World Journal of Gastroenterology

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DOI: 10.3748/wjg.v21.i30.9189

World J Gastroenterol 2015 August 14; 21(30): 9189-9208
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

META-ANALYSIS

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

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Conflict-of-interest statement: The authors declared no conflict-of-interest.

Data sharing statement: No additional data available.

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Received: March 12, 2015
Peer-review started: March 13, 2015
First decision: March 26, 2015
Revised: April 15, 2015
Accepted: June 15, 2015
Article in press: June 16, 2015
Published online: August 14, 2015

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

eligible for inclusion. Antioxidant therapy significantly reduced the length of hospital stay in AP patients {mean difference -2.59 d (95%CI: -4.25-(-0.93)], P = 0.002}. Although, antioxidant therapy had no significant effect on serum C reactive protein (CRP) after 5-7 d in AP patients [mean difference -9.57 (95%CI: -40.61-21.48, P = 0.55], it significantly reduced serum CRP after 10 d {mean difference -45.16 [95%CI: -89.99-(-0.33)], P = 0.048}. In addition, antioxidant therapy had no significant effect on CP-induced pain [mean difference -2.13 (95%CI: -5.87-1.6), P = 0.26]. Antioxidant therapy had no significant effects on the incidence of all types of PEP [mean difference 1.05 (95%CI: 0.74-1.5), P = 0.78], severe PEP [mean difference 0.92 (95%CI: 0.43-1.97), P = 0.83], moderate PEP [mean difference 0.82 (95%CI: 0.54-1.23), P = 0.33], and mild PEP [mean difference 1.33 (95%CI: 0.99-1.78), P = 0.06]. Furthermore, while antioxidant therapy had no significant effect on serum amylase after less than 8 h sampling [mean difference -20.61 (95%CI: -143.61-102.39), P = 0.74], it significantly reduced serum amylase close to 24-h sampling {mean difference -16.13 [95%CI: -22.98-(-9.28)], P < 0.0001}.

CONCLUSION: While there is some evidence to support antioxidant therapy in AP, its effect on CP and PEP is still controversial.

Key words: Acute pancreatitis; Chronic pancreatitis; Post-endoscopic retrograde cholangiopancreatography pancreatitis; Antioxidants; Meta-analysis

Core tip: Antioxidant therapy reduces the length of hospital stay in acute pancreatitis patients. Although antioxidant therapy shows 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 C reactive protein (CRP) after 5-7 d sampling, but significantly reduces serum CRP after 10 d sampling. Evidence to support the efficacy of antioxidant therapy in the management of chronic pancreatitis and post-endoscopic retrograde cholangiopancreatography pancreatitis is limited. Further trials should be based on etiology-differentiated designs.

Gooshe M, Abdolghaffari AH, Nikfar S, Mahdaviani P, Abdollahi M. Antioxidant therapy in acute, chronic and post-endoscopic retrograde cholangiopancreatography pancreatitis: An updated systematic review and meta-analysis. *World J Gastroenterol* 2015; 21(30): 9189-9208 Available from: URL: http://www.wjgnet.com/1007-9327/full/v21/i30/9189.htm DOI: http://dx.doi.org/10.3748/wjg.v21.i30.9189

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[5].

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[8]. CP can eventually give rise to several complications that should be treated accordingly. Principally, the only observable symptom in chronic pancreatitis is pain[9].

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, zeaxanthin, 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[16]. The quality scale ranges 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 $\leqslant$ 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 Mulrow-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].

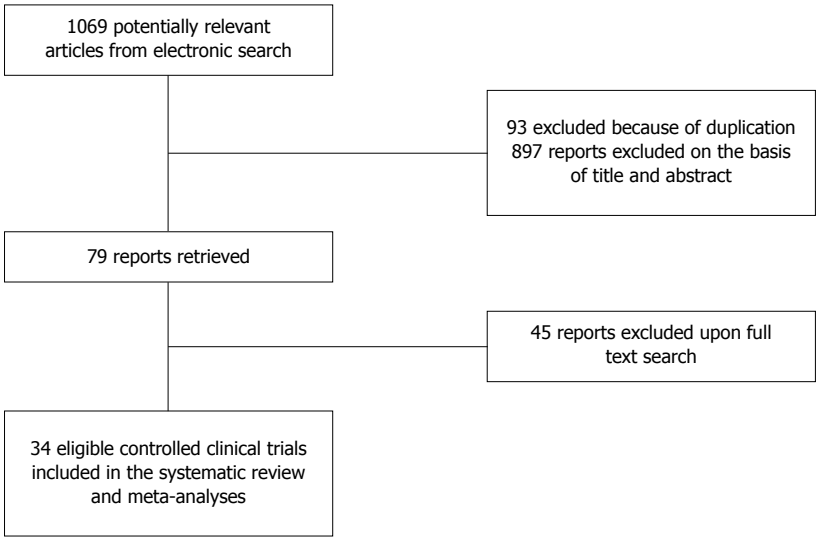


Figure 1 Flow diagram of study selection.

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

Ref.	Drug/ supplements	Study design	Jadad score	Participants	Treatment (intervention)		Outcome (results)		Adverse effects/ events
					Case	Control	Clinical	Laboratory	
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 10000 IU vitamin A intramuscularly; per day; for 14 d	20 patients; placebo	Multi-organ dysfunction[1] Length of hospital stay[1]	Serum GSH[1] Serum SOD[1]	
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	30 patients; placebo	Length of hospital stay and compli-cations ↓	Serum MDA[1] 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)	38 patients; 100 mL/d of 20% AGD intravenous infusion/ for 10 d starting on the day 5 (late treatment)	Infection rate ↓ Operation rate ↓ Mortality ↓ Hospita-lization ↓ Duration of ARDS ↓ Renal failure ↓ Acute hepatitis ↓ Encepha-lopathy ↓ Entero-paralysis ↓	TAC ↓ Vitamin C ↑ -	-

