

LEADING ARTICLE

Systematic review and meta-analysis: Is there any role for antioxidant therapy for pain in chronic pancreatitis

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Abstract

Chronic pancreatitis (CP) is an irreversible disease with increased oxidative stress. The therapeutic role of antioxidants for pain reduction in CP is debatable. A systematic review of articles in PubMed and Embase until February 2020 was performed. Only randomized controlled trials conducted on humans to evaluate the therapeutic effects of antioxidants for pain in CP were included. Studies of other design, non-human studies, and those that did not objectively assess pain were excluded. Twelve articles and four articles were eligible for qualitative and quantitative analysis, respectively. The four included studies had a total of 352 participants. Pain reduction as measured by a visual analog scale was not significantly different in the antioxidant group compared to placebo (standardized mean difference = -0.14 [95% confidence interval [CI] = -0.44 to 0.17]; $P = 0.38$). Number of pain-free participants was also similar (odds ratio [OR] = 1.59 [0.97–2.59]; $P = 0.06$). There was no difference in outcome when comparing different etiologies of CP or age group. The reduction in the number of analgesics used did not differ between both groups. Antioxidants were not associated with increased adverse events (OR = 2.59 [CI = 0.77 – 8.69]; $P = 0.12$). A qualitative analysis on the effect on quality of life did not suggest any significant improvement with antioxidants. There was no significant pain reduction or change in quality of life in CP patients with use of antioxidants. This makes their routine use in the management of CP questionable. However, further studies may identify a subgroup where they are more useful.

Introduction

Chronic pancreatitis (CP) represents the irreversible stage of inflammation in the pancreas. It is a common reason for emergency visits and rarely requires admission for a few days.¹ The prevalence has been estimated to be about 10–20 per 100 000 in the western population; however, a much higher prevalence is seen in the Indian subcontinent.^{2,3} There is also a difference in the age of onset of disease, with younger patients in Asia.⁴ Cardinal manifestations of CP include severe abdominal pain, exocrine insufficiency, and endocrine insufficiency. Pain is one of the most common and debilitating features of CP and adversely affects the quality of life.⁵ Although surgical and endoscopic methods are frequently used to treat pain, medical management remains the first step in management.⁶ The pathogenesis of pain in CP is multifactorial and may be due to increased intraductal pressure, interstitial hypertension, and ischemia and may also be neurogenic in origin.⁷ Based on probable mechanisms, various approaches for pain control have been attempted.

Oxidative stress is one of the proposed mechanisms for pain generation in CP.⁸ Patients with CP have lower levels of antioxidants and increased free radical activity, compared to normal healthy adults, and upregulation of stress response genes in CP.^{9–12} Theoretically, it is very tempting to assume that increasing the level of antioxidants may reverse the process or at least halt the progression of disease. Antioxidants have been shown to be useful for pain relief, as well as reduction of other complications of CP.¹³ However, these questions remain unanswered as various studies have shown different results, and the use of antioxidants is still at the discretion of the treating clinician.¹⁴

Antioxidants are substances that were initially thought to decrease free radical damage and thought to ameliorate the effects of this damage in various disease models.¹⁵ Natural antioxidants include vitamins A, C, and E and other molecules like curcumin, which have been used in trials for CP.¹⁶ However, in recent times, combinations of antioxidants that are commercially available are preferred in patients with CP.^{17,18}

Today, analgesia in CP is managed by a multidisciplinary approach.¹⁹ Antioxidants are one of the options available for management of pain.⁶ The results from prior studies have been contradictory, and no consensus has yet been reached. The present meta-analysis is aimed to assess the effect of antioxidants in pain reduction, adverse events, and effect on quality of life (QoL) in patients with CP compared to placebo. The meta-analysis was conducted using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.

Methods

Literature search and selection criteria. This review was conducted in accordance with the PRISMA guidelines. A formal search was performed to identify all previous studies that had investigated the effect of antioxidants for pain relief in CP. Table 1 lists the Population, Intervention, Comparator, Outcomes, Study design (PICOS) criteria for inclusion of studies. Only randomized controlled trials were included. No strict criteria for pain assessment were used for inclusion. Articles having a different design; unpublished data like thesis, review articles, and editorials; and trial including pediatric patients and nonhuman studies were excluded. Trials were included irrespective of the blinding, number of participants, language, or year of publication. The minimum duration of intervention for inclusion of trials was 4 weeks.

