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Systematic Review

Antioxidant Therapy for Pain Relief in Patients with Chronic Pancreatitis: Systematic Review and Meta-analysis

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Background: Currently, there is no specific therapy for chronic pancreatitis (CP). The treatment of micronutrient antioxidant therapy for painful CP has been sporadically used for more than 30 years, however, its efficacy are still poorly understood.

Objective: The purpose of this meta-analysis is to investigate the safety and efficacy of antioxidant therapy for pain relief in patients with CP.

Setting: University Hospital in China

Study Design: Systematic review and meta-analysis

Methods: Two authors independently reviewed the search results and extracted data and disagreements were resolved by discussion. Effects were summarized using standardized mean differences (SMDs), weighted mean differences, or odds ratio (OR) according to the suitable effect model. MEDLINE, PsycINFO, Scopus, EMBASE, and the Cochrane Central Register of Controlled Trials were searched from 1980 through December 2012. Randomized controlled trials (RCTs) that studied antioxidant supplementation for pain relief in patients with CP were analyzed.

Results: Nine randomized controlled trials (RCTs) involving 390 patients were included. Overall, there was no association of antioxidant therapy with pain reduction in CP patients (SMD, –0.55; 95% CI, –1.22 to 0.12; $P = 0.67$). However, antioxidant therapy significantly increased blood levels of antioxidants in CP patients versus the placebo group (SMD, 1.08; 95% CI, 0.74 to 1.43; $P < 0.00001$). Interestingly, combined antioxidant (selenium, β-carotene, vitamin C, vitamin E, methionine) therapy was found to be associated with pain relief (SMD, -0.93; 95% CI, -1.72 to -0.14; $P = 0.02$), while the trials in which a single antioxidant was used revealed no significant pain relief (SMD, -0.12; 95% CI, -1.23 to 0.99; $P = 0.83$) in CP patients. Strong evidence was obtained that the antioxidants increased adverse effects (OR, 6.09; 95% CI, 2.29 to 16.17, $P < 0.01$); nevertheless, none was serious.

Limitations: Because of the small sample, a consolidated conclusion cannot be reached based on current RCTs. Large-sample RCTs are needed to clarify the analgesic effect of antioxidants in CP patients.

Conclusions: Combined antioxidant therapy seems to be a safe and effective therapy for pain relief in CP patients. Measures of total antioxidant status may not help to monitor the efficacy of antioxidant therapy for patients with CP.

Key words: Antioxidant, pain, chronic pancreatitis, meta-analysis

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Chronic pancreatitis (CP) is a progressive inflammatory disease of the pancreas resulting in gradual loss of normal pancreatic parenchymal architecture and subsequent fibrosis (1). For patients with CP, abdominal pain is the most common presentation (2), which may significantly decrease quality of life and sometimes lead to severe malnutrition (3). Currently, there remains no effective medical therapy for pain relief in patients with CP (4). Surgical and endoscopic therapies have been considered as alternative, rather than complementary, approaches to relieve pain in patients with CP (5). However, none of these procedures is commonly performed and their efficacies remain controversial (6).

CP has been reported to arise as a result of pathological exposure of the pancreatic acinar cells to short-lived oxygen free radicals--a process termed oxidative stress, which may be caused by increased exposure to xenobiotics such as alcohol, nicotine, and petrochemical fumes (7,8). Oxidative stress can cause cell damage either directly by cell membrane destruction, toxicity from free radical peroxidation products, or through altering signaling pathways (9,10). Free radical peroxidation products may cause degranulation of mast cells and inflammation mediated by chemotaxis and pain (11). Some reports have shown increased oxidative stress in patients with alcoholic and idiopathic CP (12-14), suggesting that antioxidant therapy may be beneficial in patients with CP.

Since the early 1990s, the efficacy of antioxidant therapy in reducing pain among patients with CP has been investigated in several small-sample studies (15-21). However, these studies were controversial and insufficient to support a significant clinically meaningful therapeutic effect for antioxidant therapy. Recently, a randomized trial by Siriwardena et al (4) noted that antioxidant therapy did not have any beneficial effect on pain relief or improving quality of life in patients with CP. Interestingly, these findings are at odds with their earlier study results (22) as well as another recent randomized trial by Bhardwaj et al (23). What should a clinician take from these contradictory results in order to optimally manage these difficult patients (24)?

Aiming to provide recommendations for clinical decisions and future research, we performed the current meta-analysis to systematically review and summarize the literature on antioxidant therapies for pain relief in patients with CP.

Methods

Based on the QUORUM guidelines (Quality of Reporting of Meta-analyses) (25) and the recommendations of the Cochrane Collaboration (26), the meta-analysis was performed.

Data Sources and Searches

The electronic databases screened were MEDLINE (1980 through December 2012), PsycINFO (1980 through December 2012), Scopus (1980 through December 2012), EMBASE (1980 through December 2012), and the Cochrane Library (Issue 11 of 12, December 2012), including the Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, and Health Technology Assessments. Searches were limited to human patients and performed for all languages and types of publication. The search terms were chronic pancreatitis, CP, pancreatic inflammation, antioxidant, vitamin, superoxide dismutase, manganese, glutamine, butylated hydroxyanisole, taurine, glutathione, curcumin, catalase, peroxidase, lutein, xanthophylls, zeaxanthin, selenium, riboflavin, zinc, carotenoid, cobalamin, retinol, alpha-tocopherol, ascorbic acid, beta-carotene, carotene; and all MeSH terms for pharmacologically active antioxidants, oxidative stress, micronutrient, pain relief, and treatment. The full search strategy in Fig. 1 was developed for MEDLINE and was adapted for the other electronic databases. Three of us (G-HC, JH, YZ) manually and independently screened reference sections of relevant original articles, reviews, and meta-analyses.

Study Selection

Studies were included according to the following criteria: CP diagnosed based on symptoms and medical examination; any randomized controlled trial (RCT) or controlled clinical trial designed with a control group receiving a placebo and another group receiving antioxidant therapy. Corresponding authors of RCTs with an incomplete data presentation (e.g., missing means, standard deviations of pretest and posttest data, or standard deviations of change scores) were contacted when necessary.