Fuentes-Orozco *et al*[20], 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	Duration of shock ↓ 15 d APACHE Ⅱ core ↓ Infectious morbidity ↓ Hospital stay day[1] Mortality[1]	Serum IL10 ↑ Serum IL-6 ↓ CRP ↓ Ig A ↑ Protein ↑ Albumin ↑ Leucocyte ↓	-
Sahin *et al*[21], 2007	Glutamine enriched total parenteral nutrition (TPN)	Randomized; double blind; placebo-controlled	3	40 patients with AP	20 patients; 0.3 g/kg per day glutamine; for 7-15 d	20 patients; placebo	Complication rates ↓	Total lymphocyte ↑ Nitrogen balance was (+) in treated group *vs* (-) in control group Transferrin level ↑ Fasting blood sugar, albumin[1] BUN[1] Creatinine[1] Total cholesterol concentrations[1] AST[1] ALT[1] LDH activities[1] Leukocytes, CD4, CD8[1]	
Siriwardena *et al*[22], 2008	Combined antioxidant (N-acety-lcysteine, selenium, vitamin C)	Randomized; double blind; placebo-controlled	5	43 patients with severe AP	22 patients; N-acetylcysteine, selenium and vitamin C; for 7d	21 patients; placebo	Organ dysfun-ction[1] APACHE- Ⅱ[1] Hospita-lization[1] All case mortality[1]	Serum Zn, Ca and P Serum lipase ↓ Amylase activities↓ CRP ↓ Serum vitamin C[1] Serum selenium[1] GSH/GSSG ratio[1] CRP[1]	-
Pearce CB *et al*[23], 2006	Glutamine, arginine, tributyrin and antioxidants	Randomized; double blind; placebo-controlled	5	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 isonitro-genous control feed was undertaken		CRP ↑ CAPAP↓	Diarrhea (1 patient) Vomiting (2 patients)
Du *et al*[24], 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	Hospita-lization ↓ Deterioration of disease ↓ Improvement of disease ↑ Cure rate ↑	TNF-α ↓ IL-1 ↓ IL-8 ↓ CRP ↓ Serum interleukin-2 receptor ↓ Plasma vitamin C ↑ Plasma lipideroxide ↑ Plasma vitamin E ↑ Plasma β-carotene ↑ Whole blood glutathione ↑ Activity of erythrocyte surperoxide dismutase ↑ Erythrocyte catalase ↑	Hyper-natremia (2 patients) -
Ockenga *et al*[25], 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	Hospita-lization ↓ Duration of TPN ↓ Cost of TPN[1]	Cholinesterase ↑ Albumin ↑	-

de Beaux *et al*[26], 1998	Glutamine	Randomized; double-blind; controlled	5	14 patients with AP	6 patients; 0.22 g/kg per day of glycyl-glutamine in standard TPN; for 7 d	7 patients; standard TPN		Lymphocyte count ↑ CRP ↓ Lymphocytic proliferation (by DNA synthesis) ↑ TNF[1] IL6[1] IL8↓	-
Sharer *et al*[27], 1995	Glutathione precursors (S-adenosyl methionine and N-acety-lcysteine)	Randomized	2	79 patients with AP	SAMe 43 mg/kg and N-acetylcysteine 300 mg/kg	-	APACHE Ⅱ score reduction[1] Complication rate[1]	-	-
Bilton *et al*[28], 1994	S- adenosyl methionine (SAMe) Selenium and β-carotene + SAMe	Randomized; double-blind; crossover; placebo-controlled	5	20 patients with AP or CP	20 patients; SAMe 2.4 g/d; 10 wk 20 patients; SAMe 2.4 g/d, Selenium 600 μg and β-carotene 9000 IU; 10 wk	Placebo	Days in hospital[1] Mortality[1] Attack rate and background pain[1]	Free radical activity ↓ Serum Selenium ↓ Serum β-carotene ↓ Serum vitamin E ↓ Serum vitamin C ↓ Serum SAMe ↑ Free radical activity ↓ Serum selenium ↓ Serum β-carotene ↑ Serum vitamin E ↑[1] Serum vitamin C ↓ Serum SAMe ↑	-

[1]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.

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

Ref.	Drug/ supplements	Study design	Jadad score	Parti-cipants	Treatment (intervention)		Outcome (results)		Adverse effects/events
					Case	Control	Clinical	Laboratory	
Dhingra *et al*[29], 2013	Combined antioxidant (organic selenium, vitamin C, β 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 β 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 ↓	Platelet-derived growth factor (PDGF) AA ↓ Transforming growth factor β 1[1] Thiobarbituric acid-reactive substances[1] Ferric-reducing ability of plasma ↑ TBARS ↓ FRAP ↑	
Shah *et al*[30], 2013	Combined antioxidant (vitamin C, vitamin E, β carotene, selenium, methionine)	Randomized; double blind; placebo-controlled	5	14 patients with CP	7 patients; Antox tablet: vitamin C, vitamin E, β carotene, selenium, methionine (Pharma Nord, Morpeth, United Kingdom); 6 m	7 patients; placebo	Opiate usage[1]	Serum vitamin C ↑ Serum vitamin E ↑ Serum b carotene Serum vitamin A ↑ WCC[1] Hb[1] CRP[1] Serum selenium[1] IL 1b, 4, 6, and 10[1] TNF-α[1]	

