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

Gooshe M *et al*. Antioxidant therapy in pancreatitis

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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 cholangiography pancreatitis (PEP).

**METHODS:** PubMed, Scopus, Google Scholar, Cochrane library database, and Evidence based medicine 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 trials was assessed by the Jadad score based on description of randomization, blinding, and dropouts (withdrawals). The results of studies were pooled and meta-analyzed to provide estimates of the efficacy of antioxidant therapy.

**RESULTS:** Thirty-five trials out of 1069 potentially relevant studies with data for 4898 patients were found eligible to include. Antioxidant therapy significantly reduced the length of hospital stay in AP patients [mean difference -2.59 (95%CI: -4.25 to -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 to 21.48), *P =* 0.55], it significantly reduced serum CRP after 10 d [mean difference -45.16 (95%CI: -89.99 to -0.33), *P =* 0.048]. Meanwhile, antioxidant therapy had no significant effect on CP-induced pain [mean difference -2.13 (95%CI: -5.87 to 1.6), *P =* 0.26]. Antioxidant therapy had no significant effects on the incidence of all kinds of PEP [mean difference 1.05 (95%CI: 0.74 to 1.5), *P =* 0.78], sever PEP [mean difference 0.92 (95%CI: 0.43 to 1.97), *P =* 0.83], moderate PEP [mean difference 0.82 (95%CI: 0.54 to 1.23), *P =* 0.33], and mild PEP [mean difference 1.33 (95%CI: 0.99 to 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 to 102.39), *P =* 0.74], it significantly reduced serum amylase close to 24-h sampling [mean difference -16.13 (95%CI: -22.98 to -9.28), *P* < 0.0001].

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

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

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**Core tip:**Antioxidant therapy reduces the length of hospital stay in acute pancreatitis (AP) patients. While, 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 cholangiography pancreatitis is limited. Further trials should be based on etiology-differentiated designs.

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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 has been 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 the gut-related hospitalization in the United States is AP[6]. Several complicated factors are associated with development of AP but alcohol abuse and ductal obstruction caused by gallstones or bacterial infection are the main ones[5].

Furthermore, pancreatitis remains the most common adverse event of endoscopic retrograde cholangiopancreatography (ERCP). The incidence of post ERCP pancreatitis (PEP) has wide discrepancies, ranging from 1% to 40% for normal population, with 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, we have so far met with limited success in this context.

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 for developing chronic pancreatitis, idiopathic, genetic, and autoimmunity factors considered as 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 that is called oxidative stress[10,11].

Interestingly, there are ample evidence suggesting that oxidative stress is a common pivotal factor in the pathogenesis of AP, CP and PEP[12]. While, 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 to expect positive effects by the use of antioxidants in pancreatitis.

The question of whether antioxidant supplements might protect against pancreatitis has drawn much attention in the recent years and meta-analysis has shown some positive effects[15], although 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 severity and rate of PEP were included. Data were searched from PubMed, Scopus, Google Scholar and Cochrane library database up to August 2014.

The search terms were: 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***

Jadad score, which indicates the quality of the studies based on their description of randomization, blinding, and dropouts (withdrawals) were used to assess the methodological quality of trials[16]. The quality scale ranges from 0 to 5 points with a low quality report of score 2 or less and a high quality report of score at least 3. 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 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 considered significant. In 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 plot.

**RESULTS**

From the 1069 studies identified through the literature search, 35 randomized controlled trials were identified 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].

Amongst 35 papers, 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, 2 and 3).

Furthermore, the effects of early stopping 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 recruited. Tables 1, 2, and 3 detail the characteristics of 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 kinds of PEP in patient undergoing ERCP, and serum amylase of patients undergoing ERCP were included in the meta-analysis.

