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EDITORIAL

Antioxidant therapy in the management of acute, chronic and post-ERCP pancreatitis: A systematic review

Seyed Sajad Mohseni Salehi Monfared, Hamed Vahidi, Amir Hossein Abdolghaffari, Shekoufeh Nikfar, Mohammad Abdollahi

Seyed Sajad Mohseni Salehi Monfared, Endocrinology and Metabolism Research Centre, Tehran University of Medical Sciences, Tehran 1411413137, Iran
Hamed Vahidi, Student Scientific Research Center, Tehran University of Medical Science, Tehran 1417614411, Iran
Amir Hossein Abdolghaffari, Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran 1417614411, Iran
Shekoufeh Nikfar, Food & Drug Affairs and Food & Drug Laboratory Research Center, Ministry of Health & Medical Education, Tehran 1314715311, Iran
Mohammad Abdollahi, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, and Endocrinology & Metabolism Research Centre, Tehran University of Medical Sciences, Tehran 1417614411, Iran
Author contributions: Mohseni Salehi Monfared SS reviewed the data and drafted the manuscript; Vahidi H carried out the bibliography and collected the data; Abdolghaffari AH collected the data and prepared tables; Nikfar S conducted the meta-analysis, reviewed the data and the manuscript; Abdollahi M supervised the entire study and edited the manuscript.
Correspondence to: Mohammad Abdollahi, Professor, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, and Endocrinology & Metabolism Research Centre, Tehran University of Medical Sciences, Tehran 1417614411, Iran. mohammad@tums.ac.ir
Telephone: +98-21-66959104 Fax: +98-21-66959104
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Abstract

We systematically reviewed the clinical trials which recruited antioxidants in the therapy of pancreatitis and evaluated whether antioxidants improve the outcome of patients with pancreatitis. Electronic bibliographic databases were searched for any studies which investigated the use of antioxidants in the management of acute pancreatitis (AP) or chronic pancreatitis (CP) and in the prevention of post-endoscopic retrograde cholangio-pancreatography (post-ERCP) pancreatitis (PEP) up to February 2009. Twenty-two randomized, placebo-controlled, clinical trials met our criteria and were included in the review. Except for a cocktail of antioxidants which showed improvement in outcomes in three different clinical trials, the results of the administration of other antioxidants in both AP and CP clinical trials were incongruent and heterogeneous. Furthermore, antioxidant therapy including allopurinol and N-acetylcysteine failed to prevent the onset of PEP in almost all trials. In conclusion, the present data do not support a benefit of antioxidant therapy alone or in combination with conventional therapy in the management of AP, CP or PEP. Further double blind, randomized, placebo-controlled clinical trials with large sample size need to be conducted.

Key words: Antioxidant; Post-endoscopic retrograde cholangio-pancreatography pancreatitis; Oxidative stress; Therapy; Acute pancreatitis; Chronic pancreatitis

Peer reviewer: Dr. Peter Draganov, Division Gastroenterology, Hepatology and Nutrition, University of Florida, Gainesville, 1600 SW Archer Road, PO Box 100214, Florida 32610, United States

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INTRODUCTION

Pancreatitis, both chronic and acute, contributes to thousands of annual hospital admissions and consecutive complications[1]. Acute pancreatitis (AP), an acute inflammatory condition, is thought to be due to activation of enzymes in the pancreatic acinar cells, with inflammation spreading into the surrounding tissues[2]. Patients with AP were either treated with strict bowel rest or given parenteral nutrition to allow the pancreas to rest until the serum enzyme levels returned to normal[3]. Chronic pancreatitis (CP) is a progressive inflammatory disorder that is characterized by recurrent episodes of severe abdominal pain. Affected patients typically suffer years of disabling pain, and conventional therapeutic interventions are often unable to offer satisfactory analgesia[4].

Oxidative stress caused by short lived intracellular reactive oxygen and nitrogen species, can oxidize lipids in the cell membrane, proteins, depolarize the mitochondrial

membrane, and induce DNA fragmentation. Active free radicals in the body can be produced during diseases or exposure to xenobiotics[5,6].

Basic and clinical evidence suggests that the pathogenesis of both AP and CP can be associated with oxidative stress seeming independent of the etiology of pancreatitis, because oxidative stress is observed in different experimental pancreatitis models[7,8]. Findings show that free radical activity and oxidative stress indices such as lipid peroxide levels are higher in the blood and duodenal juice of patients with AP or CP[9,10].

Based on the mentioned findings, the idea of using antioxidant regimens in the management of both AP and CP as a supplement and complementary in combination with its traditional therapy is rational and reasonable. As a result of this hypothesis, antioxidant therapy should improve the inflammatory process that is involved in pancreatitis and therefore ameliorate the recovery rate.