Siriwardena *et al*[31], 2012	Combined antioxidant (selenium, d-a-tocopherol acetate, ascorbic acid, l-methionine)	Randomized; double blind; placebo-controlled	5	70 patients with CP	33 patients; 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	37 patients; placebo	Quality of life[1] Average daily pain scores[1] Opiate use[1] Number of hospital admissions[1] Outpatient visits[1]	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*[32], 2010	Combined antioxidant (vitamin C, vitamin E, β carotene, selenium, methionine)	Randomized; placebo-controlled	2	137 patients with CP	68 patients; Antox tablet: vitamin C, vitamin E, β carotene, selenium, methionine (Pharma Nord, Morpeth, United Kingdom); at least 6 m	69 patients; placebo	Median visual analogue pain score ↓ Cognitive, emotional, social, physical and role function ↑ Analgesics and opiate usage ↓	-	-
Bhardwaj *et al*[33], 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 (Betamore G, Osper Pharmanautics, India); per d; for 6 m	76 patients; placebo	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 (all during the first month of treatment)
Kirk *et al*[34], 2006	Combined antioxidant (selenium, β- carotene, L-methionine, vitamins C and E)	Randomized; double-blind; placebo-controlled; crossover	4	72 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 methionone; 4 times per day; for 10 wk	36 patients; placebo; 4 times per d; for 10 wk	Quality of life ↑ Pain ↓ Physical and social functioning ↑ Health perception ↑ Emotional functioning, energy, mental health:[1]	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*[35], 2005	Curcumin	Randomized; single blind; placebo-controlled	3	20 patients with tropical pan-creatitis (CP)	8 patients; capsule: 500 mg curcumin (95%) with 5 mg of piperine; 3 times per day; for 6 wk	7 patients; placebo (lactose)	Median visual analogue pain score[1] Severity of Pain[1]	Erythrocyte MDA ↓ GSH level[1]	-
Banks *et al*[36], 1997	Allopurinol	Randomized, double-blind, two-period crossover clinical trial	4	26 patients with CP	13 patients; 300 mg/d All opurinol; 4 wk	13 patients, placebo	Pain[1]	Uric acid level ↓	-

Bilton *et al*[28], 1994	S- adenosyl methionine (SAMe) Selenium and β-carotene + SAMe	Randomized; double-blind; crossover; placebo-controlled	5	20 patients with AP or CP	20 patients; SAMe 2.4 g/d; 10 wk 20 patients; SAMe 2.4 g/d, Selenium 600 μg and β-carotene 9000 IU; 10 wk	Placebo	Attack rate and background pain[1]	Free radical activity ↓ Serum selenium ↓ Serum β-carotene ↓ Serum vitamin E ↓[1] Serum vitamin C ↓ Serum SAMe ↑ Free radical activity ↓ Serum selenium ↓ Serum β-carotene ↑ Serum vitamin E ↑[1] Serum vitamin C ↓ Serum SAMe ↑	-
Salim *et al*[39], 1991	Allopurinol; dimethyl sulfoxide	Randomized; double-blind; placebo-controlled	4	78 patients with CP	25 patients; allopurinol; 50 mg 4 times per day, with analgesic regimen (IM pethidine hydrochloride; 50 mg every 4 hours, and IM metoclopramide hydrochloride; 10 mg every 8 h)	27 patients; placebo with analgesic regimen	Pain free patients ↑ Hospitalization ↓ Epigastric tenderness ↓	WBC count ↓ Serum amylase ↓ Serum LDH ↓	Allergies General malaise Headache Nausea Vomiting Dyspepsia Abdominal pain
Uden *et al*[37,38], 1990, 1992	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 4 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 (Mc Gill) ↓	Free radical activity ↓ Serum selenium ↑ Serum β-carotene ↑ Serum vitamin E ↑ Serum SAMe ↓	-

[1]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.

While, three of seven trials reported a decrease in inflammatory biomarkers[20,24,28], one trial reported an increase in inflammatory biomarkers[25]. Indeed, three of the five studies demonstrated a significant decrease in CRP levels[20,21,24,25]. In addition, one study reported a reduction in the levels of serum amylase and lipase[21]. It is noteworthy that one of twelve studies assessing the antioxidant therapies reported diarrhea, vomiting and hypernatremia in 5 patients[23].

Antioxidant therapy in CP

In the context of CP, all of the studies (twelve studies) assessed clinical presentations[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[32-34]. Two of three studies showed a significantly shorter hospital stay in the treatment groups[33,39]. In addition, six of eleven trials reported a reduction of pain[29,32-34,37-39].

On the other hand, eleven of twelve studies assessed laboratory outcomes, as outcomes of antioxidant therapy[28-39]. Eight of nine studies showed a significant decrease in serum free radical activity and a significant increase in serum antioxidant levels[28-31,33,34,37,38]. Furthermore, one of two trials reported a decrease in inflammatory biomarkers[39]. In addition, one study reported a decrease in the levels of serum amylase[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

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
					Case	Control	Primary	Other		
Abbasinazari *et al*[40], 2011	Allopurinol	Randomized double blind clinical trial	3	74	29 patients;	45 patients; no medication	Rate of PEP[1] (11.5% *vs* 12.5%)	Serum amylase activity[1]	-	-
Martinez-Torres *et al*[41], 2009	Allopurinol	Randomized; double-blind; placebo-controlled	5	170	85 patients; 300 mg oral allopurinol 15 h and 3 h before ERCP	85 patients; placebo	Rate of PEP ↓ (2.3% *vs* 9.4%)	Serum amylase activity ↓	-	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[1] (7.3% *vs* 2.9%)	TNF-α[1] IL-6[1]	-	-
	Octreotide				180 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[1] (5% *vs* 2.9%)	TNF-α ↓ IL-6[1]		
Romagnuolo *et al*[43], 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[1] (5.5% *vs* 4.1%)	Disease-related adverse events[1] Procedure-related complications[1] Hospitalization[1]	-	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

Kapetanos *et al*[44], 2007	Pentoxifylline	Randomized;	2	320	158 patients; 400 mg oral pentoxifylline, 40 h, 32 h, 24 h, 16 h and 8 h before ERCP (total dose 2 g)	162 patients; no medication	Rate of PEP[1] (5.6% *vs* 3%)	Hemorrhage[1] Serum amylase activity[1]	Nausea and vomiting in 10% of the patients who received the drug	-
Milewski *et al*[45], 2006	N-acety-lcysteine	Randomized; placebo-controlled	2	106	55 patients; 600 mg oral N-acety-lcysteine 24 h and 12 h before ERCP and 1200 mg Ⅳ for 2 d after the ERCP	51 patients; isotonic Ⅳ saline b.d for 2 d after the ERCP	Rate of PEP[1] (7.3% *vs* 11.8%)	Urine amylase activity[1] Serum amylase activity[1]	-	-
Katsinelos *et al*[46], 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 ↓ (3.2% *vs* 17.8%)	Hospita-lization ↓ Severity of Pancreatitis ↓	-	-
Katsinelos *et al*[47], 2005	N-acety-lcysteine	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[1] Hospita-lization[1]	-	Nausea Skin rash Diarrhea Vomiting	2 patients with suspected SOD
Mosler *et al*[48], 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[1] (13.0% *vs* 12.1%)	Severity of pancreatitis[1]	-	4% absolute benefit in high-risk patients; 4% absolute harm in average risk
Lavy *et al*[49], 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[1] (10% *vs* 9.4%)	Severe pancreatitis ↓	-	-
Budzyńska *et al*[50], 2001	Allopurinol	Randomized; placebo-controlled	3	300	99 patients; 200 mg oral Allopurinol 15 h and 3 h before ERCP	101 patients; placebo	Rate of PEP[1] (12.1% *vs* 7.9%)	Severity of pancreatitis[1]	-	3-arm study, with third arm (n = 100) given prednisone

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

malaise, and abdominal pain[33,34,39].