***Antioxidant therapy in AP***

In the context of the AP, ten of twelve studies assessed clinical presentations, as outcomes of antioxidant therapy[17-22,24,25,27,28]. One of four studies reports that antioxidant therapy reduced the mortality rate following antioxidant therapy[19]. Four of eight studies showed a significantly shorter hospital stay in the treatment groups[17,19,24,25]. Besides, four of eight trials reported a reduction of complication and organ dysfunction[17,19,21,24]. However, one study declared 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 the serum free radical activity and a significant increase in serum antioxidant levels[17,24,28]. 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]. Besides, one study reported a reduction in 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 the 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]. Besides, 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 the 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]. Besides, one study reported a decrease in 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 malaise, and abdominal pain[33,34,39].

***Antioxidant therapy in PEP***

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

One of four studies assessing laboratory outcomes, reported a significant decrease in the 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 in comparison to placebo therapy on length of hospital stay in acute pancreatitis patients:** The summary for standardized effect size of mean differences of length of hospital stay in AP in 303 patients for antioxidants therapy for six included trials comparing to placebo[17,18,20-22,24] was -2.59 with 95%CI: -4.25 to -0.93 (*P =* 0.002, Figure 2a). The Cochrane *Q* test for heterogeneity indicated that the studies are not heterogeneous (*P =* 0.16) and could be combined but because of 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 of length of hospital stay in AP patients among antioxidants *vs* placebo therapy was 2.17 (95%CI: 1.04 to 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 in comparison to placebo therapy in serum CRP in acute pancreatitis patients after 5-7 d:** The summary for standardized effect size of mean differences of serum CRP in 171 AP patients after 5-7 d for antioxidants therapy for three included trials comparing to placebo[20,22,24] was -9.57 with 95%CI: -40.61 to 21.48 (*P =* 0.55, Figure 3A). The Cochrane *Q* test for heterogeneity indicated that the studies are not heterogeneous (*P =* 0.56) 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 CRP in AP patients among antioxidants *vs* placebo therapy could not be evaluated because of too few strata.

**Effect of antioxidants in comparison to placebo therapy in 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 comparing to placebo[20,21] was -45.16 with 95%CI: -89.99 to -0.33 (*P =* 0.048, Figure 3B). The Cochrane *Q* test for heterogeneity indicated that the studies are not heterogeneous (*P =* 0.44) 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 CRP in acute pancreatitis patients among antioxidants *vs* placebo therapy could not be evaluated because of too few strata.

**Effect of antioxidants in comparison to placebo therapy in pain reduction in chronic pancreatitis patients:** The summary for standardized effect size of mean differences of pain reduction in CP in 189 patients for antioxidants therapy for two included trials comparing to placebo[31,33] was -2.13 with 95%CI: -5.87 to 1.6 (*P =* 0.26, Figure 4). The Cochrane *Q* test for heterogeneity indicated that the studies are 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 among antioxidants *vs* placebo therapy could not be evaluated because of too few strata.

**Effect of antioxidants in comparison to placebo therapy in incidence of all kind of PEP in patient undergoing ERCP:** The summary for RR of all kind of PEP in patient undergoing ERCP for twelve included trials in eleven studies[40-50] comparing antioxidants to placebo was 1.05 with 95%CI: 0.74 to 1.5 (*P =* 0.78, Figure 5a-a). The Cochrane *Q* test for heterogeneity indicated that the studies are 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 kind of PEP” in 1849 patients among antioxidants *vs* placebo therapy was -0.78 (95%CI: -3.22 to 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 in comparison to placebo therapy in incidence of severe PEP in patient undergoing ERCP:** The summary for RR of severe PEP in patient 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 to 1.97 (*P =* 0.83, Figure 5b-a). The Cochrane *Q* test for heterogeneity indicated that the studies are 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 regression of normalized effect *vs* precision for all included studies for “severe PEP” in 1709 patients among antioxidants *vs* placebo therapy was 0.21 (95%CI: -2.12 to 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 in comparison to placebo therapy in incidence of moderate PEP in patient undergoing ERCP:** The summary for RR of moderate PEP in patient 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 to 1.23 (*P =* 0.33, Figure 5c-a). The Cochrane *Q* test for heterogeneity indicated that the studies are 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 among antioxidants *vs* placebo therapy was -0.37 (95%CI: -1.57 to 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 in comparison to placebo therapy in incidence of mild PEP in patient undergoing ERCP:** The summary for RR of mild PEP in patient 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 to 1.78 (*P =* 0.06, Figure 5d-a). The Cochrane *Q* test for heterogeneity indicated that the studies are 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 among antioxidants *vs* placebo therapy was 0.25 (95%CI: -1.73 to 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 in comparison to placebo therapy in serum amylase of patients undergoing ERCP after less than 8 h sampling:** The summary for standardized effect size of mean differences of serum amylase in 500 patients undergoing ERCP after less than 8 h sampling for antioxidants therapy for three included trials comparing to placebo[40,44,45] was -20.61 with 95%CI: -143.61 to 102.39 (*P =* 0.74, Figure 5A). The Cochrane *Q* test for heterogeneity indicated that the studies are 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 among antioxidants *vs* placebo therapy could not be evaluated because of too few strata.