In addition, pancreatitis is the most common serious complication of endoscopic retrograde cholangiopancreatography (ERCP), occurring in 1%-7% of cases[11]. Although, the exact mechanisms involved in the pathophysiology of post-ERCP pancreatitis (PEP) are not clear, the role of oxidative stress cannot be neglected. Therefore, the use of antioxidants before, during or after this intervention has already been studied in a few clinical trials[12,13]. Although some clinical trials have proved the benefits of using various antioxidants in AP or CP, there are still controversies[14].

To our knowledge, there is no definite consensus on the benefits of antioxidant therapy in the management of AP or CP. Our objective was to systematically review and summarize the literature on antioxidant therapies for AP and CP as well as PEP, to provide recommendations for future research.

METHODS

PubMed, Scopus, Google Scholar, Cochrane library database, and Evidence based medicine reviews were searched for any relevant studies that investigated the use of antioxidants in the management of AP or CP and in the prevention of PEP up to February 2009. We also hand-searched references in key articles. The search terms were: AP or CP, pancreatic inflammation, antioxidant, vitamin, superoxide dismutase, manganese, glutamine, butylated hydroxyanisole, taurine, glutathione, curcumin, catalase, peroxidase, lutein, xanthophylls, zeaxanthin, selenium, riboflavin, zinc, carotenoid, cobalamin, retinol, alpha-tocopherol, ascorbic acid, beta-carotene, carotene and all MeSH terms for pharmacologically active antioxidants. Studies were limited to clinical trials and those written in the English language.

To assess the quality of clinical trials, we employed the Jadad score, a previously validated instrument that assesses trials based on appropriate randomization, blinding, and description of study withdrawals or dropouts[15]. 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); (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 $\leqslant 2$ and a high-quality report score is at least 3.

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 which used 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[16] to changes in plasma cytokines, were included.

Data from selected studies were extracted in the form of 2×2 tables. All included studies were weighted and pooled. The data were analyzed using Statsdirect (2.7.3). Relative risk (RR) and 95% confidence intervals (95% CI) were calculated using the Mantel-Haenszel and DerSimonian-Laird methods. The Cochran Q test was used to test heterogeneity. The event rate in the experimental (intervention) group against the event rate in the control group was calculated using L'Abbe plot as an aid to explore the heterogeneity of effect estimates. Funnel plot analysis was used as a publication bias indicator.

RESULTS AND DISCUSSION

A total of 211 potentially relevant papers were identified, of which 22 papers were eligible[4,16-36]. Amongst the 22 papers, 19 (86%) scored 3 and only three studies[17,25,31] scored 2 or lower according to the Jadad score. Table 1 presents controlled clinical trials of antioxidants in patients with AP or CP. Trials that used antioxidants to prevent PEP are summarized in Table 2. To perform a meta-analysis we included only four studies in which allopurinol was used in PEP.

Antioxidants in AP and CP

Glutamine: Glutamine is the most abundant amino acid both in plasma and in the intracellular free amino acid pool. It is essential for a wide variety of physiologic processes, in particular, the growth and function of immune cells including lymphocytes and macrophages[17]. Glutamine is normally synthesized *de novo* by a number of cells and therefore is not an essential amino acid. Although glutamine is an antioxidant, in conditions of excess glutamine utilization such as sepsis, trauma, major surgery or severe AP, endogenous glutamine production may not be adequate and glutamine depletion occurs[23].

In four studies[17,18,22,23] glutamine was supplemented to standard total parenteral nutrition (TPN) in AP patients. In one randomized controlled study (n = 28), glutamine was used in AP in combination with standard TPN and demonstrated a decrease in the duration of TPN therapy and hospitalization without a change in the total

Table 1 Controlled clinical trials of antioxidants in patients with acute or chronic pancreatitis