We conducted a literature search on PubMed and EMBASE with the following MeSH terms and keywords: “chronic pancreatitis” combined with various substitutes for terms for antioxidants. The search terms included were as follows: (“chronic pancreatitis” OR “tropical pancreatitis” OR “idiopathic pancreatitis”) AND pain AND (“allopurinol” OR “antioxidants” OR “ascorbic acid” OR “beta carotene” OR “carotenoid” OR “catalase” OR “free radical scavengers” OR “glutathione” OR “methionine” OR “micronutrients” OR “selenium” OR “taurine” OR “tocopherol”). No restriction of year or language of publication was used. References of the included articles were also searched to identify any missed studies.

Two authors (Srikant Mohta and Namrata Singh) performed the literature search, reviewed each study individually, and decided whether it should be included or not based on predecided inclusion and exclusion criteria. Disagreements between two authors were resolved by discussion. In case disagreement persisted, other authors (Anoop Saraya and Deepak Gunjan) reviewed the study and took the final decision.

Table 1 Population, intervention, comparator, outcomes, study design criteria for inclusion of studies

Parameter	Inclusion criteria
Population	Humans with chronic pancreatitis
Intervention	Administration of antioxidants
Comparator	Patients treated with placebo
Outcome	Pain
Study design	Randomized controlled human trials

Outcome measures. Our primary outcome was to compare overall pain relief after treatment with antioxidant compared to placebo. Secondary outcomes included assessment of adverse events and change in QoL with use of antioxidants in CP. We considered QoL an outcome when studies reported it quantitatively as an activity of daily living, loss of man days, or if a specific questionnaire for QoL was used.

Data abstraction and quality assessment. Data were extracted independently by two authors (Srikant Mohta and Namrata Singh). In case of any conflict, a consensus was reached between the authors. If conflict still persisted, it was resolved by a third author (Anoop Saraya). The information that was extracted from each of the studies included first author, year of publication, design of the study, type of intervention, dose and duration of intervention, etiology of CP, duration of follow up, pain outcomes, QoL, and adverse events. Based on the information extracted, pain characteristics and outcomes in both groups were noted. All data were entered in Microsoft excel for analysis.

Risk of bias was assessed using the tool in the Cochrane Handbook for Systematic Review of Interventions.²⁰ The six domains used for overall assessment included: sequence allocation, allocation concealment, blinding, incomplete data outcome, selective outcome reporting, and other sources of bias. Each domain was adjudged according to the predetermined definitions of “high risk” and “low risk.” A judgment of “unclear risk” was made when there was no evidence of high or low risk in the selected studies.

Statistical analysis. The meta-analysis of extracted data was conducted using Cochrane Review Manager 5.3 (<http://ims.cochrane.org/revman>). When pain was analyzed with a similar scale (visual analog scale), standardized mean difference (SMD) was used as a measure of effect size. In case of other outcomes like number of pain-free participants and adverse events, effect was measured as odds ratio (OR) with 95% confidence interval (CI). Some trials reported incomplete information, in which case means and standard deviations were estimated based on median, range, and sample sizes wherever possible.

Heterogeneity was calculated using the Higgins χ^2 test, and inconsistency was quantified by I^2 . A χ^2 test with a P value <0.10 was considered to indicate the presence of heterogeneity, and an $I^2 > 50\%$ was considered to suggest marked inconsistency in effect between studies. A fixed-effects model was used if heterogeneity was less than 50%; otherwise, a random-effects model was used.

Results

Our literature search revealed a total of 668 articles. For various reasons, as given in Figure 1, a total of 656 articles were excluded, so 12 studies were included in our study for qualitative analysis. Of these, a few studies were not included for quantitative analysis. The study by Bilton *et al.* was excluded as the it included patients with both recurrent pancreatitis and CP, with no distinction available between the outcomes of both groups.²¹ The study by Deprez *et al.* reported only baseline pain scores.²² Kirk's study did not give any objective parameter to assess pain,