Antioxidant therapy in PEP

In the context of PEP, two of eleven studies showed a significant drop in the rate of PEP[41-46]. In addition, one of two studies reported a significant decrease in the rate of hospitalization in the treatment group[46]. On the other hand, two studies showed that antioxidant therapy did not affect disease-related complications[43,44].

One of four studies assessing laboratory outcomes, reported a significant decrease in serum amylase activity[41]. Moreover, one trial reported a non-significant alteration in urine amylase levels[45]. Also, one of two studies demonstrated a significant decrease in serum TNF[42]. Two of eleven trials reported adverse events such as nausea, diarrhea, vomiting and skin rash[44,47].

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[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-

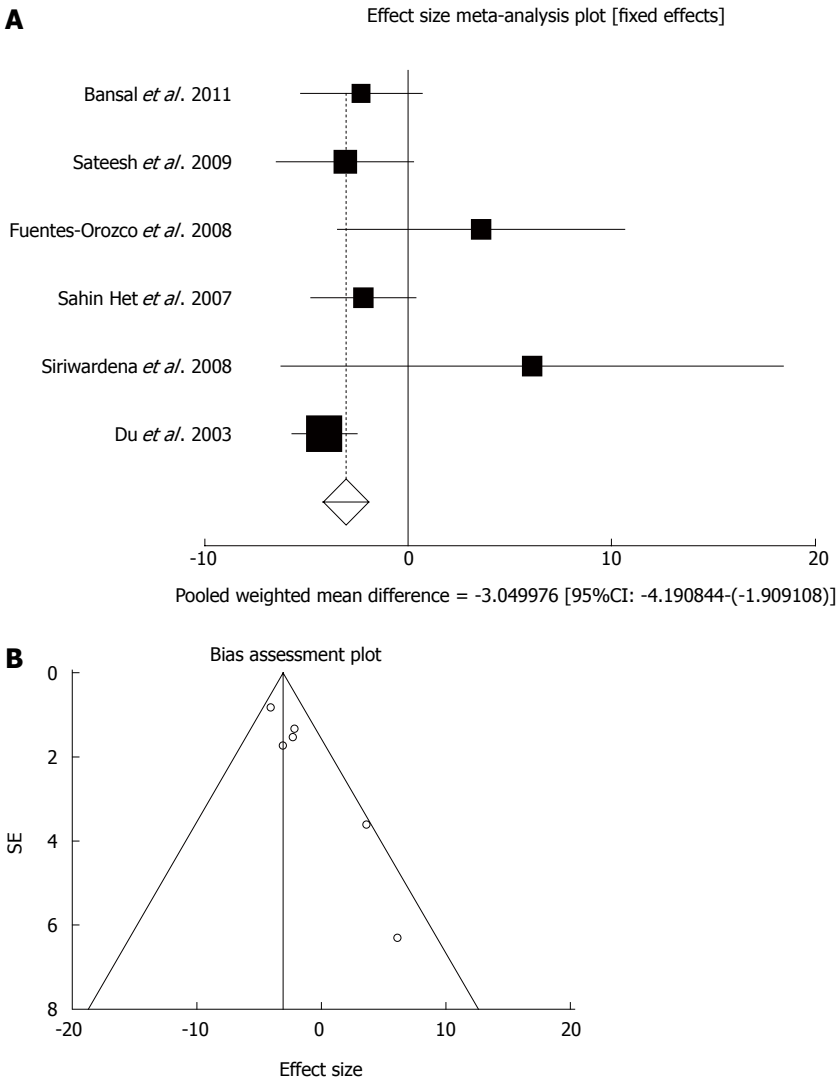


Figure 2 Individual and pooled effect size for standardized mean for the outcome of "rate of hospitalization in acute pancreatitis" in the studies considering antioxidants compared to placebo therapy in 303 patients (A) and publication bias indicators for the outcome of "rate of hospitalization in chronic pancreatitis" in the studies considering antioxidants compared to placebo therapy in 303 patients (B).

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, 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, 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.