Study/ Ref.	Drug/supplements	Study design	Jadad score	Participants	Treatment (intervention)		Outcome (results)		Adverse effects/events
					Case	Control	Clinical	Laboratory	
Bhardwaj *et al*[16] 2009	Combined antioxidant (organic selenium, vitamin C, β-carotene, α-tocopherol and methionine)	Randomized; double blind; placebo-controlled	5	147 patients with CP	71 patients; combined antioxidants: 600 μg organic selenium, 0.54 g ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol and 2 g methionine; per day; for 6 mo	76 patients; placebo	Number of painful days per month[2] Numbers of oral analgesic tablets and parenteral analgesic injections per month[2] Hospitalization[2] Percentage of patients become pain-free[2] Number of man-days lost per month[2]	Lipid peroxidation (TBARS)[2] Serum SOD[2] Total antioxidant capacity (FRAP)[1] Serum vitamin A[1] Serum vitamin C[1] Serum vitamin E[1] Erythrocyte superoxide dismutase[2]	Headache & constipation (all during the first month of treatment)
Xue *et al*[17] 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)	38 patients; 100 mL/d of 20% AGD intravenous infusion/for 10 d starting on the day 5 (Late treatment)	Infection rate[2] Operation rate[2] Mortality[2] Hospitalization[2] Duration of ARDS[2] Renal failure[2] Acute hepatitis[2] Encephalopathy[2] Enteroparalysis[2] Duration of shock[2] 15-d APACHE Ⅱ core[2]		-
Fuentes-Orozco *et al*[18] 2008	Glutamine	Randomized; double blind; controlled	4	44 patients with AP	22 patients; 0.4 g/kg per day of L-alanyl-L-Glutamine in standard TPN; 10 d	22 patients; standard TPN; 10 d	Infectious morbidity[2] Hospital stay day[3] Mortality[3]	Serum IL-10[1] Serum IL-6[2] CRP[2] Ig A[1] Protein[1] Albumin[1] Leucocyte[2] Total lymphocyte[1] Nitrogen balance was (+) in treated group *vs* (-) in control group	-
Siriwardena *et al*[19] 2007	Combined antioxidant (N-acetylcysteine, selenium, vitamin C)	Randomized; double blind; placebo-controlled	5	43 patients with severe AP	22 patients; N-acetylcysteine, selenium and vitamin C; for 7 d	21 patients; placebo	Organ dysfunction[3] APACHE-Ⅱ[3] Hospitalization[3] All case mortality[3]	Serum vitamin C[3] Serum selenium[3] GSH/GSSG ratio[3] CRP[3]	-
Kirk *et al*[4] 2006	Combined antioxidant (selenium, β-carotene, L-methionine, vitamins C and E)	Randomized; double-blind; placebo-controlled; crossover	4	36 patients with CP	36 patients; Antox tablet: 75 mg of selenium, 3 mg β-carotene, 47 mg vitamin E, 150 mg vitamin C, and 400 mg methionon; four times per day; for 10 wk	36 patients; placebo; four times per day; for 10 wk	Quality of life[1] Pain[2] Physical and social functioning[1] Health perception[1] Emotional functioning, energy, mental health[3]	Plasma selenium[1] Plasma vitamin C[1] Plasma vitamin E[1] Plasma β-carotene[1]	Two patients complained of nausea and one of an unpleasant taste during treatment with Antox
Durgaprasad *et al*[20] 2005	Curcumin	Randomized; single blind; placebo-controlled	3	20 patients of tropical pancreatitis (CP)	Eight patients; capsule: 500 mg curcumin (95%) with 5 mg of piperine; three times per day; for 6 wk	Seven patients; placebo (lactose)	Pain[3]	Erythrocyte MDA[2] GSH level[3]	-

Du *et al*[21] 2003	Vitamin C	Randomized; controlled	3	84 patients with AP	40 patients; IV vitamin C; 10 g/d; for 5 d	44 patients; IV vitamin C; 1 g/d; for 5 d	Hospitalization[2] Deterioration of disease[2] Improvement of disease[1] Cure rate[1]	Tnf-α[2] IL-1[2] IL-8[2] CRP[2] Serum interleukin-2 receptor[2] Plasma vitamin C[1] Plasma lipideroxide[1] Plasma vitamin E[1] Plasma β-carotene[1] Whole blood glutathione[1] Activity of erythrocyte superoxide dismutase[1] Erythrocyte catalase[1]	-
Ockenga *et al*[22] 2002	Glutamine	Randomized, double blind; controlled	4	28 patients with AP	Standard TPN which contains 0.3 g/kg per day L-alanine-L-glutamine; at least 1 wk	Standard TPN	Hospitalization[2] Duration of TPN[2] Cost of TPN[3]	Cholinesterase[1] Albumin[1] lymphocyte count[1] CRP[2]	-
de Beaux *et al*[23] 1998	Glutamine	Randomized; double-blind; controlled	5	14 patients with AP	Six patients; 0.22 g/kg per day of glycyl-glutamine in standard TPN; for 7 d	Seven patients; standard TPN	-	Lymphocytic proliferation (by DNA synthesis)[1] TNF[3] IL-6[3] IL-8[2]	-
Banks *et al*[24] 1997	Allopurinol	Randomized, double-blind, two-period crossover clinical trial	4	13 patients with CP	13 patients; 300 mg/d allopurinol; 4 wk	13 patients; placebo	Pain[3]	Uric acid level[2]	-
Sharer *et al*[25] 1995	Glutathione precursors (S-adenosyl methionine and N-acetylcysteine)	Randomized	-	79 patients with AP	SAMe 43 mg/kg and N-acetylcysteine 300 mg/kg	-	APACHE Ⅱ score reduction[3] Complication rate[3] Days in hospital[3] Mortality[3]	-	-
Bilton *et al*[26] 1994	S-adenosyl methionine (SAMe)	Randomized; double-blind; crossover; placebo-controlled	5	20 patients with AP or CP	20 patients; SAMe 2.4g/d; 10 wk	Placebo	Attack rate and background pain[3]	Free radical activity[2] Serum selenium[2] Serum β-carotene[2] Serum vitamin E[2,3] Serum vitamin C[2] Serum SAMe[1]	-
	Selenium and β-carotene + SAMe				20 patients; SAMe 2.4 g/d, Selenium 600 μg and β-carotene 9000 IU; 10 wk			Free radical activity[2] Serum selenium[2] Serum β-carotene[1] Serum vitamin E[1,3] Serum vitamin C[2] Serum SAMe[1]	
Salim[27] 1991	Allopurinol; dimethyl sulfoxide	Randomized; double-blind; placebo-controlled	4	78 patients with CP	25 patients; allopurinol; 50 mg four times per day, with analgesic regimen (IM pethidine hydrochloride; 50 mg every 4 h, and IM metoclopramide hydrochloride; 10 mg every 8 h)	27 patients; placebo with analgesic regimen	Pain[2] Hospitalization[2] Epigastric tenderness[2]	WBC count[2] Serum amylase[2] Serum LDH[2]	Allergies General malaise Headache Nausea Vomiting Dyspepsia Abdominal pain