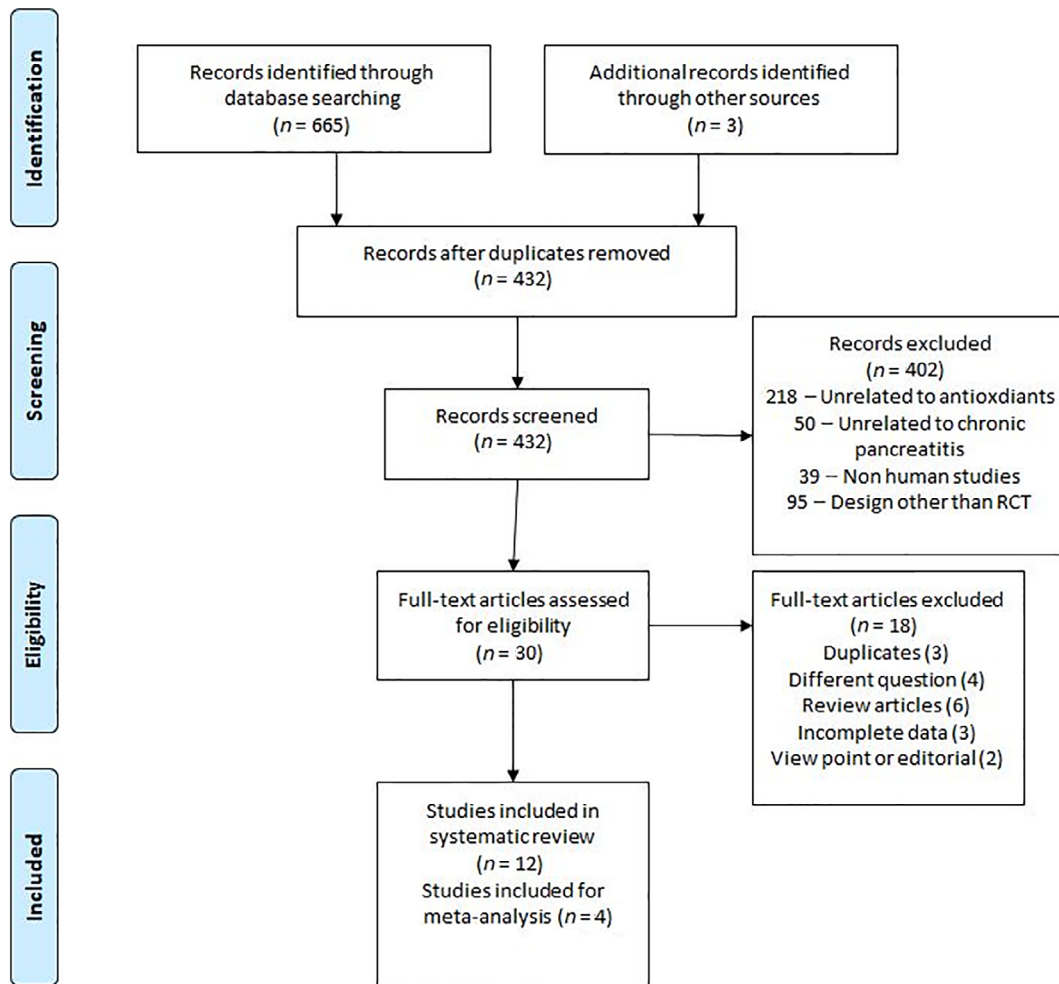


Figure 1 Study flow diagram for literature search.

so it could not be included for meta-analysis, but the data on QoL were used for the systematic review.²³ Nandi's study was available only in abstract form and so was excluded.²⁴ The studies by Durgaprasad *et al.*¹⁶ and Banks *et al.*²⁵ were excluded as the interventions used (curcumin and allopurinol, respectively) are not utilized as antioxidants in the present era. The study by Jarosz *et al.*²⁶ was excluded from quantitative analysis in view of the high risk of performance, detection, and attrition bias and incompleteness of data. Finally, the study by Salim *et al.* was excluded as they used a short duration (3 days) of antioxidants in CP.²⁷ After excluding the above, four studies with a total of 352 patients were included for quantitative analysis in our study.^{17,18,28,29}

The characteristics of the studies included in meta-analysis and some important studies for qualitative analysis are represented in Table 2. The antioxidant used in all the four included studies was a combination of antioxidant molecules, which are commercially available and used frequently by clinicians in the management of patients of CP. The median duration of antioxidant use in the studies was 24 weeks. The etiologies of included CP were combined in most trials. Two of the studies were from

India^{17,18} and two from the United Kingdom.^{28,29} All of them were placebo controlled trials. The dosage, timing, and frequency of the individual components of antioxidants varied between studies.

