine (Betamore G, Osper Pharmacautics, India); per d; for 6 m | Number of painful days per month↑ Numbers of oral analgesic tablets and parenteral analgesic injections per month↑ Hospitalization↑ Percentage of patients become pain-free↑ Number of man-days lost per month↑ Lipid peroxidation (TBARS)↑ Serum SOD↑ Total antioxidant capacity (FRAP)↑ Serum vitamin A↑ Serum vitamin C↑ Serum vitamin E↑ Erythrocyte superoxide dismutase↑ Headache & Constipation↑ |
| Kirk et al.<sup>[34]</sup>, 2006 | Combined antioxidant (selenium, β-carotene, L-methionine, vitamins C and E) | Randomized; double blind; placebo-controlled; crossover | 4 | 72 patients with CP, Antox tablet: 75 mg of selenium, 3 mg β-carotene, 47 mg vitamin E, 150 mg vitamin C, and 400 mg methionine; 4 times per day; for 10 wk | Quality of life↑ Pain↑ Physical and social functioning↑ Health perception↑ Emotional functioning, energy, mental health↑ Plasma selenium↑ Plasma vitamin C↑ Plasma vitamin E↑ Plasma β-carotene↑ Two patients complained of nausea and one of an unpleasant taste during treatment with Antox |
| Durgaprasad et al.<sup>[35]</sup>, 2005 | Curcumin | Randomized; single blind; placebo-controlled | 3 | 20 patients with tropical pancreatitis (CP), 8 patients; capsule: 500 mg curcumin (95%) with 5 mg of piperine; 3 times per day; for 6 wk | Median visual analogue pain score↑ Severity of Pain↑ Erythrocyte MDA↑ GSH level↑ |
| Banks et al.<sup>[36]</sup>, 1997 | Allopurinol | Randomized, double blind, two-period crossover clinical trial | 4 | 26 patients with CP, Allopurinol: 4 wk 13 patients; 300 mg/d All 13 patients, placebo | Pain↑ Uric acid level↓ |
While, three of seven trials reported a decrease in inflammatory biomarkers\textsuperscript{[20,24,28]}, one trial reported an increase in inflammatory biomarkers\textsuperscript{[25]}. Indeed, three of the five studies demonstrated a significant decrease in CRP levels\textsuperscript{[20,21,24,25]}. In addition, one study reported a reduction in the levels of serum amylase and lipase\textsuperscript{[21]}. It is noteworthy that one of twelve studies assessing the antioxidant therapies reported diarrhea, vomiting and hyponatremia in 5 patients\textsuperscript{[23]}.  

**Antioxidant therapy in CP**

In the context of CP, all of the studies (twelve studies) assessed clinical presentations\textsuperscript{[28-39]}. Three of four studies reported that antioxidant therapy improved the quality of life as well as cognitive, emotional, social, physical and role function\textsuperscript{[32-34]}. Two of three studies showed a significantly shorter hospital stay in the treatment groups\textsuperscript{[33,39]}. In addition, six of eleven trials reported a reduction of pain\textsuperscript{[29,32-34,37-39]}. On the other hand, eleven of twelve studies assessed laboratory outcomes, as outcomes of antioxidant therapy\textsuperscript{[28-39]}. Eight of nine studies showed a significant decrease in serum free radical activity and a significant increase in serum antioxidant levels\textsuperscript{[28-31,33,34,37,38]}. Furthermore, one of two trials reported a decrease in inflammatory biomarkers\textsuperscript{[39]}. In addition, one study reported a decrease in the levels of serum amylase\textsuperscript{[39]}. However, three of twelve studies assessing the antioxidant therapies reported adverse effects such as GI complications (nausea, vomiting, dyspepsia, diarrhea, and constipation), unpleasant taste, allergies, heartburn, headaches, general