Uden *et al*[28,29] 1992, 1990	Combined antioxidant (selenium, β-carotene, vitamin C, vitamin E, methionine)	Randomized; double-blind; crossover; placebo-controlled	5	28 patients with CP	26 patients; dimethyl sulfoxide; 500 mg four times per day; with analgesic regimen 23 patients; daily doses of 600 mg organic selenium, 9000 IU β-carotene, 0.54 g vitamin C, 270 IU vitamin E and 2 g methionine; 10 wk	23 patients; placebo	Pain[2]	Free radical activity[2] Serum selenium[1] Serum β-carotene[1] Serum vitamin E[1] Serum SAMe[2]	-

[1]Significant increase as compared with control; [2]Significant decrease as compared with control; [3]No significant difference between groups. 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; TNF-α: Tumor necrosis factor-α; IL: Interleukin.

Table 2 Controlled clinical trials of antioxidant therapy to prevent post-ERCP pancreatitis

Ref.	Drug/ supplements	Study design	Jadad score	*n*	Treatment (intervention)		Outcome (results)		Adverse effects/events	Other comments
					Case	Control	Primary	Other		
Romagnuolo *et al*[30] 2008	Allopurinol	Randomized; double blind; placebo-controlled	4	586	293 patients; 300 mg oral allopurinol 60 min before ERCP	293 patients; placebo	Rate of PEP[3] (5.5% *vs* 4.1%)	Disease-related adverse events[3] Procedure-related complications[3] Hospitalization[3]	-	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
Milewski *et al*[31] 2006	N-acetylcysteine	Randomized; placebo-controlled	2	106	55 patients; 600 mg oral N-acetylcysteine 24 and 12 h before ERCP and 1200 mg IV for 2 d after the ERCP	51 patients; isotonic IV saline twice for 2 d after the ERCP	Rate of PEP[3] (7.3% *vs* 11.8%)	Urine amylase activity[3] Serum amylase activity[3]	-	-
Katsinelos *et al*[32] 2005	Allopurinol	Randomized; double blind; placebo-controlled	4	250	125 patients; 600 mg oral allopurinol 15 and 3 h before ERCP	118 patients; placebo	Rate of PEP[2] (3.2% *vs* 17.8%)	Hospitalization[2] Severity of pancreatitis[2]	-	-
Katsinelos *et al*[33] 2005	N-acetylcysteine	Randomized; double-blind; placebo-controlled	3	256	124 patients; 70 mg/kg 2 h before and 35 mg/kg at 4 h intervals for a total of 24 h after the procedure	125 patients; placebo (normal saline solution)	Rate of PEP[3] Hospitalization[3]	-	Nausea; skin rash; diarrhea; vomiting	-
Mosler *et al*[34] 2005	Allopurinol	Randomized; double blind; placebo- controlled	4	701	355 patients; 600 mg 4 h and 300 mg 1 h oral allopurinol before ERCP	346 patients; placebo	Rate of PEP[3] (13.0% *vs* 12.1%)	Severity of pancreatitis[3]	-	-
Lavy *et al*[35] 2004	Natural β-carotene	Randomized; double-blind; placebo-controlled	5	321	141 patients; 2 g oral β-carotene 12 h before ERCP	180 patients; placebo	Rate of PEP[3] (10% *vs* 9.4%)	Severe pancreatitis[2]	-	-
Budzyńska *et al*[36] 2001	Allopurinol	Randomized; placebo-controlled	3	300	99 patients; 200 mg oral allopurinol 15 and 3 h before ERCP	101 patients; placebo	Rate of PEP[3] (12.1% *vs* 7.9%)	Severity of pancreatitis[3]	-	-

[1]Significant increase as compared with control; [2]Significant decrease as compared with control; [3]No significant difference between groups. PEP: Post endoscopic pancreatitis.

cost of parenteral feeding[22]. Another similar study (n = 44) showed that even though TPN therapy containing glutamine reduces infectious morbidity, it has no significant effect on hospitalization and total mortality[18]. However, both studies showed laboratory improvement in AP after administration of glutamine such as an increase in serum albumin or decrease in C-reaction protein (CRP).