**Effect of antioxidants in comparison to placebo therapy in serum amylase of patients undergoing ERCP after less than 24-h sampling:** The summary for standardized effect size of mean differences of serum amylase in 426 patients undergoing ERCP after less than 24-hour sampling for antioxidants therapy for two included trials comparing to placebo[44,45] was -16.13 with 95%CI: -22.98 to -9.28 (*P <* 0.0001, Figure 5B). The Cochrane *Q* test for heterogeneity indicated that the studies are 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 among 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 but time is needed to have the best alleviating effects. Meanwhile, we found out 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 ameliorative role of antioxidant supplements in the reduction of pain in CP. Although in this meta-analysis, we aimed to include as much 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, 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 with the results of previous meta-analyses[15,52,53]. Controversially, while we found no significant effect of antioxidant therapy in decreasing serum amylase in PEP patients after less than 8 hours sampling, serum amylase after less than 24 hours 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 but we reached to conclusion that existing trials have inevitable differences in the use of antioxidant or the design of study. Furthermore, excluding languages other than 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 is not confirmed. Although there are several safe and efficacious compounds that can control oxidative stress, yet little success for antioxidant therapy in inflammatory disorders such as pancreatitis has been reported. Lack of proper understanding of the pathological processes underlying pancreatitis can be the reason behind this failure. Evolving evidences suggest 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 are limited evidences supporting the efficacy of antioxidant therapy in PEP (as a particular kind of AP). Thus, in order to come toward making antioxidant therapy a realistic goal, outcomes should be differentiated, based on their etiology.

Antioxidants, as with all drugs, come with a price of adverse events. Therefore, complications of such compounds are yet to be specified, though they seem less theoretical than supposed.

Current advances in the field of antioxidant therapy should provide the impetus to bring antioxidant agents to more clinical trials. However, a long path may still lie ahead before such therapies make their way into routine clinical use.

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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 has been 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 cholangiography pancreatitis (PEP). So, it is necessitated to systematically evaluate the efficacy and adverse effects of Antioxidant therapy in the management of different kinds 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. While, 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***

Meta-analysis confirms efficacy of antioxidant therapy in the management of AP.

***Peer-review***

In this study, the authors have analyzed the correlation between CD11c expression in immune cells and gastric cancer progression. The study has provided evidence that low expression level of CD11c is strongly associated with increased incidence of death and relapse risk of patients.