| Study | Intervention | Study Design | Patients | Outcome | Free radical activity ↓ | Effects | Notes |
|-------|-------------|--------------|----------|---------|-------------------------|--------|-------|
| Bilton et al\textsuperscript{[26]}, 1994 | S-adenosyl methionine (SAMe) + Selenium | Randomized, double-blind, crossover/placebo-controlled | 5/20 | Placebo attack rate and background pain | Serum SAMe ↓ | GI complications | No significant difference between groups. ↓: Significant increase as compared with control; ↑: Significant decrease as compared with control; TBARS: Thiobarbituric acid reactive substances; FRAP: Ferric reducing antioxidant power; SOD: Superoxide dismutase; AGD: Alanyl-glutamine dipeptide; CRP: C-reactive protein; MDA: Malondialdehyde; LDH: Lactate dehydrogenase; APACHE II: Acute Physiology and Chronic Health Evaluation II; GSH: Glutathione; TPN: Total parenteral nutrition. |
| Salim et al\textsuperscript{[39]}, 1991 | Allopurinol; dimethyl sulfoxide | Randomized, double-blind, crossover/placebo-controlled | 4/78 | Pain free patients | Serum amylase ↑ | General malaise | |
| Uden et al\textsuperscript{[37,38]}, 1990, 1992 | Combined antioxidant (selenium, β-carotene, vitamin C, vitamin E, methionine) | Randomized, double-blind, crossover/placebo-controlled | 5/28 | Pain (McGill) ↓ | Serum SAMe ↓ | Abdominal pain | |
Table 3  Controlled clinical trials for antioxidant management to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis

| Ref. | Drug/supplements | Study design | Jadad score | n | Treatment (intervention) | Outcome (results) | Adverse effects/events | Other comments |
|------|------------------|--------------|-------------|---|--------------------------|-------------------|-----------------------|----------------|
| Abbasinazari et al.[40], 2011 | Allopurinol | Randomized double blind clinical trial | 3 | 74 | 29 patients; no medication | Rate of PEP<sup>3</sup> (11.5% vs 12.5%) | - | - |
| Martínez-Torres et al.[41], 2009 | Allopurinol | Randomized; double-blind; placebo-controlled | 5 | 170 | 85 patients; placebo | 85 patients; 300 mg oral allopurinol 15 h and 3 h before ERCP | Serum amylase activity ↓ (2.3% vs 9.4%) | 21.7% absolute benefit in patients with high-risk procedures favoring allopurinol, no difference in low-risk procedures |
| Kapetanos et al.[42], 2009 | Pentoxifylline | Randomized; 2 | 590 | 205 patients; 400 mg oral Pentoxifylline, 40 h, 32 h, 24 h, 16 h and 8 h before ERCP (total dose 2 g) | 205 patients; no medication | Rate of PEP<sup>3</sup> (7.3% vs 2.9%) | - | - |
| | Octreotide | | | | | | | |
| Kapetanos et al.[42], 2009 | Octreotide | Randomized;  | 586 | 205 patients; 0.5 mg subcutaneous octreotide, 64 h, 56 h, 48 h, 40 h, 32 h, 24 h, 16 h and 8 h before ERCP (total dose 4 mg) | 205 patients; no medication | Rate of PEP<sup>3</sup> (5% vs 2.9%) | TNF-α ↓, IL-6 ↑ | - |
| Romagnuolo et al.[43], 2008 | Allopurinol | Randomized; double blind; placebo-controlled | 4 | 586 | 293 patients; placebo | 293 patients; 300 mg oral allopurinol 60 min before ERCP | Rate of PEP<sup>3</sup> (5.5% vs 4.1%) | Disease-related adverse events<sup>3</sup>, Procedure-related complications<sup>3</sup>, Hospitalization<sup>3</sup> | In the non-high-risk group (n = 520), the crude PEP rates were 5.4% for allopurinol and 1.5% for placebo (P = 0.017), favoring placebo, indicating harm associated with allopurinol, whereas in the high-risk group (n = 66), the PEP rates were 6.3% for allopurinol and 23.5% for placebo (P = 0.050), favoring allopurinol |
malaise, and abdominal pain\textsuperscript{[33,34,39]}.\footnote{No significant difference between groups. ↑: Significant increase as compared with control; ↓: Significant decrease as compared with control; PEP: Post-endoscopic pancreatitis.}

**Antioxidant therapy in PEP**

In the context of PEP, two of eleven studies showed a significant drop in the rate of PEP\textsuperscript{[41-46]}. In addition, one of two studies reported a significant decrease in the rate of hospitalization in the treatment group\textsuperscript{[46]}. On the other hand, two studies showed that antioxidant therapy did not affect disease-related complications\textsuperscript{[43,44]}. One of four studies assessing laboratory outcomes, reported a significant decrease in serum amylase activity\textsuperscript{[41]}. Moreover, one trial reported a non-significant alteration in urine amylase levels\textsuperscript{[43]}. Also, one of two studies demonstrated a significant decrease in serum TNF\textsuperscript{[42]}. Two of eleven trials reported adverse events such as nausea, diarrhea, vomiting and skin rash\textsuperscript{[43,47]}.

