SYSTEMATIC REVIEWS

Antioxidant drugs to prevent post-endoscopic retrograde cholangiopancreatography pancreatitis: What does evidence suggest?

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Abstract

AIM: To determine whether or not the use of antioxidant supplementation aids in the prevention of post- endoscopic retrograde cholangiopancreatography pancreatitis.

METHODS: A systematic review of randomized controlled trials (RCTs) was made to evaluate the preventive effect of prophylactic antioxidant supplementation in post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP). The inclusion criteria included: acute post-endoscopic retrograde cholangiopancreatography pancreatitis in adults; randomized clinical trials with the use of any antioxidant as an intervention compared with placebo, to reduce PEP. The outcome measure was the incidence and severity of PEP. Twelve RCTs involving 3110 patients since 1999 were

included. The antioxidants used were selenite, β-carotene, and pentoxifylline (each one in one trial), N-acetylcysteine (NAC) in three trials, and allopurinol in six trials. The group of patients treated with NAC received different doses; either oral or intravenous, and allopurinol-treated patients received five different oral doses in two different administration periods. The results are expressed with raw numbers, proportions, as well as mean and standard deviations. The incidence of pancreatitis between groups was analyzed with Pearson's χ^2 test or Fisher's exact test (*F*). The main outcome is expressed as relative risks and 95%CI.

RESULTS: The incidence of pancreatitis in all antioxidant treatment groups was 8.6%, whereas it was 9.7% in the control group. The antioxidants used were selenite, β-carotene, and pentoxifylline (each one in one trial), NAC in three trials, and allopurinol in six trials. In allopurinol trials, three different dosifications were used; two trials reported a low dosage (of less than 400 mg), two trials reported a moderate dose (600 mg) and the remaining two employed higher doses (more than 900 mg). Supplementation was not associated with a significant reduction in the incidence of PEP [relative risk (RR) = 0.93; 95%CI: 0.82-1.06; *P* = 0.28]. In addition, the incidences of PEP in patients treated with allopurinol and those treated with other antioxidants were similar to that observed in patients who received the placebo (RR for trials with allopurinol, 0.92; 95%CI: 0.78-1.08; *P* = 0.31) and, with the use of other antioxidants, the incidence of PEP was 8.9%, whereas it was 9.7% in the control group (RR = 0.95; 95%CI: 0.77-1.18; *P* = 0.19).

CONCLUSION: Antioxidant supplementation shows no beneficial effect on the incidence of PEP. There is a lack of robust trials to support the use of antioxidants for prevention.

Key words: Antioxidant drugs; Endoscopic retrograde cholangiopancreatography; Pancreatitis; Prophylaxis

Core tip: Acute pancreatitis is considered one of the most serious complications after endoscopic retrograde cholangiopancreatography (ERCP). The mechanism of post-ERCP pancreatitis remains unclear but several studies show that free radicals play a role in its pathogenesis. Antioxidant drugs have been tested using different routes of administration and dosifications. The analysis of all randomized clinical trials published since 1999 did not revealed any significant reduction in the incidence and severity of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) when compared with placebo. There is currently a lack of robust trials to support the use of antioxidants for the prevention of PEP. Well-designed placebo-controlled randomized controlled trials are warranted to determine any beneficial effect.

INTRODUCTION

Pancreatitis is the most common complication of endoscopic retrograde cholangiopancreatography (ERCP)[1-4], with a reported incidence ranging from 1.8% to 7.2% in most prospective series[5-9]. However, the reported incidence may be up to 30%, depending on the criteria used to diagnose pancreatitis, the type and duration of patient follow-up, and the type of case mix[10]. More commonly, hyperamylasemia occurs in up to 30% of patients undergoing ERCP[11].

The generally accepted criteria for the diagnosis of post-ERCP pancreatitis (PEP) were proposed in 1991 during a consensus workshop. These criteria include the new onset of pancreatic-type abdominal pain associated with at least a three-fold increase in serum amylase or lipase occurring within 24 h after ERCP. The pain symptoms need to be sufficiently severe to require admission to a hospital or to extend the length of stay of patients who are already hospitalized[12]. Most of the episodes of acute pancreatitis are catalogued as mild. However, based on the presence of organ failure or local complications, acute severe pancreatitis occurs after 0.3% to 0.6% of ERCP procedures[10,13-15].