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**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** |
| Dipika 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 ~Length of hospital stay ~ | Serum GSH ~Serum SOD ~Serum MDA ~ |  |
| 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 complications ↓ | TBARS ↓SOD ↓TAC ↓Vitamin C ↑ |  |
| 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 ↓Hospitalization ↓Duration of ARDS ↓Renal failure ↓Acute hepatitis ↓Encephalopathy ↓Enteroparalysis ↓Duration of shock ↓15-d APACHE IIcore ↓ | - | - |
| 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 | Infectious morbidity ↓Hospital stay day ~Mortality ~ | Serum IL10 ↑Serum IL-6 ↓CRP ↓Ig A ↑Protein ↑Albumin ↑Leucocyte ↓Total lymphocyte ↑Nitrogen balance was (+) in treated group versus(–) in control group | - |
| 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 ↓ | Transferrin level ↑Fasting blood sugar, albumin ~BUN ~Creatinine~Total cholesterol concentrations~AST~ALT~LDH activities~Leukocytes, CD4, CD8~Serum Zn, Ca and P Serum lipase ↓Amylase activities↓CRP ↓ |  |
| Siriwardena *et al*[22], 2008 | 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 7d | 21 patients; placebo | Organ dysfunction ~APACHE- II ~Hospitalization ~ All case mortality ~ | Serum vitamin C ~Serum selenium ~GSH/GSSG ratio ~CRP ~ | - |
| Pearce CB *et al*[23], 2006 |  Glutamine, arginine, tributyrin and antioxidants  | Randomized; double blind; placebo- controlled | 5 | 31 patients withsevere AP | 15patients;glutamine, arginine, tributyrin and antioxidants; for 3d; If patients required further feeding the study was continued up to 15 days  | 16 patients;placeboisocaloric isonitrogenous control feed was undertaken |  | CRP ↑CAPAP↓ | Diarrhea (1 patient)Vomiting (2 patients)Hypernatremia (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 | Hospitalization ↓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 ↑ | - |
| Ockenga *et al*[25], 2002 | Glutamine | Randomized, double blind; controlled | 4 | 28 patients with AP | Standard TPN which contains 0.3 g/kg/d L-alanine-L-glutamine; at least 1 wk | Standard TPN | Hospitalization ↓Duration of TPN ↓Cost of TPN ~ | Cholinesterase ↑Albumin ↑Lymphocyte count ↑CRP ↓ | - |
| De Beaux *et al*[26], 1998 | Glutamine | Randomized; double-blind; controlled  | 5 | 14 patients with AP | 6 patients; 0.22 g/kg/d of glycyl-glutamine in standard TPN; for 7 d | 7 patients; standard TPN | - | Lymphocytic proliferation (by DNA synthesis) ↑TNF ~ IL6 ~IL8↓ | - |
| Sharer *et al*[27], 1995 27 | Glutathione precursors (S-adenosyl methionine and N-acetylcysteine) | Randomized | 2 | 79 patients with AP | SAMe 43 mg/kg and N-acetylcysteine 300 mg/kg | - | APACHE II score reduction~Complication rate~Days in hospital~Mortality~ | - | - |
| Bilton *et al*[28],1994 | S- adenosyl methionine (SAMe) | Randomized; double-blind; crossover; placebo- controlled | 5 | 20 patients with AP or CP | 20 patients; SAMe2.4g/d; 10 wk | Placebo | Attack rate and background pain ~ | Free radical activity ↓Serum Selenium ↓Serumβ-carotene ↓Serum vitamin E ↓Serum vitamin C ↓Serum SAMe ↑ | - |
| Selenium and β-carotene + SAMe | 20 patients; SAMe 2.4 g/d, Selenium 600µg and β-carotene 9000IU; 10 wk | Free radical activity ↓Serum Selenium ↓Serumβ-carotene ↑Serum vitamin E ↑~Serum vitamin C ↓Serum SAMe ↑ |