Data Extraction

Two of us (WW, S-XW) independently screened the titles and abstracts of potentially eligible studies. The full text articles were examined independently by 2 of

us (G-HC, YZ) to determine whether they met the inclusion criteria. Three of us (JH, Y-LD, JC) independently extracted data (study characteristics and results) using data extraction forms. The collected data were then entered into RevMan 5.1 (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark) using the double-entry system. Point estimates for selected variables were extracted and checked by the other 2 reviewers. In cases of disagreement between the 2 reviewers, a consensus was achieved through discussion among all of the reviewers. A record of reasons for excluding studies was kept. We selected pain, antioxidant status, as well as adverse effects as outcome measures for antioxidant therapy in CP.

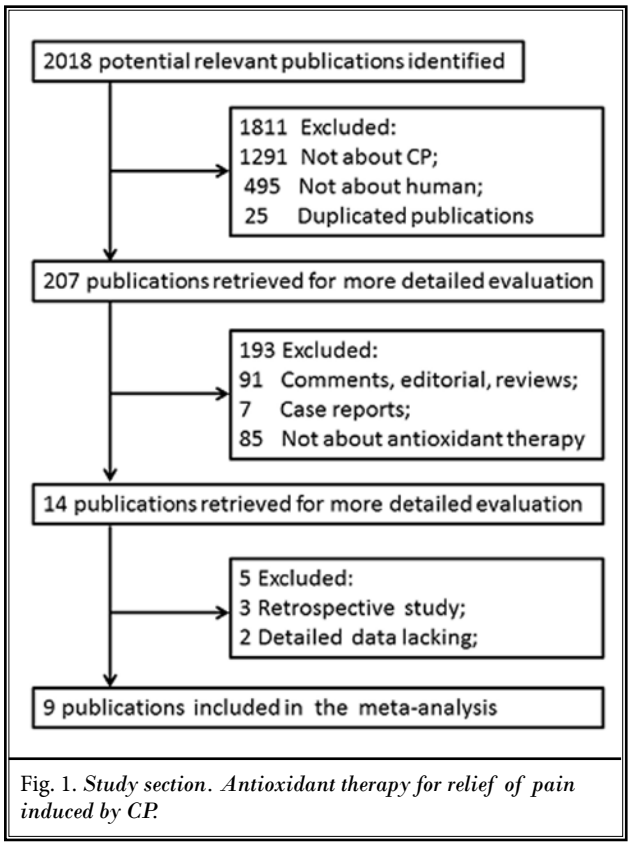


Fig. 1. *Study section. Antioxidant therapy for relief of pain induced by CP.*

Definitions

1. Measurement of pain: pain intensity measured by categorical scales, visual analog scales, pain diaries (mean difference in pain scores or recorded frequency of exacerbation of pain) or reduction in the number of painful days per month.
2. Antioxidant status: we selected the 4 most common antioxidant biomarkers (selenium, β-carotene, vitamin C and vitamin E) to reflect the antioxidant status.
3. The Jadad test (5 items) (27) was applied for assessing methodological quality as high (score 5), moderate (score 4), or low (scores 1- 3).

Data Collection and Analysis

We collected the following data and information:

1. General study information such as title, authors, publication source, publication year and country
2. Characteristics of the study: design, study setting, quality criteria (e.g., randomization method, allocation procedure, blinding of patients, caregivers and outcome assessors, withdrawals and dropouts)
3. Characteristics of the study population (e.g., sample size, age, gender, and etiology)
4. Characteristics of the intervention, such as treatment comparators, duration of therapy
5. Outcome measures as mentioned above
6. Outcome measures at the end of the controlled phase, and any summary measures with standard deviations, confidence intervals and P values, where given, dropout rate and reasons for withdrawal.

Nonparametric tests (Mann-Whitney U test, Kruskal Wallis test) were used for comparing continuous variables. A 2-sided *P* value of 0.05 or lower was considered significant. Meta-analyses were conducted using RevMan 5.1 according to the Cochrane Handbook for Systematic Reviews of Interventions (28).

We used the standardized mean difference (SMDs) to calculate for pain and antioxidant status outcomes because they were determined in different trials using different scales. Odds ratio (OR) was used in evaluating the antioxidants' related side effects. To calculate SMDs, we used means and change scores and their standard deviations. When these values were shown in a graph manner without any description of absolute value, we first tried to contact the authors. Measurements from the graph were used if we could not get data from the authors. When only the standard error was reported, it was converted into standard deviation (28).

Twelve statistics were used to measure heterogeneity of the RCTs. If the I2 value was less than 50%, a fixed-effects meta-analysis was applied. If the I2 value was 50% or more, a random-effects meta-analysis was used (28). We used Cohen categories (29) to evaluate the magnitude of the effect size, calculated by SMD,

or OR, and designated a D greater than 0.2 through 0.5 as a small effect size, a D greater than 0.5 up to 0.8 as a medium effect size, and a D greater than 0.8 as a large effect size. We used the following descriptors to classify meta-analysis results (30): "strong" indicated consistent findings in multiple (at least 2) high- or moderate-quality RCTs; "moderate" indicated consistent findings in multiple low-quality RCTs or one high- or moderate-quality RCT; "limited" indicated one low-quality RCT; and "conflicting" indicated inconsistent findings among multiple RCTs.

Visual assessment of the funnel plot calculated by RevMan 5.1 software was used to investigate potential publication bias (i.e., the association of publication probability with the statistical significance of study results). Publication bias may lead to asymmetrical funnel plots (31).

Results

Study Selection

The flow chart of our study is shown in Fig.1. The literature search yielded 2,018 citations. Initially, 207 publications met our inclusion criteria. The excluded 1,811 publications contained 495 animal experiments, 25 duplicate publications, and 1,291 publications not about chronic pancreatitis. On more detailed review, an additional 193 papers were excluded for the following reasons: comments, editorial, case reports, reviews, and publications not about chronic pancreatitis. Five more publications were further excluded because of retrospective research (11,32,33) and a lack of detailed data (22,34). The remaining 9 studies met our selection criteria and were included in the meta-analysis (4,15-21,23).