**Meta-analysis**

Effect of antioxidants compared with placebo on length of hospital stay (d) in acute pancreatitis patients: The summary for standardized effect size of mean differences in length of hospital stay in 303 AP patients for antioxidants therapy for six included trials compared to placebo\textsuperscript{[17,18,20-22,24]} was -2.59 with 95%CI: -4.25-(-0.93) (P = 0.002, Figure 2A). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous (P = 0.16) and could be combined, but due to publication bias the random effects for individual and summary of effect size for standardized mean was applied. For evaluation of publication bias, Egger regression of normalized effect vs precision for all included studies on length of hospital stay in AP patients treated with antioxidants vs placebo therapy was 2.17 (95%CI: 1.04-3.31, P = 0.006) and Begg-
Mazumdar Kendall’s test on standardized effect vs variance indicated tau= 0.47, \( p = 0.27 \) (Figure 2B).

**Effect of antioxidants compared with placebo on serum CRP in acute pancreatitis patients after 5-7 d:** The summary for standardized effect size of mean differences in serum CRP in 171 AP patients after 5-7 d for antioxidants therapy for three included trials compared to placebo\(^{20,22,24}\) was \(-9.57\) with 95%CI: -40.61-21.48 \( (p = 0.55, \text{Figure 3A}) \). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous \( (P = 0.56) \) and could be combined, but due to few included trials, the random effects for individual and summary of effect size for standardized mean was applied. Publication bias for included studies for serum CRP in AP patients treated with antioxidants vs placebo therapy could not be evaluated because of too few strata.

**Effect of antioxidants compared with placebo on serum CRP in acute pancreatitis patients after 10 d:** The summary for standardized effect size of mean differences of serum CRP in 84 AP patients after 10 d for antioxidants therapy for two included trials compared to placebo\(^{20,21}\) was \(-45.16\) with 95%CI: -89.99-(-0.33) \( (P = 0.048, \text{Figure 3B}) \). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous \( (P = 0.44) \) and could be combined, but due to few included trials, the random effects for individual and summary of effect size for standardized mean was applied. Publication bias for included studies for serum CRP in AP patients treated with antioxidants vs placebo therapy could not be evaluated because of too few strata.
Effect of antioxidants compared with placebo on pain reduction in chronic pancreatitis patients:
The summary for standardized effect size of mean differences of pain reduction in 189 CP patients for antioxidants therapy for two included trials compared to placebo\cite{31,33} was -2.13 with 95%CI: -5.87-1.6 (\(p = 0.26\), Figure 4). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous (\(p = 0.0003\)) and could not be combined, thus the random effects for individual and summary of effect size for standardized mean was applied. Publication bias for included studies of pain reduction in CP patients treated with antioxidants vs placebo therapy could not be evaluated because of too few strata.

Effect of antioxidants compared with placebo on the incidence of all types of PEP in patients undergoing ERCP:
The summary for RR of all types of PEP in patients undergoing ERCP for twelve included trials in eleven studies\cite{40-50} comparing antioxidants to placebo was 1.05 with 95%CI: 0.74-1.5 (\(p = 0.78\), Figure 5A-a). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous (\(p = 0.02\), Figure 5A-b) and could not be combined, thus the random effects for individual and summary for RR was applied. For evaluation of publication bias Egger regression of normalized effect vs precision for all included studies for “all types of PEP” in 1849 patients treated with antioxidants vs placebo therapy was -0.78 (95%CI: -3.22-1.67, \(p = 0.5\)) and Begg-Mazumdar Kendall’s test on standardized effect vs variance indicated tau= -0.06, \(p = 0.73\) (Figure 5A-c).