Proinflammatory cytokine release was assessed in another study with a small patient number (n = 14). Glutamine supplementation did not significantly influence tumor necrosis factor-α or interleukin (IL)-6 release, but, in contrast, median IL-8 release was reduced by day 7 in the glutamine group while it was increased in the conventional group[23]. Another non-blinded study examined the administration of glutamine in AP for 10 d starting either on the day of admission or 5 d after admission. Investigators reported an improvement in all clinical findings including hospitalization, infection, and mortality rate[17]. No adverse effects were reported in these trials.

Allopurinol: Allopurinol, a xanthine oxidase inhibitor that historically has been effective in preventing attacks of acute gouty arthritis, is an effective anti-oxidant with anti-apoptotic effects. It has been shown that allopurinol is a hydroxyl radical scavenger[37,38]. Two studies used allopurinol to reduce chronic pain in CP[24,27]. In one clinical trial (n = 78), CP patients with chronic pain were admitted to hospital and received an analgesic regimen of pethidine with or without allopurinol. Their results showed that allopurinol could reduce pain and gastric tenderness. Hospitalization was also decreased in allopurinol-treated patients[27]. Another clinical study (n = 13) showed that 4 wk of allopurinol administration did not reduce pain in CP when compared with placebo[24]. Allergy, general malaise, and gastrointestinal disturbances were adverse events of allopurinol.

Vitamin C: Ascorbic acid or vitamin C is a monosaccharide antioxidant. This water-soluble vitamin is a reducing agent and can neutralize oxygen species. Vitamin C is an important antioxidant which protects the body from damage caused by inflammation, and high-dose vitamin C can improve immune function[21]. Vitamin C alone was only investigated in one study and other studies used vitamin C in combination with other antioxidants which will be discussed later. In one randomized study (n = 83), 10 g/d of vitamin C was used intravenously compared to 1 g/d of vitamin C in the control group for 5 d in patients with AP. Their results indicated that 10 g vitamin C decreases hospitalization and duration of disease, and increases the cure rate. Proinflammatory cytokines and CRP were also diminished by vitamin C administration[21].

Combined antioxidants (selenium, β-carotene, vitamin C, vitamin E and methionine): A combination of various antioxidants including selenium, β-carotene, vitamin C, vitamin E, and methionine was studied in three controlled clinical trials[4,16,28]. In the first clinical trial, the efficacy of antioxidant therapy in the management of pancreatitis was determined using the above combination in CP patients (n = 28). Their results showed that this cocktail can reduce the pain which is experienced by patients[28]. Another study with a slightly larger sample size (n = 36) used the above combination at the same doses but with greater bioavailability in CP patients. In this trial, congruent with the previous trial, pain was reduced after 10 wk of the combined antioxidants. Indeed, quality of life, physical and social functioning, and health perception were also enhanced as a result of antioxidant therapy[4]. The latest published controlled clinical trial in the field of antioxidants and pancreatitis has also used this combination at the same doses as the previous studies. In this larger clinical trial (n = 147), the antioxidants were administered for 6 mo, and showed that, similar to the two preceding trials, pain and hospitalization were reduced[16]. All three studies showed that serum concentrations of the above-mentioned antioxidants were higher after a period of intake and laboratory indices of oxidative stress markers such as lipid peroxidation, free radical activity, and total antioxidant capacity improved after therapy. Another cohort study which is not presented in Table 1 examined this combination of antioxidants in 12 CP patients and showed that this combination reduces pain and hospitalization[39]. Headache, nausea, vomiting, and constipation were some of the adverse effects of this combination. A clinical trial studied the effect of selenium, vitamin C and N-acetylcysteine (NAC) combination for 7 d in 43 AP patients. All primary endpoints including hospitalization, Acute Physiology and Chronic Health Evaluation Ⅱ score, and organ dysfunction were statistically similar between the placebo and antioxidant-treated groups[19].

Curcumin: Curcumin is a polyphenolic compound commonly found in the dietary spice turmeric[40]. Curcumin is an inhibitor of nuclear factor-κB and has various biological activities such as anti-inflammatory, antioxidant, antiseptic, and anticancer activity[41]. In the one available pilot study (n = 20), patients with CP received 500 mg of curcumin with 5 mg of piperine or placebo for 6 wk. There was a significant reduction in erythrocyte malondialdehyde levels following curcumin therapy when compared with placebo. A significant increase in glutathione (GSH) levels was also observed. There was no corresponding improvement in pain and no adverse effects were reported[20].