Description of the Included Studies

The detailed characteristics of these included studies are described in Table 1. Overall, 390 patients were included in our study, of which 230 patients received antioxidant therapy and 160 received placebo treatment. Five of 9 studies were conducted in Europe, 3 in Asia, and one in the US. There were 5 studies with high methodological quality (score 5), 3 with moderate quality (score 4), and one with low quality (score 3). The median age of patients ranged from 23.6 ± 12.8 years (20) to 49.8 ± 12.7 years (4) in the antioxidant group and ranged from 27.8 ± 16.8 years (20) to 50 ± 9 years (4) in the placebo group. The percentage of male patients ranged from 60% (18) to 95% (16) in the antioxidant group and 50% (18) to 100% (20) in the placebo group. One study (16) was conducted on patients with alcohol-induced chronic pancreatitis and one (20) on patients with nonalcoholic chronic pancreatitis. The rest of the studies were conducted on both types of patients. Four of 9 studies investigated the

Table 1. *A brief summary of characteristics of included studies.*

Source (Country)	Patients						Intervention		Sample Size		Adverse events		Study design	Jadad score
	Age, Y		Sex (male:female)		Etiology									
	A	P	A	P	A	P	Antioxidant therapy	Duration (week)	A	P	A	P		
Combined antioxidant trails														
Siriwardena et al, 2012 (UK)	49.8±12.7	50±9	23:10	27:10	alcohol 24; idiopathic 9	alcohol 27; idiopathic 10	Antox	24	33	37	8	1	Randomized; double blind; placebo-controlled	5
Bhardwaj et al, 2009 (India)	31.3±11.4	29.6±9.3	47:24	39:17	alcohol 25 idiopathic 46	alcohol 15; idiopathic 41	Antox	24	71	56	12	3	Randomized; double blind; placebo-controlled	5
Kirk et al, 2006 (UK)	NR	NR	NR	NR	NR		Antox	20	11	8	2	0	Randomized; double-blind; placebo-controlled; crossover	4
Uden et al, 1992, 1990 (UK)	41.0±14.5		15:5		recurrent acute 5; alcoholic 7; idiopathic 8		Antox	20	9	11	NR		Randomized; double-blind; crossover; placebo-controlled	5
Single antioxidant trails														
Durgaprasad et al, 2005 (India)	23.6±12.8	27.8±16.8	7:1	7:0	non-alcoholic chronic pancreatitis		Curcumin	6	8	7	0	0	Randomized; single blind; placebo-controlled	3
Banks et al, 1997 (USA)	42 (31-51)		8:5		NR		Allopurinol	10	5	8	NR		Randomized, double-blind, two-period crossover clinical trial	4
Bilton et al, 1994 (UK)	48.7±11.9	41.4±13.5	6:4	5:5	recurrent acute: 8; alcoholic: 2; idiopathic: 10		SAMe	20	10	10	NR		Randomized; double-blind; crossover; placebo-controlled	5
Salim et al, 1991 (Iraq)	41 (32-61)		21:1	22:1	alcohol-induced		Allopurinol;		21	23	8	0	Randomized; double-blind; placebo-controlled	4
	42 (31-62)	39 (31-65)	NR				dimethyl sulfoxide	NR	22					

Abbreviation: A, antioxidant; P, placebo; Antox, Combined antioxidant (organic selenium, vitamin C, β-carotene, α-tocopherol and methionine; SAMe, S-denosyl methionine

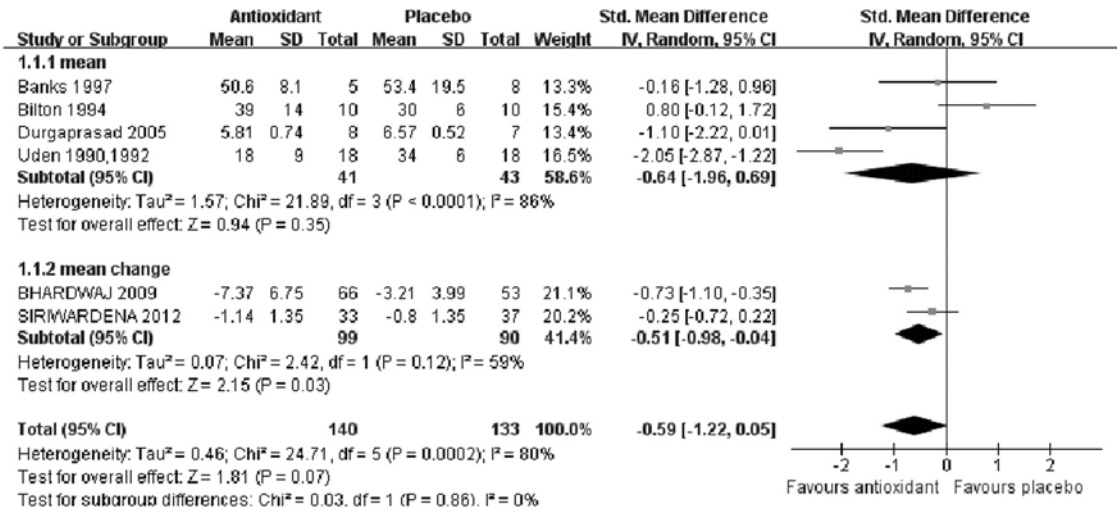


Fig. 2. Effects of antioxidants in CP for the outcome of pain.

effects of administering a single antioxidant; the other 5 took a combined antioxidant approach, which involved organic selenium, vitamin C, β-carotene, α-tocopherol and methionine. The duration of studies ranged from 6 weeks (20) to 24 weeks (4,23).

Meta-Analyses

Based on Cohen categories for evaluating the magnitude of effect sizes, overall there was no association of antioxidant therapy with a reduction in pain induced by chronic pancreatitis (Fig. 2, SMD, –0.55; 95% confidence interval [CI], –1.22 to 0.12; $P = 0.07$). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous (I2 = 80%, Fig. 2) and could not be combined. The heterogeneity generation may be due to the different measurements of each study used to assess pain. A complex stratified analysis, and random effect models for individual differences, were applied due to the limited number of included studies. However, antioxidant therapy can significantly increase blood levels of antioxidants in patients with CP compared with the placebo group (Fig. 3, SMD, 1.08; 95% CI, 0.74 to 1.43; $P < 0.00001$). Similarly, the studies were heterogeneous (I2 = 59%, Fig. 2).

A previous study (18) has demonstrated that combined antioxidant supplementation appeared to be more promising for CP treatment than single antioxidant supplementation. Thus we collected data from combined antioxidant (selenium, β-carotene, vitamin C, vitamin E, methionine) trials and single antioxidant trials separately to check that possibility. Combined antioxidant therapy was associated with pain relief in patients with CP (Fig. 4, SMD, -0.93; 95% CI, -1.72 to -0.14; $P = 0.02$), while single antioxidant trials had no association with pain reduction (Fig. 5, SMD, -0.12; 95% CI, -1.23 to 0.99; $P = 0.83$). The Cochrane Q test for heterogeneity indicated that the studies were heterogeneous (I2 = 86%, Fig. 3; I2 = 70%, Fig. 5). High heterogeneity was presented in most of the crude summaries, however, no further layer analysis was applied when considering the small effect size and limited number of included studies. A random-effects model was performed only when the I2 value was 50% or more.