Numerous attempts have been made to identify a pharmacological agent that could be used to reduce the incidence and severity of PEP. An ideal agent should be highly effective in reducing PEP, safe for the patient, well tolerated, relatively affordable, and not require a prolonged administration time. Unfortunately, nearly all of the agents investigated have fallen short of these goals, but some agents have shown some promise[16,17]. An early step in the pathogenesis of acute pancreatitis is capillary endothelial injury manifested by an increase in capillary permeability[18,19]. Subsequent research has suggested that this capillary injury might be mediated by oxygen-derived free radicals[20-22]. The manifestations of pancreatitis in an experimental animal model can be ameliorated by blocking the action of oxygen-derived free radicals[23-25]. Xanthine oxidase catalyzes the conversion of hypoxanthine to xanthine, which generates an oxygen-derived free radical. This catalyst is commonly derived from a ubiquitous inactive precursor, xanthine dehydrogenase, which is present in the pancreas and in the intestinal mucosa. Xanthine dehydrogenase is converted to

xanthine oxidase by the proteolytic cleavage of a peptide fragment. These findings have prompted attempts to prevent pancreatitis by treatment with free radical scavengers (*e.g.*, superoxide dismutase, dimethyl sulfoxide, or catalase), protease inhibitors (*e.g.*, gabexate), or xanthine oxidase inhibitors (*e.g.*, allopurinol)[26-29].

The efficacy of oral allopurinol in reducing PEP has been investigated in an *in vivo* animal model[30]. Pretreatment was associated with a significant (six-fold) reduction in the incidence of pancreatitis; furthermore, when pancreatitis did occur, it was less severe. Other dog and rat models pretreated with allopurinol have demonstrated a significant reduction in the progression of histological pancreatic injury and in the severity of experimental pancreatitis[31-33].

Based on the aforementioned findings, the idea of antioxidant supplementation for the prevention of PEP seemed rational and reasonable. Therefore, we undertook this revision of randomized controlled trials (RCTs) to evaluate the effect of prophylactic antioxidant supplementation compared with placebo or no intervention on the incidence and severity of PEP.

MATERIALS AND METHODS

This systematic review included all articles published between January 1999 and December 2014, under the terms of: "antioxidants in pancreatitis in human beings". Randomized controlled trials that included pancreatitis post ERCP were selected, making a comparison of the use of antioxidants against placebo.

The inclusion criteria included: acute pancreatitis post ERCP in adults; randomized clinical trials with an intervention of any antioxidant use compared with placebo, to reduce PEP. The outcome measure was the incidence and severity of PEP.

Data extraction and outcome measure
The authors extracted the manuscripts. All selected studies must have had the inclusion criteria, and the outcome results were captured in a database in Office® Excel® 2013 (Microsoft® Corp. Redmond, CA). Any disagreements were resolved by discussion and consensus to reach a common conclusion.

Statistical analysis
The results were expressed with raw numbers, proportions, as well as mean and standard deviations. The incidence of pancreatitis between groups was analyzed with χ^2 test or Fisher Exact Test. The main outcome is expressed as relative risks and 95% confidence intervals (95%CIs).

RESULTS
Study characteristics
The main characteristics of the 12 RCTs included in this review are presented in Table 1, and the definition and severity of PEP used in each included trial are described in Table 2. These studies were published between 1999 and 2013. The sizes of the RCTs ranged from 40 to 701 (total, 3110) patients. All 12 studies included here reported post-ERCP pancreatitis events[34-45], eight reported mild and moderate PEP events[35-39,41,42,44], and six reported severe PEP events[35-37,39,41,42].

All patients were older than 18 years and were scheduled for ERCP. The selected trials used different types of antioxidants, including sodium selenite[34], allopurinol[35,38,39,42-44], N-acetylcysteine (NAC)[36,39,44], β-carotene[36], and pentoxifylline[41]. These antioxidants were administered orally or intravenously using different regimens and formulations. Two studies used an intravenous route to administer the antioxidant[21,25], whereas the remaining 10 studies applied the antioxidant orally during the perioperative period[23,24,26-32]. The dosage, timing, and frequency of these antioxidants were quite different.