↑: Significant increase as compared with control; ↓: Significant decrease as compared with control; ~: No significant difference between groups; TBARS: Thiobarbitoric acid reactive substances; FRAP: Ferric reducing antioxidant power; SOD: Superoxid 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** | **Participants** | **Treatment (Intervention)** | **Outcome (Results)** | **Adverse effects/events** |
| **Case** | **control** | **Clinical** | **Laboratory** |
| Rajan 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 ~Thiobarbituric acid-reactive substances~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, UK); 6m | 7 patients; placebo | Opiate usage ~ | Serum vitamin C ↑ Serum vitamin E ↑Serumβ caroteneSerum vitamin A ↑WCC ~Hb ~CRP ~Serum selenium~IL 1β, 4, 6, and 10 ~TNF α~ |  |
| Ajith *et al*[31], 2012 | Combined antioxidant (selenium, d-α-tocopherol acetate, ascorbic acid, l-methionine) | Randomized; double blind; placebo-controlled | 5 | 70 patients with CP | 33 patients; Antox tablet: 38.5 mg seleniumYeast, 113.4 mg d-α-tocopherol acetate, 126.3 mg ascorbic acid, 480 mg l-methionine; per d; for 6m | 37 patients; placebo | Quality of life ~Average daily pain scores ~Opiate use ~Number of hospital admissions ~Outpatient visits ~ | SerumVitamin C ↑Serum Vitamin E ↑Serumβ 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, UK); at least 6m | 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 andmethionine) | 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 methionon; 4 times per day;for 10 wk  | 36 patients; placebo; 4 times per d; for 10w | 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-etacarotene ↑ | 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 of tropical pancreatitis (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 ~Severity of Pain ~ | Erythrocyte MDA ↓GSH level~ | - |
| Banks *et al*[36], 1997  | Allopurinol | Randomized, double-blind, two-period crossover clinical trial | 4 | 26 patients with CP | 13 patients; 300 mg/d Allopurinol;4 wk | 13 patients, placebo | Pain~ | Uric acid level ↓ | - |
| Bilton *et al*[28], 1994 | S- adenosyl methionine (SAMe) | Randomized; double-blind; crossover; placebo- controlled | 5 | 20 patients with AP or CP | 20 patients; SAMe2.4 g/d; 10 wk | Placebo | Attack rate and background pain ~ | Free radical activity ↓Serum Selenium ↓Serumβ-carotene ↓Serum vitamin E ↓~Serum vitamin C ↓Serum SAMe ↑ | - |
| Selenium and β-carotene + SAMe | 20 patients; SAMe 2.4 g/d, Selenium 600 µg and β-carotene 9000IU; 10 wk | Free radical activity ↓Serum Selenium ↓Serumβ-carotene ↑Serum vitamin E ↑~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 ↓ | AllergiesGeneral malaiseHeadacheNauseaVomitingDyspepsiaAbdominal pain |
| 26 patients; dimethyl sulfoxide; 500 mg 4 times per day; with analgesic regimen |
| 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  | 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 ↓  | - |

↑: Significant increase as compared with control; ↓: Significant decrease as compared with control; ~: No significant difference between groups; TBARS: Thiobarbitoric acid reactive substances; FRAP: Ferric reducing antioxidant power; SOD: Superoxid 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.