Glutathione precursors [S-adenosyl methionine (SAMe)]: SAMe, a highly bioactive metabolite of methionine is a precursor of glutathione, which is the key defense against reactive species. Of the two clinical trials that examined SAMe in pancreatitis, in one, SAMe was administered to AP patients[25] and in the other, SAMe was administered to CP patients[26]. SAMe did not enhance the clinical outcomes in either AP or CP patients. However, laboratory indices such as free radical activity were better after 10 wk of SAMe administration

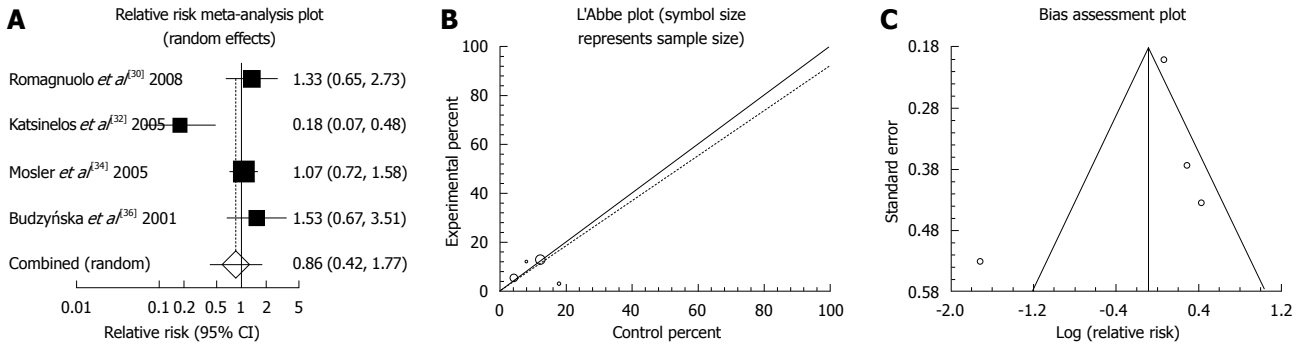

Figure 1 Individual and pooled relative risk (A), heterogeneity indicators (B), and publication bias indicators (C) for the outcome "prevention of all kinds of pancreatitis" in the studies considering allopurinol *vs* placebo therapy.

in CP patients. Methionine in combination with other antioxidants was discussed previously under the topic of combined antioxidants.

Antioxidants in PEP

NAC: NAC is a free radical scavenger capable of stimulating glutathione synthesis. NAC was used in two clinical trials. In one of these trial (n = 106), 600 mg NAC was given orally 24 h and 12 h before ERCP and 600 mg was given intravenously, twice a day for 2 d after ERCP. Their results showed that the rate of PEP was not significantly reduced. In addition, urine amylase activity, total bilirubin, alanine, aspartate aminotransferases and white blood cells showed no change[31].

In the other double-blind, placebo-controlled trial (n = 256), patients received intravenous NAC at a loading dose of 70 mg/kg 2 h before and 35 mg/kg at 4-h intervals for a total of 24 h after the procedure. Similar to the previous study, there were no statistical differences in the incidence or severity of PEP grades between the groups. The mean duration of hospitalization for pancreatitis was not different in the NAC group as compared to the placebo group[33]. The results of those studies showed the absence of any beneficial effect of NAC on the incidence and the severity of ERCP-induced pancreatitis.

Natural β-Carotene: β-carotene is a natural antioxidant which has been used as a supplement in various conditions. In a double-blind trial, 321 patients were given a single dose of natural β-carotene, 12 h prior to the procedure, and monitored for procedure complications, antioxidant levels, and plasma oxidation for 24 h post-procedure. The overall incidence of AP was not significantly different between the β-carotene and the placebo groups. The rate of severe pancreatitis was lower in the β-carotene-treated group. No reduction in the incidence of PEP was reported but there may be some protective effect of treatment with β-carotene regarding the severity of disease. Adverse events were not reported[35].

Allopurinol: There were four randomized clinical trials which used allopurinol orally before ERCP to prevent PEP (Table 3). These studies were meta-analyzed for their primary PEP outcome. The summary RR for "prevention of all kinds of pancreatitis" in the four trials[30,32,34,36] was 0.86 with a 95% CI of 0.42-1.77 and a non-significant RR (P = 0.6801, Figure 1A). The Cochrane Q test for heterogeneity indicated that the studies were heterogenous (P = 0.0062, Figure 1B) and could not be combined. Thus the random effect for individual and the summary of RR was applied. Regression of normalized effect *vs* precision for all included studies for clinical response among allopurinol *vs* placebo therapy was -1.961983 (95% CI: -14.671469 to 10.747502, P = 0.5749), and Kendall's test on standardized effect *vs* variance indicated tau = 0, P = 0.75 (Figure 1C). The summary RR for "prevention of mild pancreatitis" in three trials[30,32,36] was 1.08 with a 95% CI of 0.7-1.67, a non-significant RR (P = 0.7238, Figure 2A). The Cochrane Q test for heterogeneity indicated that the studies were homogenous (P = 0.2255, Figure 2B) and could be combined. Thus the fixed effect for individual and the summary of RR was applied. Regression of normalized effect *vs* precision for all included studies for clinical response among allopurinol *vs* placebo therapy could not be calculated because of too few strata. The summary RR for "prevention of moderate pancreatitis" in the three trials[30,32,36] was 0.655 with a 95% CI of 0.388-1.105 and a non-significant RR (P = 0.113, Figure 3A). The Cochrane Q test for heterogeneity indicated that the studies were homogenous (P = 0.0614, Figure 3B) and could be combined. Thus the random effect for individual and the summary of RR was applied. Regression of normalized effect *vs* precision for all included studies for clinical response among allopurinol *vs* placebo therapy could not be calculated because of too few strata.