Incidence of PEP
The outcome data of each included trial are described in Table 3. A total of 3110 patients were included in the 12 trials that compared antioxidants with placebo or no intervention for the prevention of PEP (1534 in the antioxidant group and 1576 in the control group). Altogether, 285 patients developed PEP (132 in the antioxidant group and 153 in the control group), with an incidence of 8.6% in the antioxidant group and 9.7% in the control group. Antioxidant supplementation was not associated with a significant reduction in the incidence of PEP [relative risk (RR) = 0.93; 95%CI: 0.82-1.06; P = 0.28]. Furthermore, when trials were divided according to the type of antioxidant, there was no significant decrease in PEP incidence (RR for trials with allopurinol, 0.92; 95%CI: 0.78-1.08; P = 0.31); the incidence in trials with other antioxidants was 8.9%, whereas it was 9.7% in the control group (RR = 0.95; 95%CI: 0.77-1.18; P = 0.19). When allopurinol studies were stratified according to the dosage of allopurinol, there was still no statistically significant preventive effect of allopurinol on mild, moderate, and severe PEP. Five doses of allopurinol were applied in these trials (300, 400, 600, 900, and 1200 mg), which were divided into three levels: low (300 and 400 mg), moderate (600 mg), and high (900 and 1200 mg).

Two RCTs[35,42] applied a low dosage of allopurinol. Budzyńska *et al*[35] showed that allopurinol did not play a significant role in the incidence and severity of PEP. Similarly, Romagnuolo *et al*[42] concluded that the overall risk of PEP did not decrease after pretreatment with allopurinol. However, it might have potential benefits in the high-risk group, but it is potentially harmful (PEP rates: allopurinol, 5.4%; placebo, 1.5%) in the non-high-risk group. Nevertheless, in this study, the percentage of patients with pancreatic duct injection was significantly higher in the allopurinol

Table 1 Main characteristics of the randomized controlled trials included in this study

Ref.	No. of patients (antioxidant/ placebo)	Patient characteristics	Antioxidant supplement	Intervention		Study design
				Antioxidant group	Control group	
Wollschläger et al[34], 1999	40 (20/20)	Patients undergoing ERCP	Selenite	Selenite, IV, 1 mg bolus/2 × 1 mg infusion, l d before ERCP	Control, no prophylaxis	Randomized, controlled
Budzyńska et al[35], 2001	200 (99/101)	Patients undergoing elective ERCP	Allopurinol	Allopurinol, orally, 200 mg, 15 h and 3 h before ERCP	Placebo, orally, 200 mg, 15 and 3 h before ERCP	Randomized, placebo-controlled
Lavy et al[36], 2004	321 (141/180)	Patients undergoing ERCP	β-carotene	β-carotene, orally, 2 g, 12 h before ERCP	Placebo, orally, 2 g, 12 h before ERCP	Randomized, double-blind, placebo-controlled
Katsinelos et al[37], 2005	249 (124/125)	Patients undergoing diagnostic or therapeutic ERCP	NAC	NAC, IV, 70 mg/kg 2 h before, and 35 mg/kg at 4 h intervals for 24 h after ERCP	Placebo IV, 70 mg/kg 2 h before, and 35 mg/kg at 4 h intervals for 24 h after ERCP	Randomized, double-blind, placebo-controlled
Katsinelos et al[38], 2005	243 (125/118)	Patients undergoing diagnostic or therapeutic ERCP	Allopurinol	Allopurinol, orally, 600 mg, 15 and 3 h before ERCP	Placebo, orally, 600 mg, 15 and 3 h before ERCP	Randomized, double-blind, placebo-controlled
Mosler et al[39], 2005	701 (355/346)	Patients undergoing diagnostic or therapeutic ERCP	Allopurinol	Allopurinol, orally, 4 h (600 mg) and 1 h (300 mg) before ERCP	Placebo, orally, 4 h (600 mg) and 1 h (300 mg) before ERCP	Randomized, double-blind, placebo-controlled
Milewski et al[40], 2006	106 (55/51)	Patients undergoing ERCP	NAC	NAC, two doses of 600 mg orally 24 h and 12 h before ERCP, and 600 mg IV for 2 d after ERCP	Placebo IV, twice a day for 2 d after ERCP	Randomized, placebo-controlled
Kapetanos et al[41], 2007	320 (158/162)	Patients undergoing ERCP	Pentoxifylline	Pentoxifylline, orally, 400 mg, 1 d before ERCP (2 and 10 pm) until the night after ERCP (6 am, 2 and 10 pm)	No intervention	Randomized, controlled
Romagnuolo et al[42], 2008	586 (293/293)	Patients undergoing ERCP	Allopurinol	Allopurinol, orally, 300 mg, 1 h before ERCP	Placebo, orally, 300 mg, 1 h before ERCP	Randomized, double-blind, placebo-controlled
Martinez-Torres et al[43], 2009	170 (85/85)	Patients undergoing ERCP	Allopurinol	Allopurinol, orally, 300 mg, 15 and 3 h before ERCP	Placebo, orally, 300 mg, 15 and 3 h before ERCP	Randomized, placebo-controlled
Abbasinazari et al[44], 2011	74 (29/45)	Patients undergoing ERCP	Allopurinol	Allopurinol, orally, 300 mg, 15 and 3 h before ERCP	Placebo, orally, 300 mg, 15 and 3 h before ERCP	Randomized, double-blind, placebo-controlled
Alavi Nejad et al[45], 2013	100 (50/50)	Patients undergoing ERCP	NAC	NAC, 1200 mg with 150 mL water orally 2 h before ERCP	Placebo, orally 2 h before ERCP	Randomized, double-blind, placebo-controlled