Adverse Events with Antioxidant Therapy

Four studies reported adverse events from antioxidants compared to placebo in a total of 282 patients (4,16,21,23). Thirty-one of 158 (19.6%) patients assigned to antioxidants reported adverse events compared to 4 of 124 (3.2%) allocated to placebo. Strong evidence was obtained for the antioxidants to have greater adverse events (OR, 6.09; 95% CI, 2.29 to 16.17, $P < 0.01$) with no heterogeneity detected between studies (I2 = 0%, $P = 0.77$) (Fig. 6). There were no serious adverse events in all studies and the most common adverse events allocated to antioxidant therapy were headache and nausea.

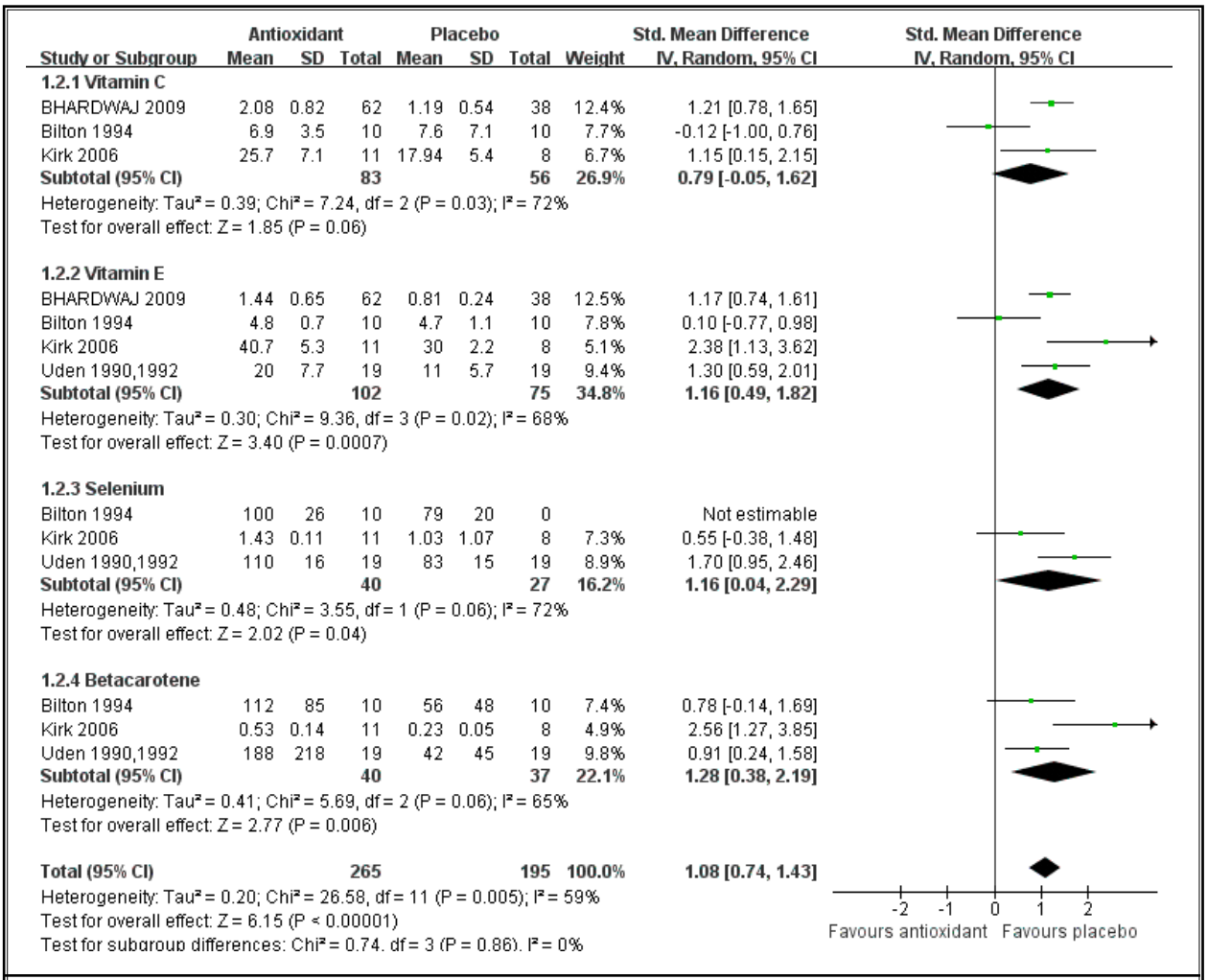


Fig. 3. *Effects of antioxidants in CP for the outcome of blood levels of antioxidants.*