Effect of antioxidants compared with placebo on the incidence of severe PEP in patients undergoing ERCP: The summary for RR of severe PEP in patients undergoing ERCP for ten included trials in nine studies\cite{40,42-44,46-50} comparing antioxidants to placebo was 0.92 with 95%CI: 0.43-1.97 (\(p = 0.83\), Figure 5B-a). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous (\(p = 0.85\), Figure 5B-b) and could be combined, thus the fixed effects for individual and summary for RR was applied. For evaluation of publication bias, Egger
Figure 4  Individual and pooled effect size for standardized mean for the outcome of “pain in chronic pancreatitis patients” in the studies considering antioxidants compared to placebo therapy in 189 patients.

A-a  Relative risk meta-analysis plot (random effects)

| Study                                    | Relative Risk (95%CI) |
|------------------------------------------|-----------------------|
| Abbasinazari et al. 2011                 | 0.93 (0.26, 3.25)     |
| Martinez-Torres et al. 2009              | 0.25 (0.06, 1.00)     |
| Kapetanos et al. 2009-Pentoxifylline     | 2.50 (1.02, 6.15)     |
| Kapetanos et al. 2009-Octreotide        | 1.71 (0.65, 4.53)     |
| Romagnuolo Het et al. 2008               | 1.33 (0.65, 2.73)     |
| Kapetanos et al. 2007                    | 1.85 (0.66, 5.16)     |
| Milewski et al. 2006                     | 0.62 (0.20, 1.93)     |
| Katsinelos et al. 2005-1                 | 0.18 (0.07, 0.48)     |
| Katsinelos et al. 2005-2                 | 1.26 (0.62, 2.55)     |
| Mosler et al. 2005                       | 1.07 (0.72, 1.58)     |
| Lavy et al. 2004                         | 1.05 (0.54, 2.03)     |
| Budzynska et al. 2001                    | 1.53 (0.67, 3.51)     |
| Combined (random)                        | 1.05 (0.74, 1.50)     |

A-b  L’Abbe plot (symbol size represents sample size)

A-c  Bias assessment plot
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B-a

Relative risk meta-analysis plot (fixed effects)

| Study                          | Relative Risk (95% CI) |
|--------------------------------|------------------------|
| Abbasinazari et al. 2011       | 1.53 (0.09, 26.16)     |
| Kapetanos et al. 2009-Pentoxifylline | 3.00 (0.25, 36.41)  |
| Kapetanos et al. 2009-Octreotide | 3.41 (0.28, 41.42)  |
| Romagnuolo Het et al. 2008     | 1.00 (0.18, 5.64)     |
| Kapetanos et al. 2007          | 2.05 (0.27, 15.57)    |
| Katsinelos et al. 2005-1       | 0.19 (0.02, 2.08)     |
| Katsinelos et al. 2005-2       | 1.01 (0.06, 17.38)    |
| Mosler et al. 2005             | 0.97 (0.17, 5.50)     |
| Lavy et al. 2004               | 0.14 (0.01, 1.46)     |
| Budzynska et al. 2001          | 3.06 (0.25, 37.05)    |
| Combined (random)              | 0.92 (0.43, 1.96)     |

B-b

L'Abbe plot (symbol size represents sample size)

C-a

Relative risk meta-analysis plot (fixed effects)

| Study                          | Relative Risk (95% CI) |
|--------------------------------|------------------------|
| Abbasinazari et al. 2011       | 0.776 (0.104, 5.661)   |
| Kapetanos et al. 2009-Pentoxifylline | 1.000 (0.058, 17.271) |
| Kapetanos et al. 2009-Octreotide | 1.138 (0.066, 19.651) |
| Romagnuolo et al. 2008         | 1.000 (0.344, 2.911)   |
| Kapetanos et al. 2007          | 3.075 (0.255, 37.298)  |
| Katsinelos et al. 2005-1       | 0.041 (0.004, 0.397)   |
| Katsinelos et al. 2005-2       | 1.411 (0.486, 4.118)   |
| Mosler et al. 2005             | 0.975 (0.501, 1.895)   |
| Lavy et al. 2004               | 1.277 (0.355, 4.584)   |
| Budzynska et al. 2001          | 0.680 (0.138, 3.339)   |
| Combined (random)              | 0.816 (0.540, 1.232)   |
Figure 5  Effect of antioxidants compared with placebo therapy on incidence. Individual and pooled relative risk (A-a), heterogeneity indicators for (A-b), and publication bias indicators for (A-c) the outcome of “all types of PEP” in the studies considering antioxidants compared to placebo therapy in 1849 patients undergoing ERCP; individual and pooled relative risk (B-a); Heterogeneity indicators (B-b); and publication bias indicators (B-c) for the outcome of “severe PEP” in the studies considering antioxidants compared to placebo therapy in 1709 patients undergoing ERCP; individual and pooled relative risk (C-a); heterogeneity indicators (C-b); publication bias indicators (C-c) for the outcome of “moderate PEP” in the studies considering antioxidants compared to placebo therapy in 1709 patients undergoing ERCP; individual and pooled relative risk (D-a); heterogeneity indicators (D-b); publication bias indicators (D-c) for the outcome of “mild PEP” in the studies considering antioxidants compared to placebo therapy in 1709 patients undergoing ERCP. PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography.
regression of normalized effect vs precision for all included studies for “severe PEP” in 1709 patients treated with antioxidants vs placebo therapy was 0.21 (95%CI: -2.12-2.54, P = 0.84) and Begg-Mazumdar Kendall’s test on standardized effect vs variance indicated tau= 0.2, P = 0.48 (Figure 5B-c).