ERCP: Endoscopic retrograde cholangiopancreatography; IV: Intravenously; NAC: N-acetylcysteine.

group (allopurinol, 129; placebo, 102; P = 0.02), which might have resulted in a higher occurrence of PEP in the non-high-risk subgroup.

Two studies[43,44] investigated the preventive effect of a moderate dose of allopurinol. Martinez-Torres et al[43] indicated that pretreatment with allopurinol decreased the incidences of hyperamylasemia and PEP in patients undergoing high-risk procedures. However, Abbasinazari et al[44] drew the opposite conclusion after using the same dose of allopurinol, *i.e.*, that there was no difference between allopurinol and placebo regarding prevention of the occurrence of PEP (P = 0.97). However, differences were found between the two RCTs regarding the drug administration time. In the research by Martinez-Torres et al[43], subjects were administered allopurinol at 15 h and 3 h before ERCP, whereas they received it at 3 h and just before ERCP in the study by Abbasinazari et al[44] It is necessary to assess whether administration time plays a part in the effect of allopurinol.

Two trials[38,39], both published in 2005, applied a high dose of allopurinol. Mosler et al[39] observed that the overall frequency of pancreatitis was 12.55% (allopurinol, 12.96%; placebo, 12.14%; P = 0.52). Moreover, there was no significant difference for mild (allopurinol, 7.9%; placebo, 6.9%), moderate (allopurinol, 4.5%; placebo, 4.6%), or severe (allopurinol, 0.6%; placebo, 0.6%) PEP separately.

By contrast, Katsinelos et al[38] held the view that the risk of PEP decreased at the highest dosage (1200 mg) of allopurinol. They observed four cases (3.2%) of mild PEP and 21 patients (17.7%) with PEP (RR = 0.29; 95%CI: 0.12-0.71; P = 0.001). In the control group, mild PEP was observed in 6.7%, moderate PEP was observed in 9.3%, and severe PEP was observed in 1.6% of individuals. The administration time of the two studies was not the same. Patients were administered allopurinol at 15 h and 3 h before ERCP in the study by Katsinelos et al[38], whereas they received it at 4 h and 1 h before ERCP in the study by

Table 2 Definition and severity of post-endoscopic retrograde cholangiopancreatography pancreatitis