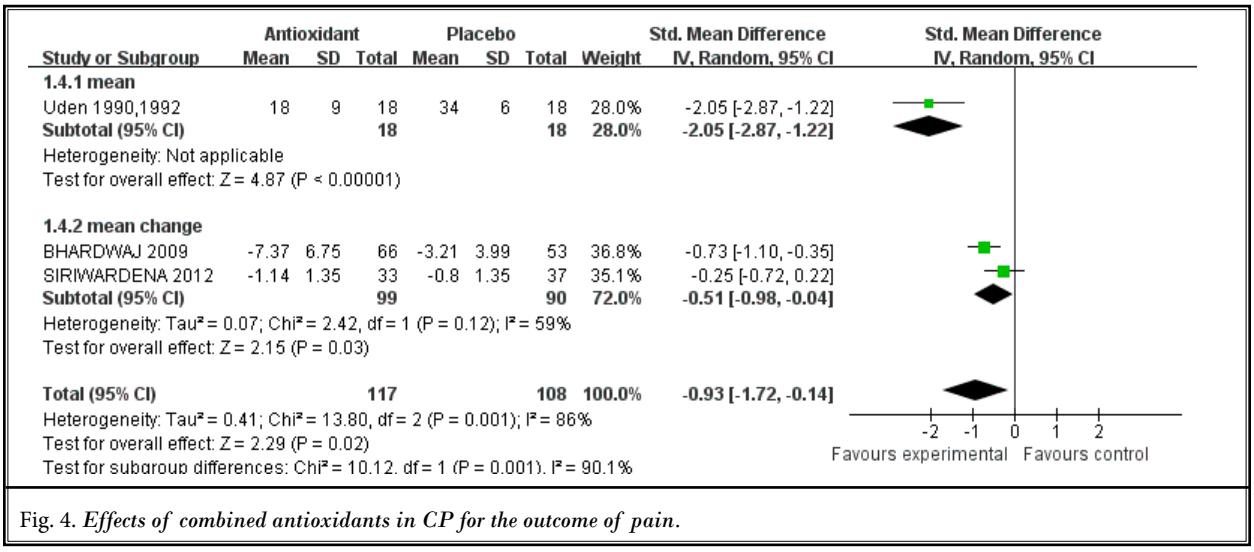


Fig. 4. *Effects of combined antioxidants in CP for the outcome of pain.*

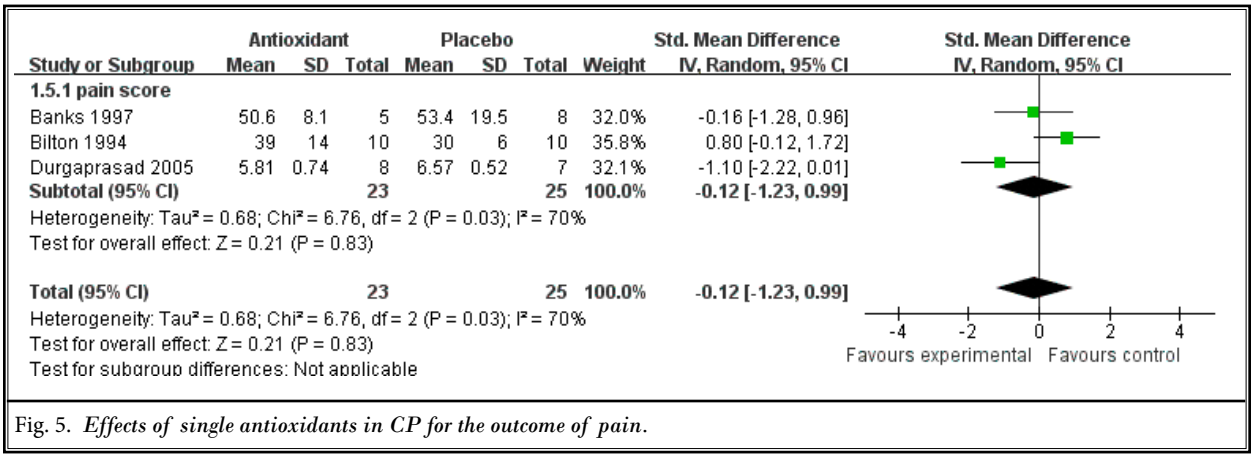


Fig. 5. *Effects of single antioxidants in CP for the outcome of pain.*

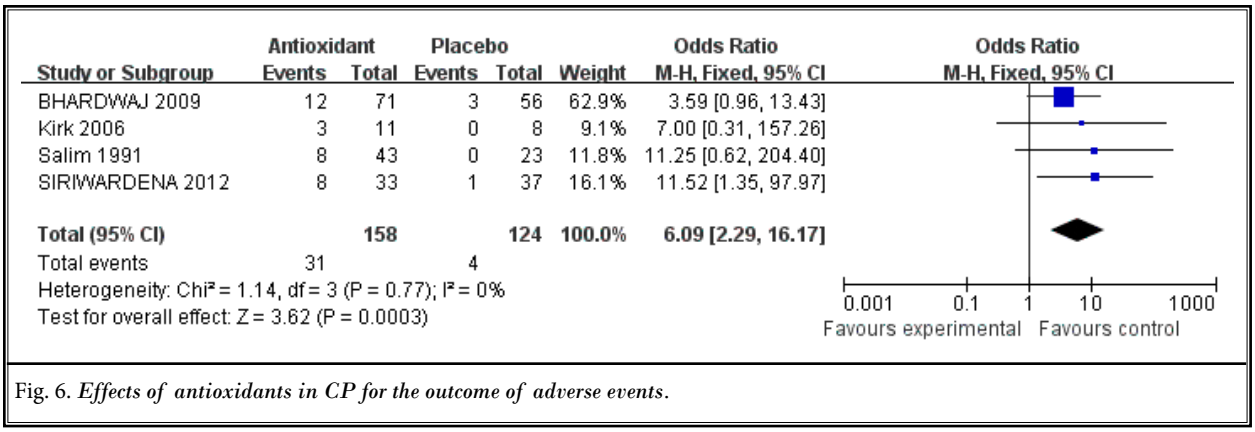


Fig. 6. *Effects of antioxidants in CP for the outcome of adverse events.*

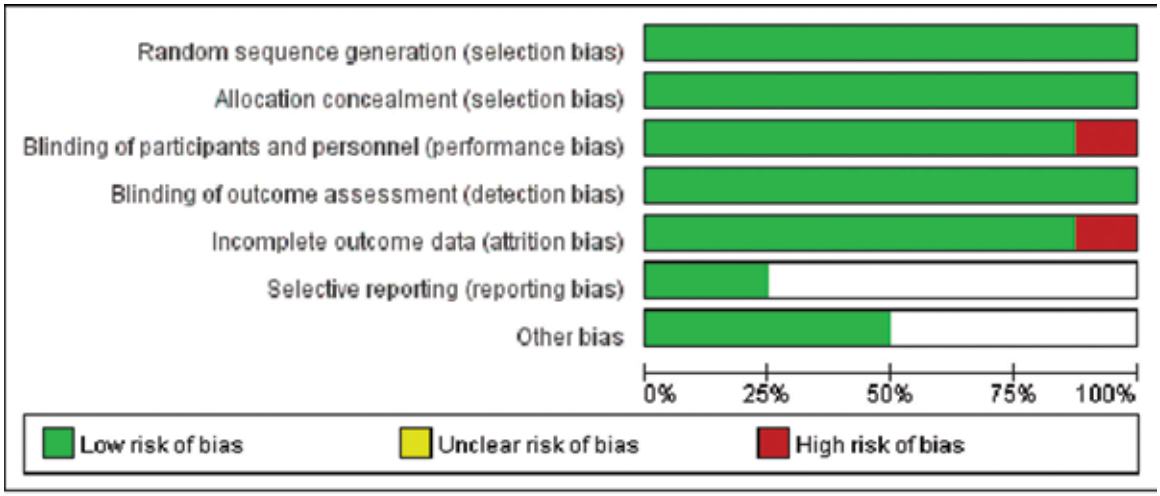
Risk of Bias in Included Studies

Assessment tables of the risk of bias are presented in Fig. 7A and Fig. 7B. High risk of bias was rated in the study of Kirk et al. (21) and Durgaprasad et al. (20) because of incomplete outcome data of pain or single blinding of participants and personnel. Sensitivity analysis was applied by excluding the study of Kirk et al. (21) and Durgaprasad et al. (20). There was no association between antioxidant therapy with a reduction in pain induced by chronic pancreatitis (Fig. 8, SMD, 0.5; 95% CI, 1.22 to 0.21; P=0.16). Antioxidant therapy significantly increased blood levels of antioxidants in patients with CP compared with placebo group (Fig. 9, SMD, 0.96; 95% CI, 0.60 to 1.31; P< 0.00001). In addition, strong evidence was obtained to show that the antioxidants can increase side effects (Fig. 10, OR, 5.99; 95% CI, 2.14 to 16.78, P < 0.0006). However, adverse effects assessing of funnel plots for subgroup analysis revealed an asymmetric distribution, suggesting publication bias (Fig. 11).

Discussion

In 2009, the efficacy of antioxidant therapy for CP was systematically reviewed but a meta-analysis was not done (35). Three years later, a review came to the conclusion that antioxidant supplementation was suggested to be superior for reducing pain and increasing the quality of life in patients with CP rather than a single antioxidant, however, without a meta-analysis