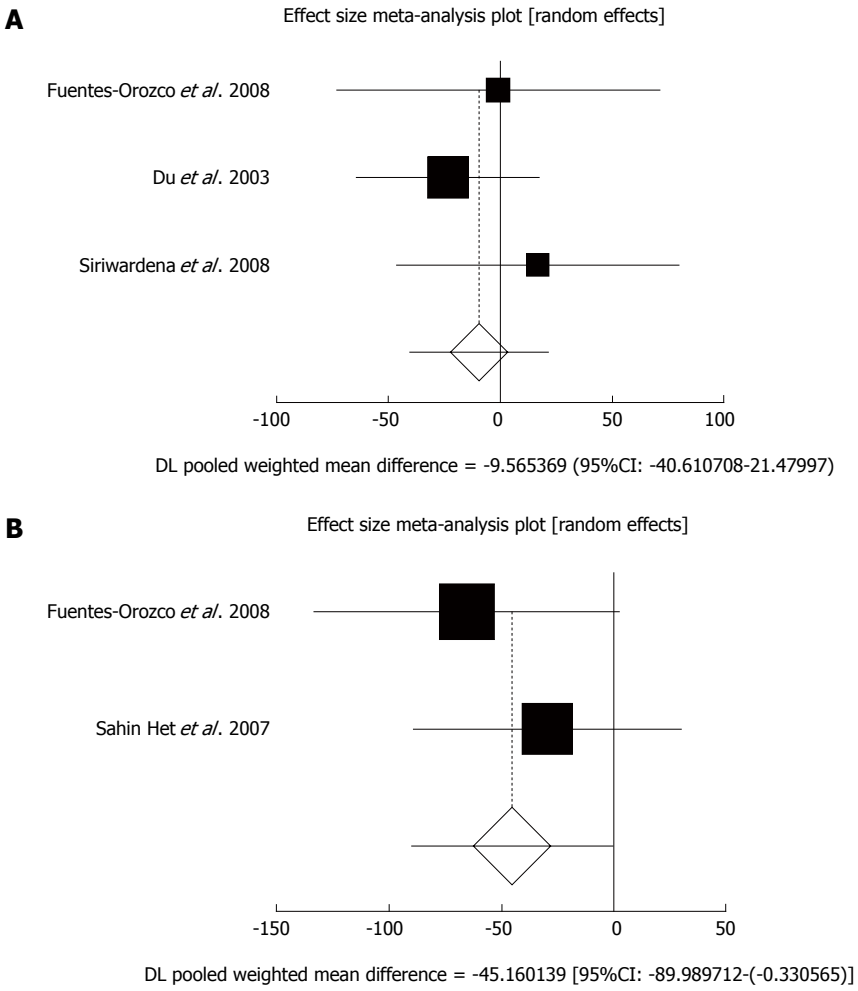


Figure 3 Individual and pooled effect size for standardized mean for the outcome of "serum C reactive protein in acute pancreatitis patients after 5-7 d sampling" in the studies considering antioxidants compared to placebo therapy in 171 patients (A) and individual and pooled effect size for standardized mean for the outcome of "serum C reactive protein in acute pancreatitis patients after 10 d sampling" in the studies considering antioxidants compared to placebo therapy in 84 patients (B).

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[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[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 be not 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[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

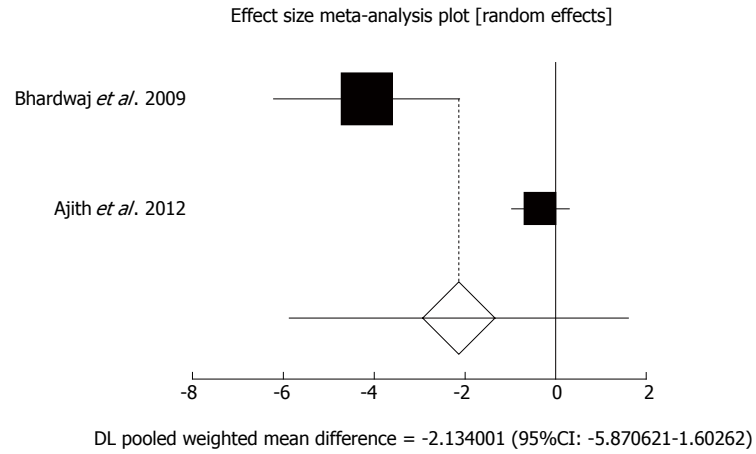
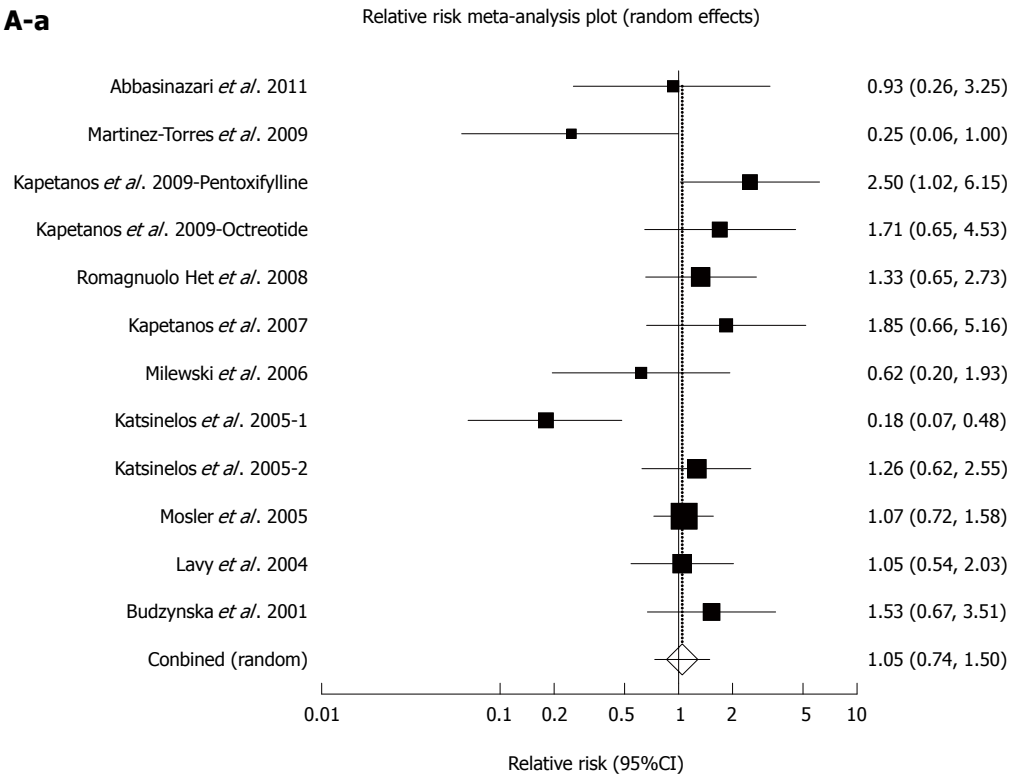
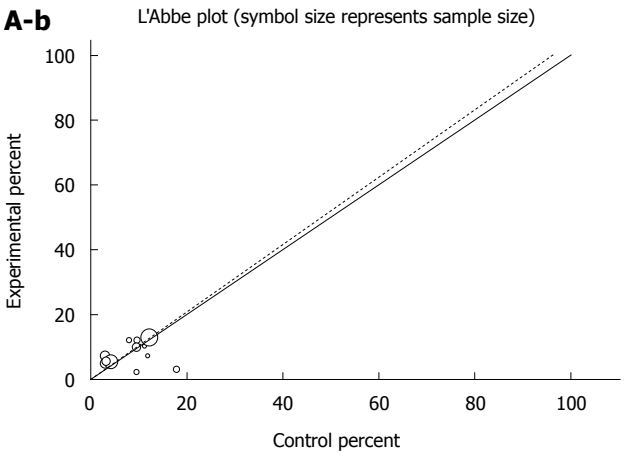
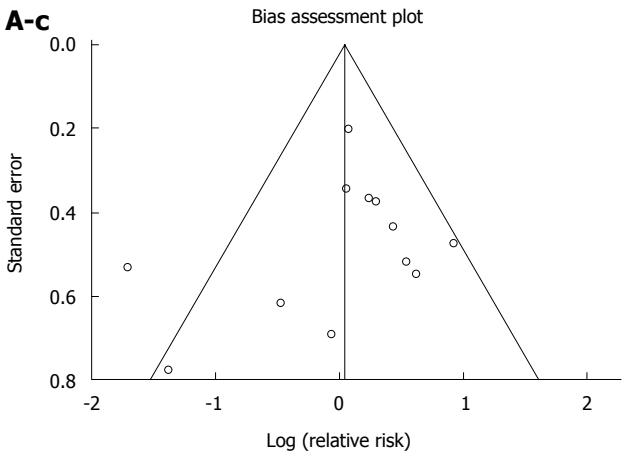