Ref.	Definition of post-ERCP pancreatitis	Severity of post-ERCP pancreatitis
Wollschläger *et al*[34], 1999	Abdominal pain attributed to pancreatitis, in association with a serum lipase or amylase level ≥ 2 times the upper limit of normal	NA
Budzyńska *et al*[35], 2001	Abdominal pain attributed to pancreatitis, together with a need for an unplanned hospitalization or an extension of a planned hospitalization by at least 2 d, and a serum amylase level ≥ 3 times the upper limit of normal at 24 h after ERCP	Mild: symptoms lasting up to 3 d and pancreas normal on the CT scan. Moderate: requiring specific therapeutic measures for 4-10 d, Balthazar's grade B/C on CT. Severe: local or systemic complications for more than 10 d, Balthazar's grade D/F on CT, or death
Lavy *et al*[36], 2004	Abdominal pain attributed to pancreatitis, in association with an amylase level ≥ 3 times the upper limit of normal	Mild: requiring 2-3 d of hospitalization. Moderate: requiring 4-10 d of hospitalization. Severe: requiring 10 d of hospitalization or requiring surgical intervention or leading to death
Katsinelos *et al*[37], 2005	Abdominal pain attributed to pancreatitis, together with a need for an unplanned hospitalization or an extension of a planned hospitalization by at least 2 d, and a serum amylase level ≥ 3 times the upper limit of normal at 24 h after ERCP	Mild: symptoms persisting for 3 d and a normal appearance of the pancreas by US and/or CT. Moderate: requirement for specific therapeutic measures for 4-10 d (Balthazar's grade B/C on CT). Severe: local or systemic complications for more than 10 d after ERCP (Balthazar's grade D/F) or death
Katsinelos *et al*[38], 2005	Abdominal pain attributed to pancreatitis, together with a need for an unplanned hospitalization or an extension of a planned hospitalization by at least 2 d, and a serum amylase level ≥ 3 times above the upper limit of normal at 24 h after ERCP	Mild: symptoms persisting for 3 d and a normal appearance of the pancreas by US and/or CT. Moderate: requirement for specific therapeutic measures for 4-10 d (Balthazar's grade B/C on CT). Severe: local or systemic complications for more than 10 d after ERCP (Balthazar's grade D/F) or death
Mosler *et al*[39], 2005	New-onset or increased abdominal pain lasting for more than 24 h, causing the unplanned admission of an outpatient for more than one night or prolonging a planned admission of an inpatient, and associated with a serum amylase level ≥ 3 times the normal level, at approximately 18 h (the next morning) after ERCP	Mild: hospitalization lasting 2-3 d. Moderate: hospitalization lasting 4-10 d. Severe: hospitalization prolonged for more than 10 d or any of the following: hemorrhagic pancreatitis, pancreatic necrosis, pancreatic pseudocyst, or the need for percutaneous drainage or surgery
Milewski *et al*[40], 2006	Clinical features consistent with acute pancreatitis beginning after ERCP and lasting for at least 24 h, associated with a serum amylase level > 5 times the normal level	NA
Kapetanos *et al*[41], 2007	Abdominal pain attributed to pancreatitis, together with a need for an unplanned hospitalization or an extension of a planned hospitalization by at least 2 d, and a serum amylase level ≥ 3 times the upper limit of normal at 24 h after ERCP	Mild: clinical pancreatitis and serum amylase at least three times higher than normal at more than 24 h after ERCP, requiring admission or prolongation of planned admission for 2-3 d. Moderate: required hospitalization for 4-10 d. Severe: required hospitalization for more than 10 d, an intervention (percutaneous drainage or surgery), or diagnosis of a pseudocyst
Romagnuolo *et al*[42], 2008	Abdominal pain attributed to pancreatitis requiring medical attention, in association with a serum lipase or amylase level > 2 times the upper limit of normal	NA
Martinez-Torres *et al*[43], 2009	Serum amylase level above 600 IU/L or ≥ 3 times the normal value, and sharp pain irradiating to the back and nausea or vomiting	Mild: two or fewer signs from Ranson's criteria. Moderate: three to six signs. Severe: more than six signs. The criteria were as follows. At admission: age, > 55 yr; WBC count, > 16000/mL; serum glucose level, > 11.1 mmol/L; SLDH/ALT, > 350 IU/L; AST level, > 250 IU/L. During initial 48 h: hematocrits, decrease of more than 0.10; BUN level, increase of more than 5 mg/dL; calcium, < 2 mmol/L; PaO₂, < 60 mmHg; base deficit, > 4 mmol/L; fluid sequestration, > 6 L
Abbasinazari *et al*[44], 2011	NA	Mild: amylase concentration at least three times the upper limit of normal at more than 24 h after ERCP, requiring admission for 2-3 d. Moderate: admission for 4-10 d. Severe: admission for more than 10 d
Alavi Nejad *et al*[45], 2013	Serum amylase level > 275 U/mL or serum lipase level > 1000 U/mL with the presence of abdominal pain	The severity of pancreatitis based on the number of hospitalized days following ERCP. Mild: < 4 d. Moderate: 4-10 d. Severe: > 10 d

CT: Computed tomography; US: Ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography; NA: Not available; AST: Aspartate aminotransferase; BUN: Blood urea nitrogen; SLDH/ALT: Serum lactate dehydrogenate to alanine aminotransferase ratio; WBC: White blood cell.