of the currently available RCTs on this topic a convincing conclusion was not reached (6). To our knowledge, this is the most recent systematic review with meta-analysis on the efficacy and safety of antioxidants therapy for CP-induced pain, however, the conclusion made by this research is not consolidated because of the potential publication bias. Our findings, together with the previous 2, may strengthen the concept that antioxidants are useful for CP-induced pain.

Quality of life is reduced in patients with CP, with 85% of patients experiencing deep and internal pain, ranging in severity from mild to unbearable (36). In light



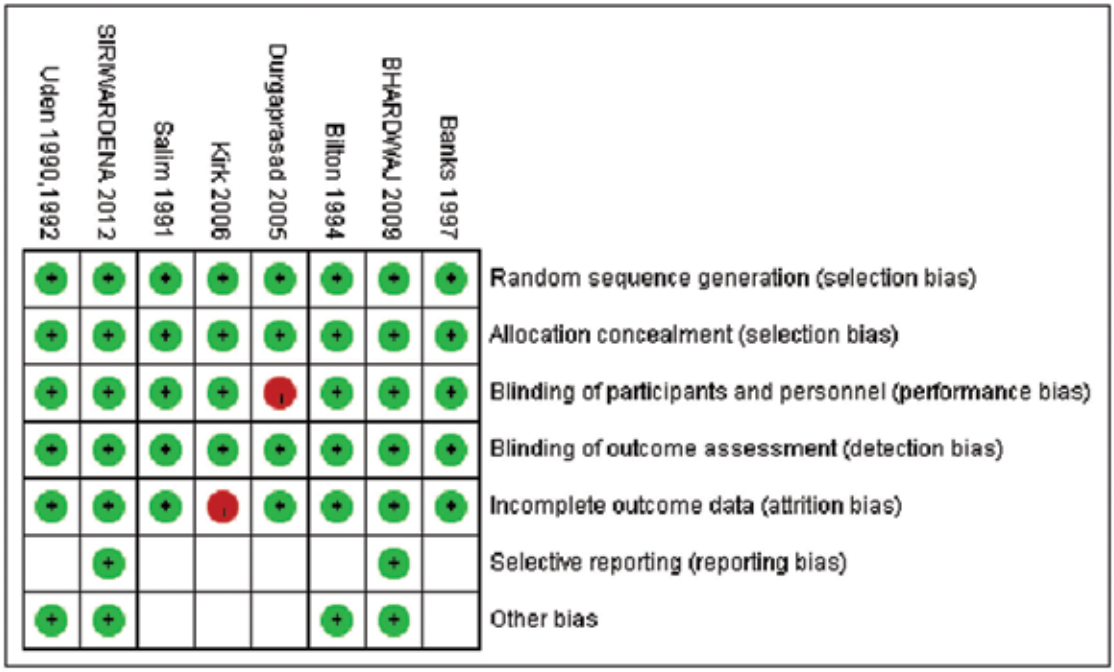


Fig. 7. *A. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies. B. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.*

of the increased oxidative state seen in patients with CP, many studies about antioxidant therapy for reducing pain induced by CP have been conducted. In the single antioxidant trials, allopurinol (16,19), dimethyl sulfoxide (DMSO) (16), SAMe (18), and even curcumin (20), the active constituent of turmeric, have been investigated for their potential efficacy. However, most of them demonstrated disappointing results except for the study by Salim et al (16), which showed the short-term efficacy of allopurinol or DMSO in the treatment of recurrent pain produced by CP. Since the first study by Uden et al (15), combined antioxidant supplement (selenium, β-carotene, vitamin C, vitamin E, methionine) has shown promising efficacy for pain relief in patients with CP in several studies (17,21-23). Subsequently, a systematic review summarized the effects of antioxidant therapy in the management of CP but not a meta-analysis because that pain reduction was assessed in a different way than