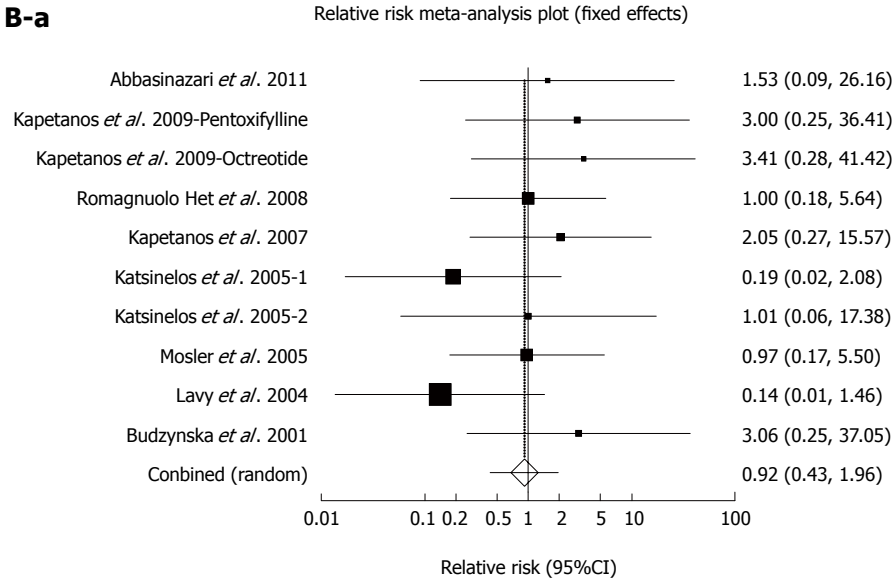
Figure 4 Individual and pooled effect size for standardized mean for the outcome of "pain in chronic pancreatitis patients" in the studies considering antioxidants compared to placebo therapy in 189 patients.



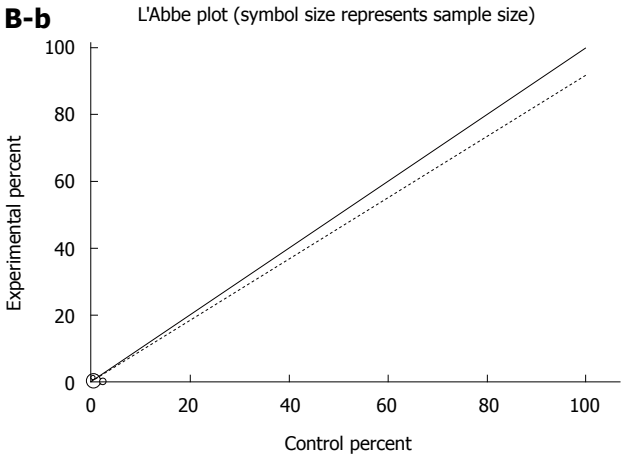




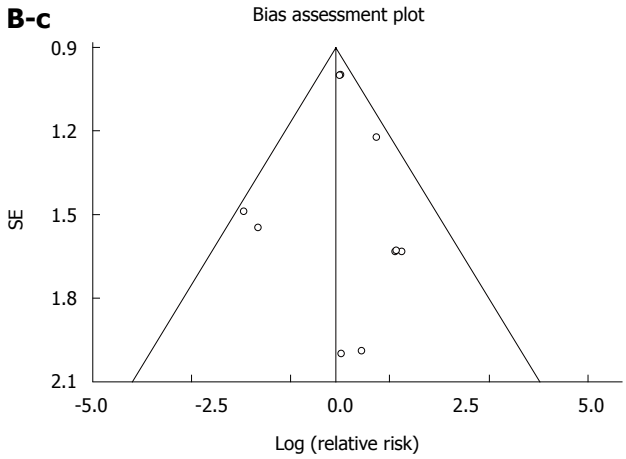
B-a


Relative risk meta-analysis plot (fixed effects)
Abbasinazari et al. 2011
Kapetanos et al. 2009-Pentoxifylline
Kapetanos et al. 2009-Octreotide
Romagnuolo Het al. 2008
Kapetanos et al. 2007
Katsinelos et al. 2005-1
Katsinelos et al. 2005-2
Mosler et al. 2005
Lavy et al. 2004
Budzynska et al. 2001
Conbined (random)
1.53 (0.09, 26.16)
3.00 (0.25, 36.41)
3.41 (0.28, 41.42)
1.00 (0.18, 5.64)
2.05 (0.27, 15.57)
0.19 (0.02, 2.08)
1.01 (0.06, 17.38)
0.97 (0.17, 5.50)
0.14 (0.01, 1.46)
3.06 (0.25, 37.05)
0.92 (0.43, 1.96)
0.01 0.1 0.2 0.5 1 2 5 10 100
Relative risk (95%CI)