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** |
| Mohammad Abbasinazari *et al*[40]*,* 2011 | Allopurinol | randomized double blind clinical trial | 3 | 74 | 29 patients; | 45 patients; no medication | Rate of PEP ~(11.5% *vs* 12.5%) | Serum amylase activity ~ | -- | - |
| Hector Martinez-Torres *et al*[41]*,* 2009 | Allopurinol | Randomized; double-blind; placebo-controlled | 5 | 170 | 85 patients; 300 mg orall allopurinol 15h and 3h 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 |
| Dimitrios Kapetanos *et al*[42]*,* 2009 | Pentoxifylline | Randomized; | 2 | 590 | 205 patients; 400 mg oral Pentoxifylline, 40 h, 32 h, 24 h, 16h and 8h before ERCP (total dose2 g) | 205 patients; no medication | Rate of PEP~(7.3% *vs* 2.9%) | TNF-α ~IL-6 ~ | -- | - |
| 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 dose4 mg) | 205 patients; no medication | Rate of PEP~(5% *vs* 2.9%) | TNF-α ↓IL-6 ~ |
| Romagnuolo *et al*[43]*,* 2008 | Allopurinol | Randomized; double blind; placebo- controlled | 4 | 586 | 293 patients;300 mg orall allopurinol 60 min before ERCP | 293 patients; placebo | Rate of PEP ~(5.5% *vs* 4.1%) | Disease-related adverse events~Procedure-related complications~Hospitalization ~ | -- | In the non–high-risk group (n=520), the crude PEP rates were 5.4% for allopurinol and 1.5%for placebo (*P =* .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 =* .050), favoring allopurinol |
| Dimitrios Kapetanos *et al*[44]*,* 2007 | Pentoxifylline | Randomized; | 2 | 320 | 158 patients; 400 mg orall pentoxifylline, , 40 h, 32 h, 24 h, 16 h and 8 h before ERCP (total dose2 g)  | 162 patients; no medication | Rate of PEP~(5.6% *vs* 3%) | Hemorrhage ~Serum amylase activity ~ | Nausea and vomiting in 10% of the patients who received the drug | - |
| Milewski *et al*[45]*,* 2006 | N-acetylcysteine | Randomized; placebo-controlled | 2 | 106 | 55 patients; 600 mg orall N-acetylcysteine 24 h and 12 h before ERCP and 1200 mgIV for 2 d after the ERCP | 51 patients; isotonic I*Vs*aline b.d for 2 d after the ERCP | Rate of PEP~(7.3% *vs* 11.8%) | Urine amylase activity ~Serum amylase activity ~ | -- | - |
| Katsinelos *et al*[46]*,* 2005 | Allopurinol | Randomized; double blind;placebo-controlled | 4 | 250 | 125 patients; 600 mg orall allopurinol 15 and 3 h before ERCP | 118 patients; placebo | Rate of PEP ↓(3.2% *vs* 17.8%) | Hospitalization ↓Severity of Pancreatitis ↓ | -- | - |
| Katsinelos *et al*[47]*,* 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 ~Hospitalization ~ | - | NauseaSkin rashDiarrheaVomiting | 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~(13.0% *vs* 12.1%) | Severity of pancreatitis ~ | - | 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 ~(10% *vs* 9.4%) | Severe pancreatitis ↓ | -- | - |
| Budzynska *et al*[50]*,* 2001 | Allopurinol | Randomized; placebo-controlled | 3 | 300 | 99 patients; 200 mg orall Allopurinol 15 h and 3 h before ERCP | 101 patients; placebo | Rate of PEP~(12.1% *vs* 7.9%) | Severity of pancreatitis ~ | -- | 3-arm study, with third arm (*n=* 100) given prednisone |

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

**Figure 1 Flow diagram for study selection.**

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

45 reports excluded upon full text search

79 reports retrieved

93 excluded because of duplication

897 reports excluded on the basis of title and abstract

1069 potentially relevant articles from electronic search



A



B

**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 comparing 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 comparing to placebo therapy in 303 patients (b).**



A



B

**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 comparing 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 comparing to Placebo therapy in 84 patients (B).**



**Figure 4** **Individual and pooled effect size for standardized mean for the outcome of “pain in chronic pancreatitis patients” in the studies considering antioxidants comparing to Placebo therapy in 189 patients.**

Relative risk meta-analysis plot (random effects)

*0.01*

*0.1*

*0.2*

*0.5*

*1*

*2*

*5*

*10*

*Budzynska, et al. 2001*

*1.53 (0.67, 3.51)*

*Lavy et al. 2004*

*1.05 (0.54, 2.03)*

*Mosler et al. 2005*

*1.07 (0.72, 1.58)*

*Katsinelos et al. 2005-2*

*1.26 (0.62, 2.55)*

*Katsinelos et al. 2005-1*

*0.18 (0.07, 0.48)*

*Milewski et al. 2006*

*0.62 (0.20, 1.93)*

*Kapetanos et al. 2007*

*1.85 (0.66, 5.16)*

*Romagnuolo et al. 2008*

*1.33 (0.65, 2.73)*

*Kapetanos et al. 2009- Octreotide*

*1.71 (0.65, 4.53)*

*Kapetanos et al. 2009- Pentoxifylline*

*2.50 (1.02, 6.15)*

*Martinez-Torres et al. 2009*

*0.25 (0.06, 1.00)*

*Abbasinazari et al. 2011*

*0.93 (0.26, 3.25)*

*combined [random]*

*1.05 (0.74, 1.50)*

*relative risk (95% confidence interval)*

A-a



A-b



A-c

Relative risk meta-analysis plot (fixed effects)