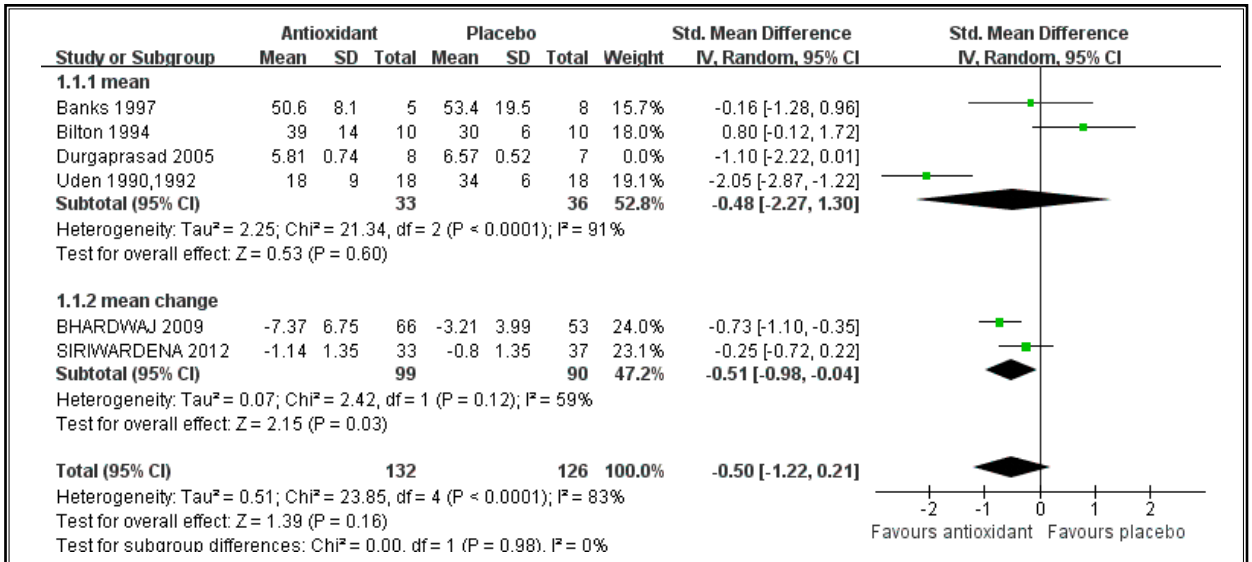


Fig. 8. *Effects of antioxidants in CP for the outcome of pain (Durgaprasad [20], study is excluded).*

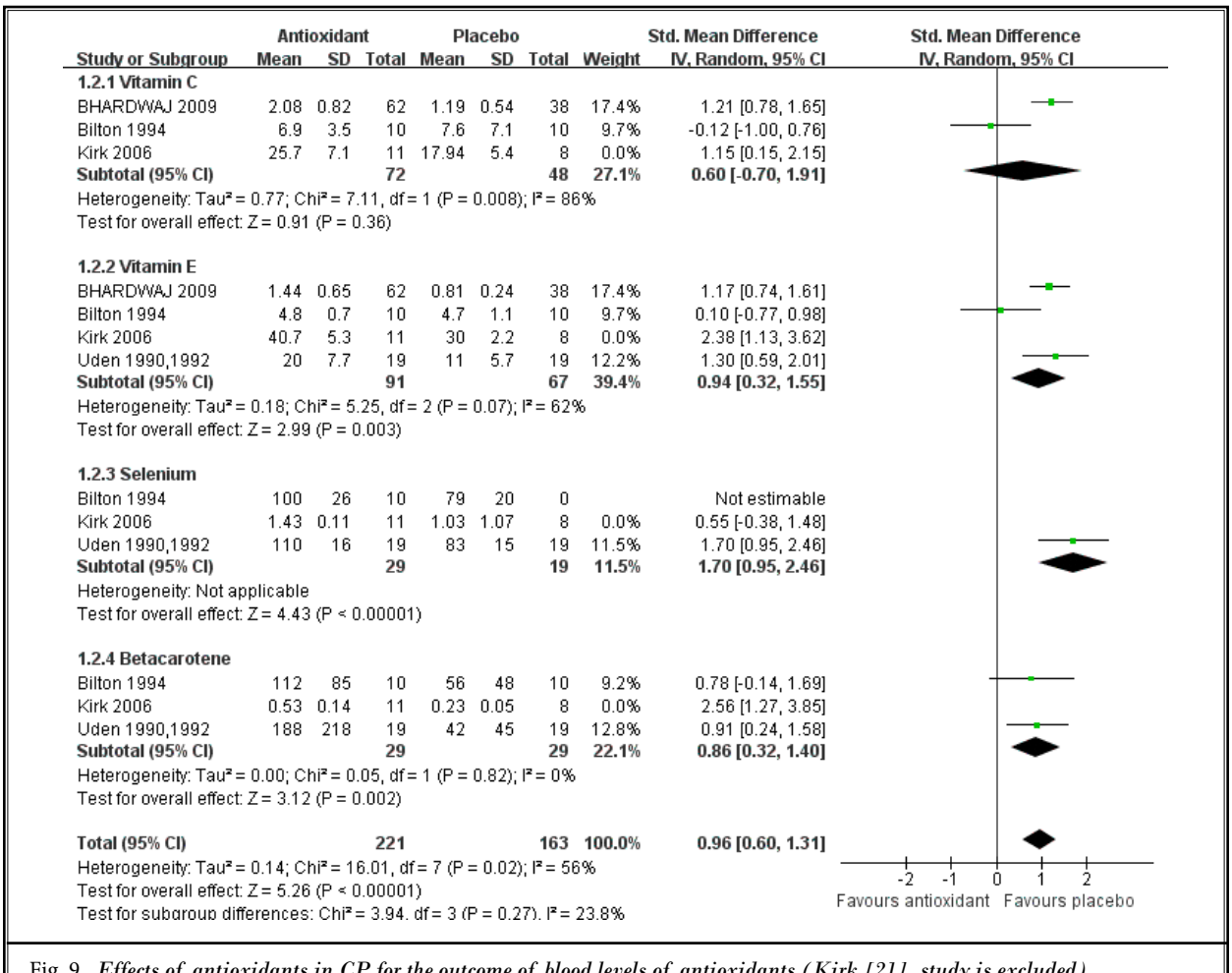


Fig. 9. *Effects of antioxidants in CP for the outcome of blood levels of antioxidants (Kirk [21], study is excluded).*

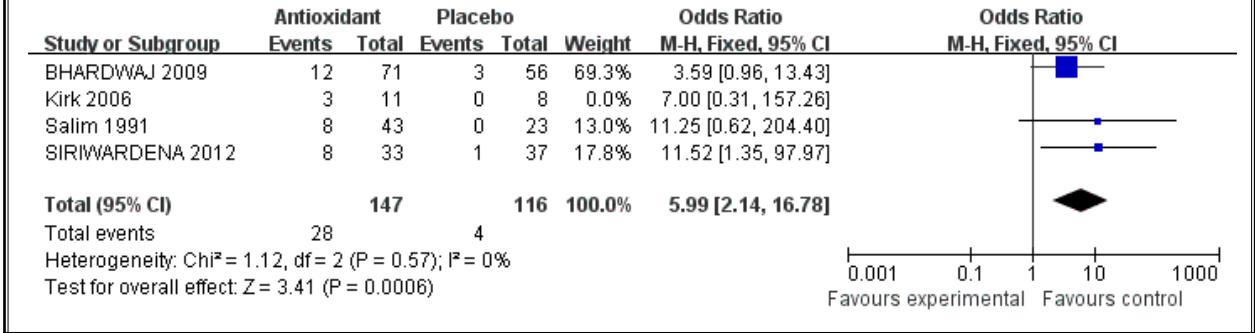


Fig.10. *Effects of antioxidants in CP for the outcome of adverse events. (Kirk [21], study is excluded).*