Table 3 Studies evaluating post-ERCP pancreatitis after allopurinol administration

Study	Allopurinol	Placebo
Romagnuolo *et al*[30] 2008	16/293	12/293
Katsinelos *et al*[32] 2005	4/121	21/118
Mosler *et al*[34] 2005	46/355	42/346
Budzyńska *et al*[36] 2001	12/99	8/101

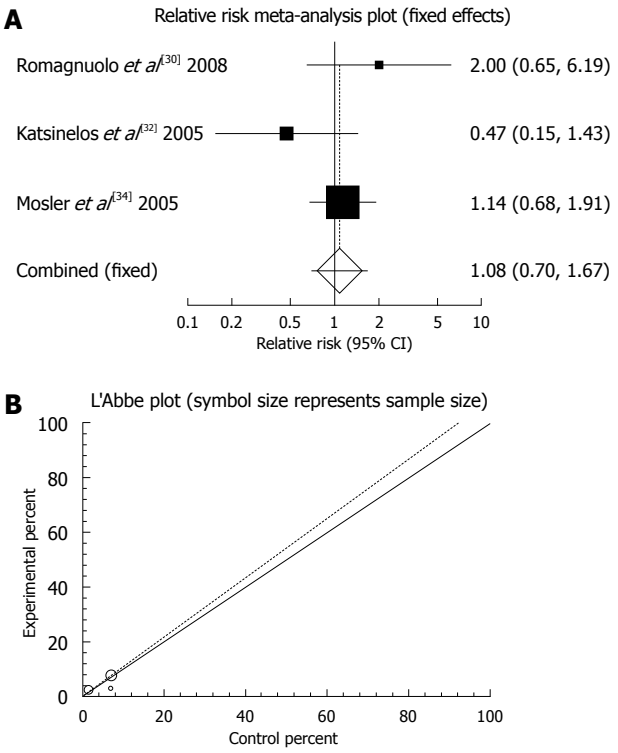

Figure 2 Individual and pooled relative risk (A) and heterogeneity indicators (B) for the outcome "prevention of all kinds of pancreatitis" in the studies considering allopurinol *vs* placebo therapy.

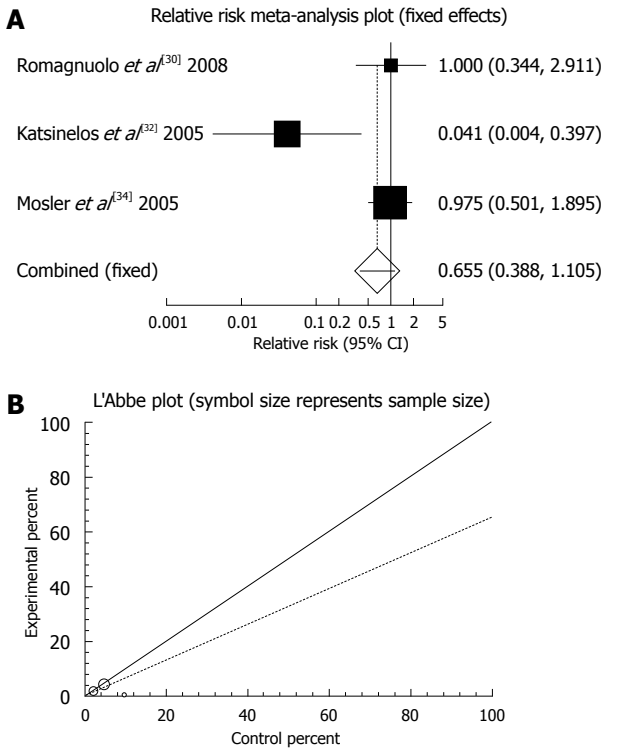

Figure 3 Individual and pooled relative risk (A) and heterogeneity indicators (B) for the outcome "prevention of moderate pancreatitis" in the studies considering allopurinol *vs* placebo therapy.