*0.01*

*0.1*

*0.2*

*0.5*

*1*

*2*

*5*

*10*

*100*

*Budzynska, et al. 2001*

*3.06 (0.25, 37.05)*

*Lavy et al. 2004*

*0.14 (0.01, 1.46)*

*Mosler et al. 2005*

*0.97 (0.17, 5.50)*

*Katsinelos et al. 2005-2*

*1.01 (0.06, 17.38)*

*Katsinelos et al. 2005-1*

*0.19 (0.02, 2.08)*

*Kapetanos et al. 2007*

*2.05 (0.27, 15.57)*

*Romagnuolo et al. 2008*

*1.00 (0.18, 5.64)*

*Kapetanos et al. 2009- Octreotide*

*3.41 (0.28, 41.42)*

*Kapetanos et al. 2009- Pentoxifylline*

*3.00 (0.25, 36.41)*

*Abbasinazari et al. 2011*

*1.53 (0.09, 26.16)*

*combined [fixed]*

*0.92 (0.43, 1.96)*

*relative risk (95% confidence interval)*

B-a



B-b



B-c

Relative risk meta-analysis plot (fixed effects)

*0.001*

*0.01*

*0.1*

*0.2*

*0.5*

*1*

*2*

*5*

*10*

*100*

*Budzynska, et al. 2001*

*0.680 (0.138, 3.339)*

*Lavy et al. 2004*

*1.277 (0.355, 4.584)*

*Mosler et al. 2005*

*0.975 (0.501, 1.895)*

*Katsinelos et al. 2005-2*

*1.411 (0.486, 4.118)*

*Katsinelos et al. 2005-1*

*0.041 (0.004, 0.397)*

*Kapetanos et al. 2007*

*3.075 (0.255, 37.298)*

*Romagnuolo et al. 2008*

*1.000 (0.344, 2.911)*

*Kapetanos et al. 2009- Octreotide*

*1.138 (0.066, 19.651)*

*Kapetanos et al. 2009- Pentoxifylline*

*1.000 (0.058, 17.271)*

*Abbasinazari et al. 2011*

*0.776 (0.104, 5.661)*

*combined [fixed]*

*0.816 (0.540, 1.232)*

*relative risk (95% confidence interval)*

C-a



C-b



C-c

Relative risk meta-analysis plot (fixed effects)

*0.1*

*0.2*

*0.5*

*1*

*2*

*5*

*10*

*Budzynska, et al. 2001*

*1.84 (0.67, 5.08)*

*Lavy et al. 2004*

*1.42 (0.61, 3.31)*

*Mosler et al. 2005*

*1.14 (0.68, 1.91)*

*Katsinelos et al. 2005-2*

*1.15 (0.45, 2.98)*

*Katsinelos et al. 2005-1*

*0.47 (0.15, 1.43)*

*Kapetanos et al. 2007*

*1.54 (0.47, 5.00)*

*Romagnuolo et al. 2008*

*2.00 (0.65, 6.19)*

*Kapetanos et al. 2009- Octreotide*

*1.52 (0.56, 4.12)*

*Kapetanos et al. 2009- Pentoxifylline*

*2.33 (0.95, 5.79)*

*Abbasinazari et al. 2011*

*1.03 (0.21, 4.88)*

*combined [fixed]*

*1.33 (0.99, 1.78)*

*relative risk (95% confidence interval)*

D-a



D-b



D-c

**Figure 5 Effect of antioxidants in comparison to placebo therapy in incidence.** Individual and pooled relative risk(a-a), heterogeneity indicators for (a-b), and publication bias indicators for (a-c) the outcome of “all kind of PEP” in the studies considering antioxidants comparing to placebo therapy in 1849 patient 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 comparing to placebo therapy in 1709 patient 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 comparing to placebo therapy in 1709 patient 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 comparing to placebo therapy in 1709 patient undergoing ERCP. PEP: post endoscopic retrograde cholangiography pancreatitis; ERCP: endoscopic retrograde cholangiopancreatography.



A



B

**Figure 6 Individual and pooled effect size for standardized mean for the outcome of “serum amylase. a**: in patients undergoing ERCP after less than 8 h sampling” in the studies considering antioxidants comparing to Placebo therapy in 500 patients (A); B: 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.