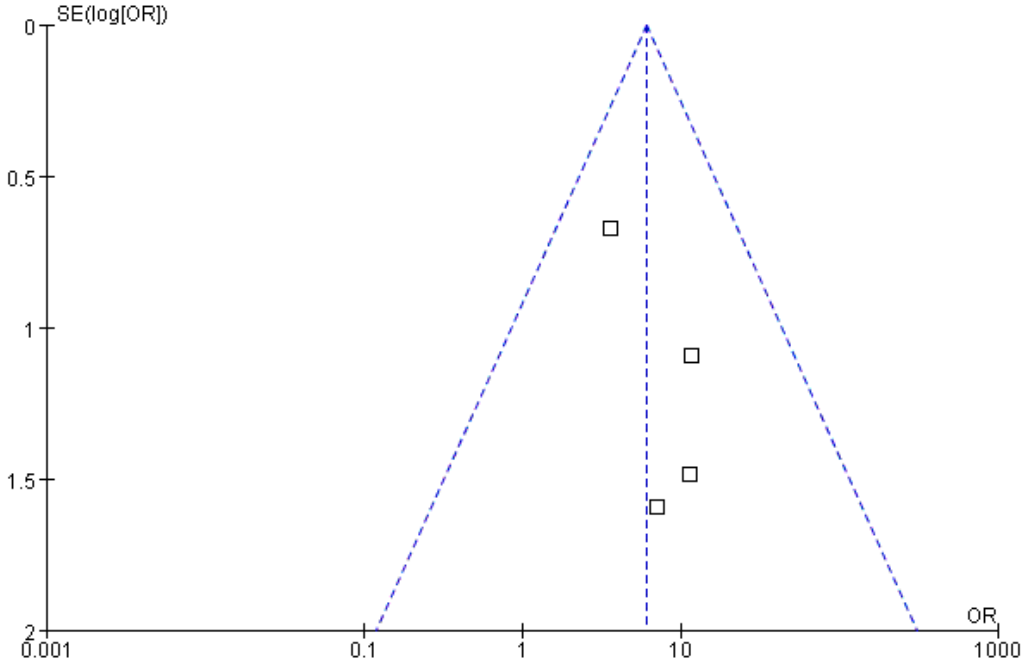


Fig.11. Publication bias analysis.

in these studies (35). Thus, the efficacy of antioxidants has remained controversial due to conflicting data and also because early studies included small sample sizes and/or lacked robust study design. It is noteworthy that Shah et al (22) in 2010 and Siriwardena et al (4) in 2012 reported controversial study results about the effects of antioxidant therapy on pain relief or improving quality of life in patients with CP. The 2012 study (4), which definitively showed the ineffectiveness of the use of antioxidant treatment in controlling pain in CP patients, may have contributed to clinician confusion.

Using statistical methods, we analyzed the results of studies to overcome the limits of earlier studies, like small sample size. We found strong evidence for the efficacy of antioxidants therapy in increasing blood levels of antioxidant biomarkers but we did not find a favorable effect of antioxidants on pain relief. Interestingly, when we focused on the combined antioxidant trials, a strong association of antioxidants with pain relief in patients with CP was observed. In addition, our study also showed that antioxidant therapy appeared to be safe and there were no serious adverse events after therapy.

Considering the antioxidant biomarkers measured were different in included studies, we selected the 4 most common antioxidant biomarkers (selenium, β-carotene, vitamin C and vitamin E) to reflect the antioxidant status. In our study, antioxidant status was significantly increased after antioxidant therapy, while the efficacy of a sole agent for antioxidant therapy remains controversial. It seemed that measures of total antioxidant status may not help to monitor the efficacy of antioxidant therapy for patients with CP. Further study is needed to explore whether some kinds of antioxidant biomarkers could be used as a valuable measurement.

In the West, alcohol abuse is the most common cause of CP, which accounts for 70% of cases (37). In India, common idiopathic chronic pancreatitis, also known as tropical pancreatitis, has a quite different clinical history from other kinds of pancreatitis (38). Early study found that there was no relation between the cause of pancreatitis and clinical outcomes (35). However, the same combined antioxidant therapy for the 2 types of patients with CP showed stark differences in analgesic efficacy (4,23). One study demonstrated a clinically meaningful improvement in pain relief, and the other showed no effect at all (24). In addition, the characteristics of patients, like age and gender, may also influence study results. For example, a recent study suggested that combined antioxidant therapy may be less effective in more elderly patients who have alcohol as the etiology (4). Thus, the particular subgroup of patients with CP that could obtain optimal analgesic benefit from combined antioxidant therapy needs further evaluation. Furthermore, the optimal combinations of antioxidants, the optimal doses of antioxidants, and the best duration of study are other important issues in future RCTs.

Limitations

This meta-analysis has limitations. First, the heterogeneity of the methods to access the degree of pain among these studies was significant. The primary reason was that pain reduction was evaluated by various methods in the studies. Furthermore, the studies were grossly disparate in their use of antioxidant agents, duration of follow-ups, and dosing regimens. The heterogeneity remained in subsequent subgroup analysis, therefore, the random-effects model was applied. Second, we sought to identify non-English studies but could not retrieve original significant data of one published study. Third, there are limitations of some methods used in this article, such as using I2 for assessing the amount of heterogeneity in random-effects meta-analysis (39) and visual assessment of the funnel plot for excluding a publication bias.

Conclusions

This systematic review and meta-analysis suggested the following: combined antioxidant therapy seems to be safe and effective for pain relief in patients with CP; measures of total antioxidant status may not help to monitor antioxidant therapy for patients with CP; subgroups of patients with CP who obtain optimal benefit from combined antioxidant therapy need further investigation.

Disclosures

Guo-Hong Cai, Jing Huang, Yan Zhao, and Jing Chen contributed equally to this work as first authors. All authors have completed the Unified Competing Interest form and declare there was no financial relationship with any organization that might have an interest in the submitted work during the previous 3 years, and there are no other relationships or activities that could appear to have influenced the submitted work. Drs. Yun-Qing Li, Wen Wang, and Sheng-Xi Wu contributed equally to this paper.

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