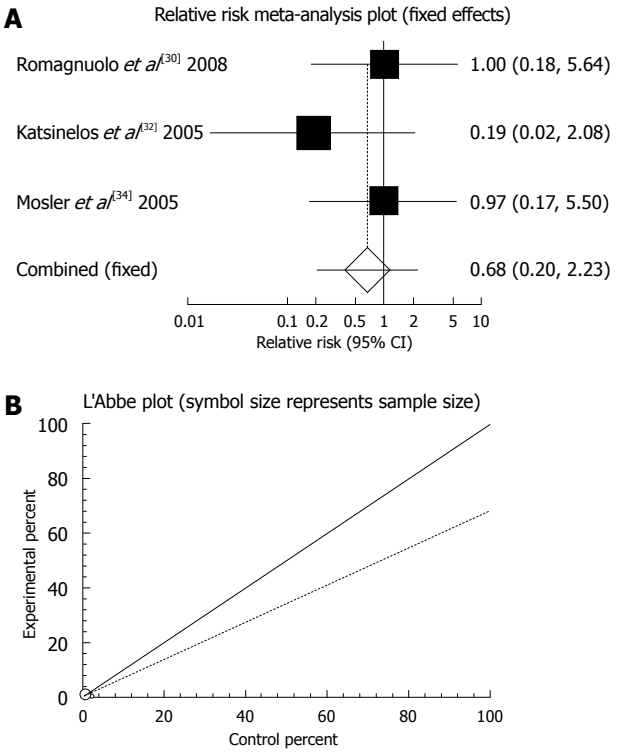

Figure 4 Individual and pooled relative risk (A) and heterogeneity indicators (B) for the outcome "prevention of severe pancreatitis" in the studies considering allopurinol *vs* placebo therapy.

The summary RR for "prevention of severe pancreatitis" of allopurinol *vs* placebo therapy among the three trials[30,32,36] was 0.68 with a 95% CI of 0.2-2.23, indicating a non-significant RR for allopurinol administration ($P = 0.5206$, Figure 4A). The Cochrane Q test for heterogeneity indicated that the studies were not significantly heterogeneous ($P = 0.6154$, Figure 4B) and the fixed effects for individual and the summary of RR was applied. Regression of normalized effect *vs* precision for all included studies for any adverse events among allopurinol *vs* placebo therapy could not be calculated because of too few strata.

Oxygen radicals play an essential role in the development of inflammation in various conditions[42-50]. The involvement of free radicals in the pathogenesis of pancreatitis has been shown in both animal and human studies[51]. Oxidative stress expedites mechanisms which lead to cell damage. It can directly destruct the cell membrane, accelerate lipid peroxidation, deplete cell reserves of antioxidants, and change signaling pathways inside the cells[52,53].

Although the pathophysiology of pancreatitis has been studied before, there is no specific therapy for this disastrous disease yet. Enteral or parenteral nutrition, antibiotic therapy, surgical procedures such as removal of abscess and necrosis, and cholecystectomy have been developed to treat AP[14]. In CP, pain management and probably surgical resection of pseudocysts are the goals of treatment. Because these treatments do not target the main problem and are recommended for symptoms and complications, investigators are still looking for new effective approaches in combination with current treatment.

Clinical studies of the evaluation of typical antioxidants on AP and CP were performed firstly at Man-

chester Royal Infirmary by Braganza and her colleagues. Two placebo controlled clinical trials[28,29] examining combined antioxidant therapy on recurrent CP showed a significant decrease in pain and an elevation in serum antioxidant biomarkers; however, in one study in which SAMe was examined as an antioxidant, alone or in combination with selenium and β-carotene, the results showed that SAMe was ineffective in patients with recurrent pancreatitis. Another two recently published clinical trials[4,16], particularly the latter study with a larger number of subjects (147), which used the same cocktail of antioxidants also showed pain reduction after administration. Therefore, the results of these studies show that such a combination of antioxidants could have a positive effect in the treatment of CP. However, we were unable to meta-analyze these three studies for pain as the primary outcome because pain reduction was assessed in a different way in each study. Except for the mentioned antioxidant cocktail, results of the administration of other antioxidants in both AP and CP clinical trials were incongruent and heterogeneous; and we cannot draw a definite conclusion on the efficacy of such therapy in the management of pancreatitis. We also evaluated the effect of etiology of pancreatitis including alcoholic, gallstone or idiopathic on the results of pain reduction and other outcomes, however, there was no relation between the cause of pancreatitis and clinical outcomes.

Furthermore, antioxidant therapy failed to prevent the onset of PEP in almost all trials (Table 2). Only one clinical trial in which 600 mg of allopurinol was administered twice before ERCP showed a significant decrease in the rate of PEP. However, our meta-analysis revealed that the RR for "prevention of mild, moderate and severe pancreatitis" of allopurinol *vs* placebo therapy was non-significant for allopurinol administration.

However, the present review indicates that there is insufficient data to support using antioxidants alone or in combination with conventional therapy in the management of AP, CP or PEP. Further double blind, randomized, placebo-controlled clinical trials with a larger sample size need to be conducted.

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