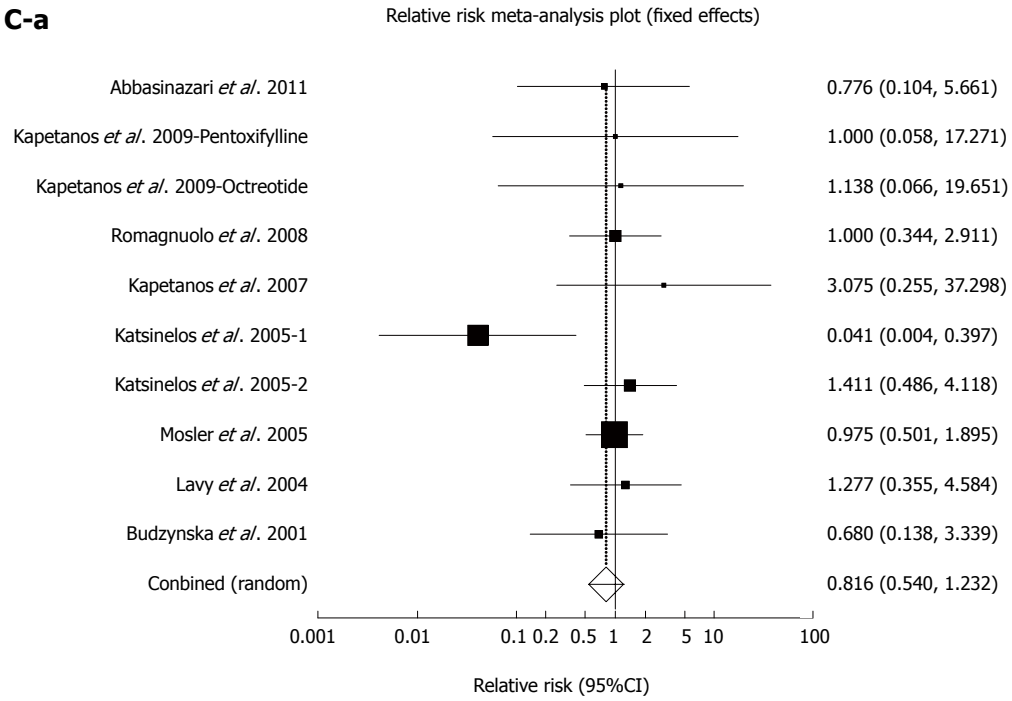
B-b


L'Abbe plot (symbol size represents sample size)
Experimental percent
0 20 40 60 80 100
Control percent

B-c


Bias assessment plot
SE
0.9 1.2 1.5 1.8 2.1
-5.0 -2.5 0.0 2.5 5.0
Log (relative risk)

C-a


Relative risk meta-analysis plot (fixed effects)
Abbasinazari et al. 2011
Kapetanos et al. 2009-Pentoxifylline
Kapetanos et al. 2009-Octreotide
Romagnuolo et al. 2008
Kapetanos et al. 2007
Katsinelos et al. 2005-1
Katsinelos et al. 2005-2
Mosler et al. 2005
Lavy et al. 2004
Budzynska et al. 2001
Conbined (random)
0.776 (0.104, 5.661)
1.000 (0.058, 17.271)
1.138 (0.066, 19.651)
1.000 (0.344, 2.911)
3.075 (0.255, 37.298)
0.041 (0.004, 0.397)
1.411 (0.486, 4.118)
0.975 (0.501, 1.895)
1.277 (0.355, 4.584)
0.680 (0.138, 3.339)
0.816 (0.540, 1.232)
0.001 0.01 0.1 0.2 0.5 1 2 5 10 100
Relative risk (95%CI)