Mosler *et al*[39]. Allopurinol is absorbed approximately to 90% of the total dose in the gastrointestinal tract. It has a rapid onset, and 70% of the drug administered can transform into a long-lasting active metabolite, oxypurinol, in the liver. Peak plasma levels of allopurinol and oxypurinol can be observed at 1.5 h and 4.5 h postadministration, respectively. The half-life of allopurinol is 1-2 h, and that of oxypurinol is about 15 h[46,47]. To assess whether the preventive effect of allopurinol is influenced by the time of administration, Cao *et al*[48] recently published a meta-analysis of six RCTs of allopurinol, and classified the administration time into two levels: long (15 and 3 h before ERCP) and short (4 and 1 h before ERCP; 3 h and just before ERCP; and 1 h before ERCP), to determine whether this variable influenced the

Table 3 Outcome data of the randomized controlled trials included in this study

Ref.	Antioxidant group						Control group					
	No. of patients (*n*)	No. of PEP cases (*n*)	PEP stratified according to severity				No. of patients (*n*)	No. of PEP cases (*n*)	PEP stratified according to severity			
			Mild	Moderate	Severe				Mild	Moderate	Severe	
Wollschläger *et al*[34], 1999	20	2	NA	NA	NA		20	3	NA	NA	NA	
Budzyńska *et al*[35], 2001	99	12	9	2	1		101	8	5	3	0	
Lavy *et al*[36], 2004	141	14	10	4	0		180	17	9	4	4	
Katsinelos *et al*[37], 2005	124	15	8	7	0		125	12	7	5	0	
Katsinelos *et al*[38], 2005	125	4	4	0	0		118	21	8	11	2	
Mosler *et al*[39], 2005	355	46	28	16	2		346	42	24	16	2	
Milewski *et al*[40], 2006	55	4	NA	NA	NA		51	6	NA	NA	NA	
Kapetanos *et al*[41], 2007	158	9	6	1	2		162	5	4	0	1	
Romagnuolo *et al*[42], 2008	293	16	8	6	2		293	12	4	6	2	
Martinez-Torres *et al*[43], 2009	85	2	2	0	0		85	8	8	0	0	
Abbasinazari *et al*[44], 2011	29	3	2	1	0		45	5	3	2	0	
Alavi Nejad *et al*[45], 2013	50	5	NA	NA	NA		50	14	NA	NA	NA	
Total	1534	132					1576	153				

ERCP: Endoscopic retrograde cholangiopancreatography; PEP: Post-ERCP pancreatitis; NA: Not available.

incidence of PEP. Those authors could not demonstrate any significant difference between the long[35,38,43] and short[39,42,44] administration groups, in contrast to the results obtained by Katsinelos *et al*[38] and Martinez-Torres *et al*[43], who demonstrated a beneficial effect of allopurinol in the prevention of PEP after using a long administration time.

DISCUSSION

Some differences arose between the six RCTs of allopurinol. As specified previously, five different doses were used, and two different regimens of administration were employed; moreover, the risk factors were inconsistent in the RCTs mentioned above[35,38,39,42-44]. For example, male sex, days of hospitalization, and administration of allopurinol were considered risk factors by Katsinelos *et al*[38], whereas previous PEP, pancreatic injection, and pancreatic therapy were predictors of PEP in the study by Martinez-Torres *et al*[43], compared with the nonsignificant risk factors, such as sex, number of pancreatic injections, biliary sphincterotomy, and pancreatic stent placement, reported by Romagnuolo *et al*[42].