Effect of antioxidants compared with placebo on the incidence of moderate PEP in patients undergoing ERCP: The summary for RR of moderate PEP in patients undergoing ERCP for ten included trials in nine studies[40,42-44,46-50] comparing antioxidants to placebo was 0.82 with 95%CI: 0.54-1.23 (P = 0.33, Figure 5C-a). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous (P = 0.66, Figure 5C-b) and could be combined, thus the fixed effects for individual and summary for RR was applied. For evaluation of publication bias, Egger regression of normalized effect vs precision for all included studies for “moderate PEP” in 1709 patients treated with antioxidants vs placebo therapy was -0.37 (95%CI: -1.57-0.83, P = 0.5) and Begg-Mazumdar Kendall’s test on standardized effect vs variance indicated tau= -0.02, P = 0.86 (Figure 5C-c).

Effect of antioxidants compared with placebo on the incidence of mild PEP in patients undergoing ERCP: The summary for RR of mild PEP in patients undergoing ERCP for ten included trials in nine studies[40,42-44,46-50] comparing antioxidants to placebo was 1.33 with 95%CI: 0.99-1.78 (P = 0.06, Figure 5D-a). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous (P = 0.76, Figure 5D-b) and could be combined, thus the fixed effects for individual and summary for RR was applied. For evaluation of publication bias, Egger regression of normalized effect vs precision for all included studies for “mild PEP” in 1709 patients treated with antioxidants vs placebo therapy was 0.25 (95%CI: -1.73-2.23, P = 0.78) and Begg-Mazumdar Kendall’s test on standardized effect vs variance indicated tau= 0.07, P = 0.86 (Figure 5D-c).

Effect of antioxidants compared with placebo on serum amylase in patients undergoing ERCP after less than 8 h sampling: The summary for standardized effect size of mean differences in serum amylase in 426 patients undergoing ERCP after less than 8 h sampling for antioxidants therapy for three included trials comparing to placebo[44,45] was -16.13 with 95%CI: -22.98-(-9.28) (P < 0.0001, Figure 6B). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous (P = 0.34) and could be combined, but because of few included trials, the random effects for individual and summary of effect size for standardized mean was applied. Publication bias for included studies for serum amylase in patients undergoing ERCP treated with antioxidants vs placebo therapy could not be evaluated because of too few strata.

Effect of antioxidants compared with placebo on serum amylase in patients undergoing ERCP after less than 24-h sampling: The summary for standardized effect size of mean differences in serum amylase in 426 patients undergoing ERCP after less than 24-h sampling for antioxidants therapy for two included trials comparing to placebo[44,45] was -16.13 with 95%CI: -22.98-(-9.28) (P < 0.0001, Figure 6B). The Cochrane Q test for heterogeneity indicated that the studies were not heterogeneous (P = 0.34) and could be combined, but because of few included trials, the random effects for individual and summary of effect size for standardized mean was applied. Publication bias for included studies for serum amylase in patients undergoing ERCP treated with antioxidants vs placebo therapy could not be evaluated because of too few strata.