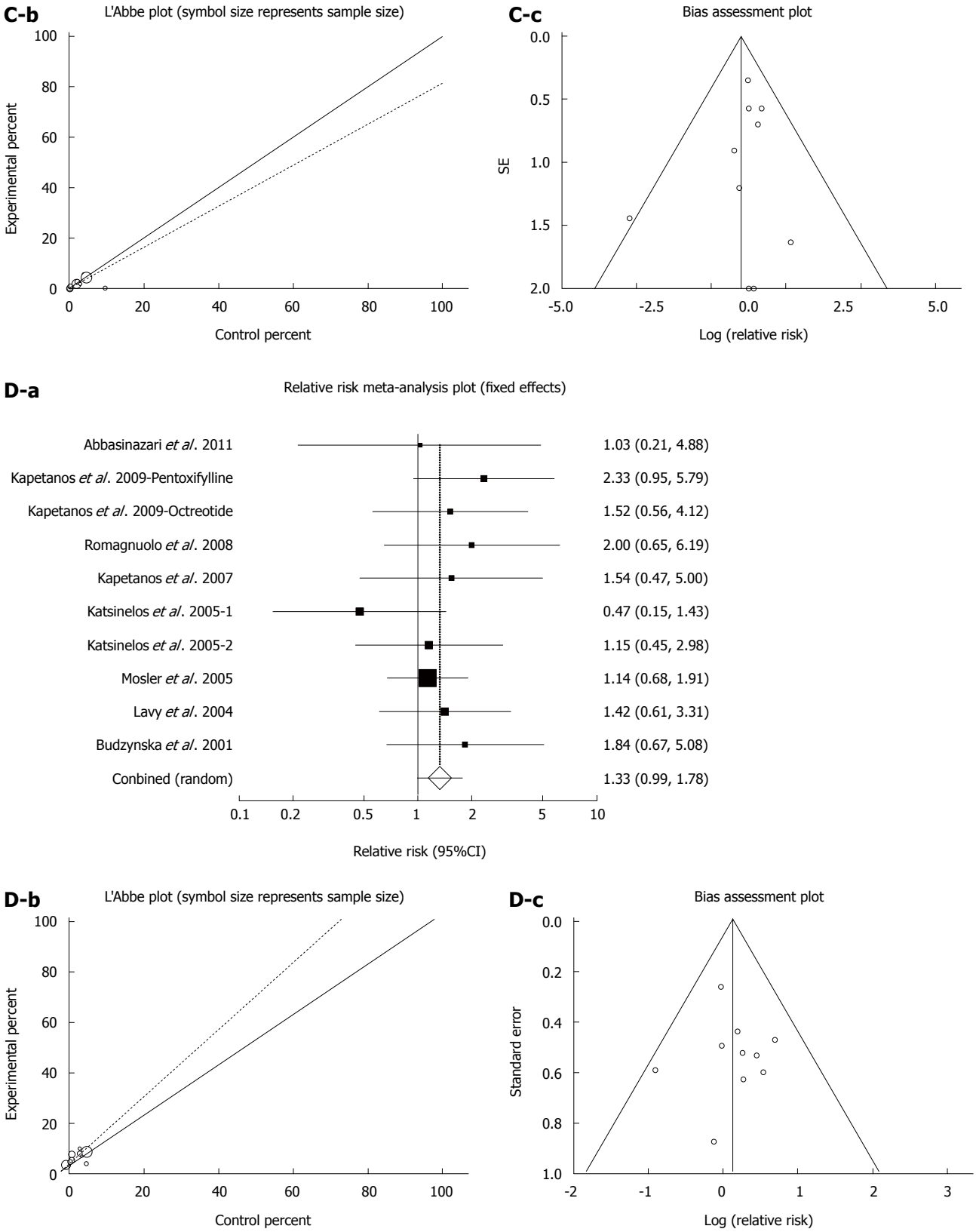


Figure 5 Effect of antioxidants compared with placebo therapy on incidence. Individual and pooled relative risk (A-a), heterogeneity indicators for (A-b), and publication bias indicators for (A-c) the outcome of "all types of PEP" in the studies considering antioxidants compared to placebo therapy in 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 for (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 500 patients undergoing ERCP after less than 8 h sampling for antioxidants therapy for three included trials compared to placebo[40,44,45] was -20.61 with 95%CI: -143.61-102.39 (P = 0.74, Figure 6A). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous (P < 0.0001) 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 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

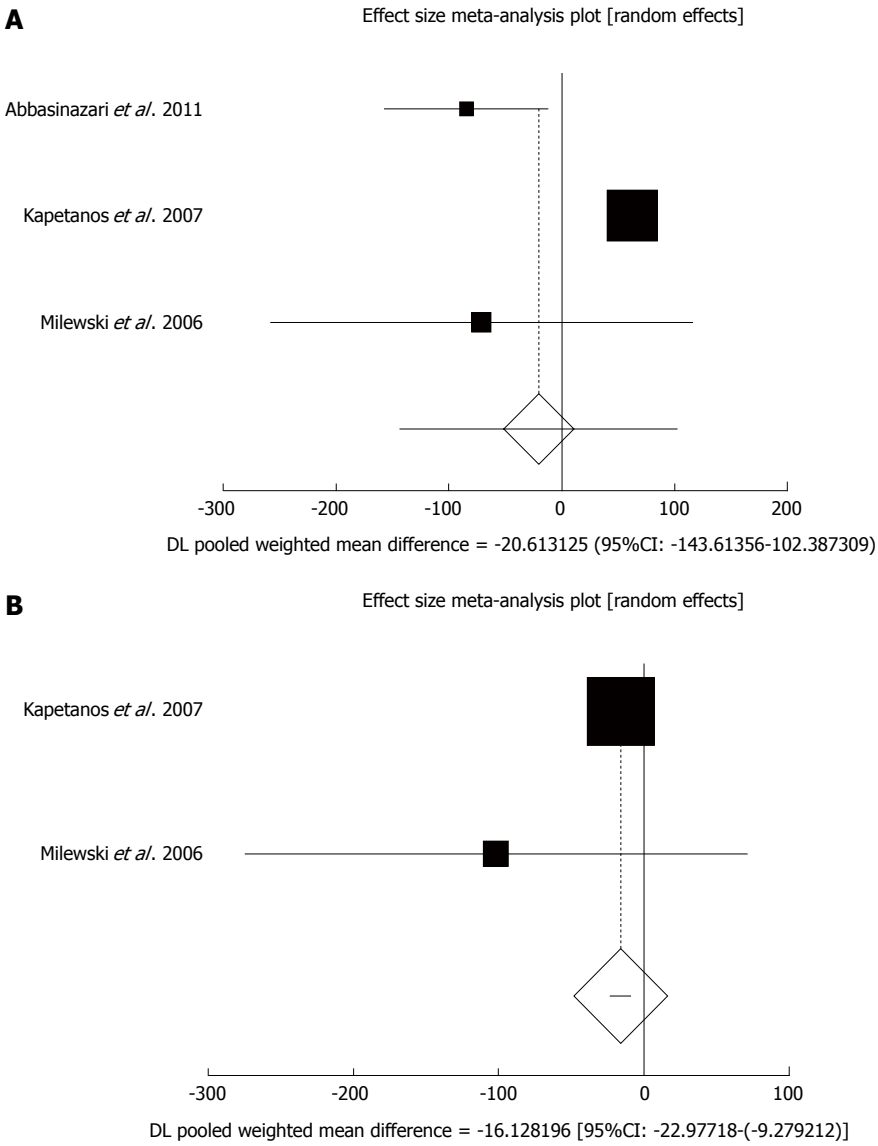


Figure 6 ndividual and pooled effect size for standardized mean for the outcome. A: Of "serum amylase in patients undergoing ERCP after less than 8 h sampling" in the studies considering antioxidants comparing to Placebo therapy in 500 patients; B: Of "serum amylase of patients undergoing ERCP after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

English may lead to language bias.

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.

ACKNOWLEDGMENTS

We gratefully and sincerely thank Dr. Alireza Aleyasin for his valuable comments. This invited paper (Number ID: 00040588) is the outcome of an in-house financially non-supported study.

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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ISSN 1007-9327