In terms of the problems mentioned above, and as recommended by Cao *et al*[48], we suggest performing a rigid determination of risk factors and classifying them into patient-related and procedure-related risk factors. Definite patient-related risk factors (suspected sphincter of Oddi dysfunction, female sex, and previous pancreatitis) and definite procedure-related risk factors (precut sphincterotomy and pancreatic injection) were listed in the European guidelines, which could act as a guide for future research[49].

In the remaining six trials, four different antioxidants were used[34,36,37,40,41,45]. The incidence of PEP in these six trials was 8.9% (49 cases among 548 patients receiving any of the four antioxidants), whereas it was 9.7% in the control group (*P* = 0.19;

RR = 0.95; 95%CI: 0.77-1.18). Considering only the trials of NAC[37,40,45], the incidence of pancreatitis was 10.4% in the treatment group and 14.1% in the control group; however, the difference was not statistically significant (*P* = 0.22; RR = 0.83; 95%CI: 0.61-1.15).

Gu *et al*[50] published the most recent meta-analysis of antioxidants as prophylactic agents for PEP. Those authors evaluated 3010 patients and found no statistically significant difference in the incidence of PEP between the antioxidant group (8.5%) and the control group (9.1%; RR = 0.92; 95%CI: 0.65-1.32; *P* = 0.66). They concluded that there was a lack of strong evidence in support of the use of antioxidants to reduce the incidence of PEP or the severity of episodes. However, they recognized the limitations of the evaluated trials, as the dose, route, and time of administration, as well as the evaluation of the patients and procedure-related risk factors, were not uniform. For these reasons, they suggested performing more powerful RCTs to test specific doses, routes, and times of administration, as well as including extensive evaluation of the severity of pancreatitis episodes, risk factors, and subrogate outcome variables, such as hyperamylasemia and length of hospital stay.

Traditionally, stent placement in pancreatic ducts of small caliber (5 Fr) has been considered as the standard treatment to prevent PEP, and it is even recommended in the management guidelines for the prevention of pancreatitis in patients at high risk[51,52]. Recently, Akbar and colleagues published the results of a meta-analysis that included a total of 29 studies, comprising 22 of pancreatic stent placement and seven of the use of nonsteroidal anti-inflammatory drugs (NSAIDs), showing that both stenting and transrectal administration of NSAIDs are superior to placebo in the prevention of post-ERCP pancreatitis. The combination of transrectal NSAIDs and the use of stents together showed no greater effectiveness in the

prevention of post- ERCP pancreatitis compared with each intervention alone[53].

Regarding pharmacological prophylaxis, it is possible that NSAIDs might be useful[48]. Since the publication by Elmunzer *et al*[15] in 2012, most medical centers have included the use of preoperative NSAIDs for the prevention of PEP. The rectal administration of 100 mg of diclofenac or indomethacin may be effective in preventing the incidence of PEP.

In conclusion, this review showed that the pro-phylactic use of antioxidants in different dosages and at different administration times had no preventive effect regarding the incidence of PEP. Further well-designed placebo-controlled RCTs are warranted to confirm the preventive effect of antioxidants in PEP.

COMMENTS

Background
Acute pancreatitis is considered one of the most serious complications after endoscopic retrograde cholangiopancreatography (ERCP). The mechanism of post-ERCP pancreatitis remains unclear but several studies show that free radicals play a role in its pathogenesis. Antioxidant drugs have been tested using different routes of administration and dosifications. The analysis of all randomized clinical trials published since 1999 did not revealed any significant reduction in the incidence and severity of post-endoscopic retrograde cholangiopancreatography pancreatitis (PEP) when compared with placebo.

Research frontiers
There is currently a lack of robust trials to support the use of antioxidants for the prevention of PEP. Well-designed placebo-controlled randomized controlled trials are warranted to determine any beneficial effect. Numerous attempts have been made to identify a pharmacological agent that could be used to reduce the incidence and severity of PEP.

Applications
Antioxidant supplementation shows no beneficial effect on the incidence of PEP. There is a lack of robust trials to support the use of antioxidants for prevention.

Peer-review
The manuscript by Fuentes-Orozco and colleagues is a review of antioxidant therapy to prevent post-ERCP. The authors appropriately focus on the randomized clinical trials (those published between 1999 and 2013). The authors present a well written and thorough review the theoretical basis for antioxidants and the available clinical work on this topic.

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