DISCUSSION

Principal findings and comparison with other studies
We established that antioxidant therapy significantly shortens hospital stay in AP patients, however, time is needed for the best effects. In addition, we found no significant decrease in serum CRP (as a marker of inflammation) following antioxidant therapy after 5-7 d, while the CRP decreased after 10 d. In addition, our results do not support an ameliorative role of antioxidant supplements in the reduction of pain in CP. Although in this meta-analysis, we aimed to include as many patients as possible, only two trials were eligible and eleven trials (456 patients) were excluded. Therefore, further trials are required to provide more solid evidence. The findings from another study[51] were not consistent with ours.

For interventions focused on PEP, the use of antioxidant supplements resulted in no major clinical evidence (rate and severity of PEP) of efficacy, although a tendency to decrease the rate and severity of PEP was observed. These findings are supported by the results of previous meta-analyses[15,52,53]. Controversially, although we found no significant effect of antioxidant therapy in decreasing serum amylase in PEP patients after less than 8 h sampling, serum amylase after less than 24 h sampling was significantly reduced.

Strengths and limitations of this study
To best of our knowledge, this is the most comprehensive systematic review with meta-analysis on the effect of antioxidant therapy in the management of acute, chronic and post-ERCP pancreatitis. In order to avoid bias, a comprehensive search and data extraction were conducted, however, we reached the conclusion that existing trials have inevitable differences in the use of antioxidants or the study design. Furthermore, excluding languages other than
Conclusion and implications for clinical practice and future research

This meta-analysis suggests that antioxidant supplements are safe and effective in the treatment of AP, while their efficacy in CP and PEP was not confirmed. Although there are several safe and efficacious compounds that can control oxidative stress, yet antioxidant therapy has shown little success in inflammatory disorders such as pancreatitis. Lack of proper understanding of the pathological processes underlying pancreatitis may be the reason behind this failure. Evolving evidence suggests that, depending on the etiology of AP, CP or PEP, different underlying pathological processes might take part in these conditions. Most of these trials targeted AP or CP regardless of their etiology. Indeed, this meta-analysis indicated that antioxidant therapy exerts alleviating effects in the management of AP, but there is limited evidence supporting the efficacy of antioxidant therapy in PEP (as a particular type of AP). Thus, in order to progress in making antioxidant therapy a realistic goal, outcomes should be differentiated, based on their etiology.

Antioxidants, as with all drugs, have adverse events. Therefore, the complications of such compounds are yet to be specified, although they seem less theoretical than supposed.

Current advances in the field of antioxidant therapy should provide the impetus for more clinical trials. However, there is still a long way before such therapies are used in routine clinical use.

Figure 6 Individual and pooled effect size for standardized mean for the outcome. A: Of “serum amylase in patients undergoing ERCP after less than 8 h sampling” in the studies considering antioxidants comparing to Placebo therapy in 500 patients; B: Of “serum amylase of patients undergoing ERCP after less than 24 h sampling” in the studies considering antioxidants comparing to Placebo therapy in 426 patients. ERCP: Endoscopic retrograde cholangiopancreatography.
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COMMENTS

Background

Pancreatitis is an inflammatory, metabolic disorder, which is the major cause of physical and socioeconomic loss worldwide. Generally, pancreatitis is categorized into two different entities of acute and chronic. Antioxidant therapy has the potential to ameliorate clinical and laboratory outcomes of acute pancreatitis (AP), chronic pancreatitis (CP) and post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). Therefore, it is necessary to systematically evaluate the efficacy and adverse effects of antioxidant therapy in the management of different types of pancreatitis.

Research frontiers

This systematic review with meta-analyses seeks to critically appraise the beneficial and harmful effects of antioxidant supplements in the management of AP, CP and PEP. The study is focused on the key outcomes of pain, hospitalization, C reactive protein (CRP) and serum amylase in CP or AP, and severity and rate of PEP.

Innovations and breakthroughs

Antioxidant therapy reduces the length of hospital stay in AP patients. Although antioxidant therapy has no significant effect on serum amylase after less than 8-h sampling, it significantly reduces serum amylase after 24-h sampling. Antioxidant therapy has no significant effect on serum CRP after 5-7 d sampling, but significantly reduces serum CRP after 10-d sampling. Future studies should focus on key outcomes of the disease dependent on the type of antioxidant.

Applications

This meta-analysis confirmed the efficacy of antioxidant therapy in the management of AP.

Peer-review

This is an interesting meta-analysis on the role of antioxidant therapy in the management of AP, PEP and CP. The manuscript is well-written and the conclusions of the study are acceptable.

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