Quality assessment and risk of bias. Risk of bias was assessed based on the authors' assessment and is shown in Table 3. All included studies had a low risk of bias and had no significant design flaws.^{17,18,28,29} A funnel plot was not conceived the number of studies was fewer than 10.

Effect on pain. All studies that were included reported outcomes related to pain. Data for pain at the end of study was available for 162 patients in the antioxidant arm and 145 patients in the placebo arm. The trials reported pain assessment in different ways.

A visual analog scale (VAS) was used in three of these studies.^{17,28,29} This is an ordinal scale of 1–10, with 10 representing the highest pain severity. When reduction in VAS was compared, there was no statistically significant difference in pain with the use of antioxidants (SMD = −0.14 [95% CI = −0.44 to

Table 2 Description of the studies included in the meta-analysis and some important studies from qualitative analysis

Study	Design	Duration (weeks)	Etiology (alcoholic: non-alcoholic) (in %)	Participant number (intention to treat)	Intervention (active)	Intervention (control)	Pain-related outcomes (analyzed in this article)	Reports of ADR	Report on QoL
Uden <i>et al.</i> ²⁸	DB, cross-over trial	10 weeks in each arm	35:65	28	Daily doses of 600 mg organic selenium, 9000 IU b-carotene, 0.54 g vitamin C, 270 IU vitamin E and 2 g methionine	Placebo	VAS	Yes	No
Banks <i>et al.</i> ²⁵	RCT (DB, PL controlled), cross-over trial	4 weeks in each arm	Not available	16	Daily dose of allopurinol 300 mg/day	Placebo	VAS	No	Yes (activities of daily living)
Durgaprasad <i>et al.</i> ¹⁶	RCT, single blind, placebo controlled	6	Not available	20	500 mg of pure extract of curcumin (95%) with 5 mg of piperine (three times per day after food)	Placebo (lactose)	VAS	Yes	No
Bhardwaj <i>et al.</i> ¹⁸	RCT (DB, PL controlled)	24	32:68	147	Daily doses of 600 mg organic selenium, 0.54 g ascorbic acid, 9000 IU b-carotene, 270 IU tocopherol and 2 g methionine	Placebo	Pain free participants	Yes	Yes (man days lost per month)
Jarosz <i>et al.</i> ²⁶	RCT (DB, PL controlled)	24	100:0	91	Vitamin C (2 x200 mg per day) and vitamin E (2 x 150 mg per day)	Placebo	Pain free participants	Yes	No
Siriwardena <i>et al.</i> ²⁹	RCT (DB, PL controlled)	24	73:27	92	Antox version 1.2 tablets, 3 times/day. Each capsule containing 2880 mg of methionine, 720 mg Vitamin C, 228 mg Vitamin E and 300 mcg of selenium	Placebo	VAS Pain free participants	Yes	Yes (EORTC – modified†)
Singh <i>et al.</i> ¹⁷	RCT (DB, PL controlled)	24	22:76	107	600 µg organic selenium, 0.54 g vitamin C, 9000 IU β-carotene, 270 IU vitamin E, and 2 g methionine	Placebo	VAS Pain-free participants	Yes	Yes (EORTC – modified†)

†EORTC modified, European Organization for Research and Treatment of Cancer QOL Questionnaire Core questions 30 (EORTC QLQ C-30 version 3.0 [both in English and vernacular language]) and Pancreatic Modification (28 questions) (QLQ PAN-28 [in English]).

DB, double blind; PL, placebo; QoL, quality of life; RCT, randomized controlled trial; VAS, visual analog scale.

Table 3 Summary of risk of bias: Review authors' judgments about each risk of bias domain for included trials

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data addressed (attrition bias)	Selective reporting (reporting bias)	Other bias
Uden <i>et al.</i> ²⁸	●	●	●	●	●	●	●
Bhardwaj <i>et al.</i> ¹⁸	●	●	●	●	●	●	●
Siriwardena <i>et al.</i> ²⁹	●	●	●	●	●	●	●
Singh <i>et al.</i> ¹⁷	●	●	●	●	●	●	●

●, Low risk of bias; ●, intermediate risk of bias; ●, high risk of bias.

0.17]; $P = 0.38$) (Fig. 2a). No significant heterogeneity was observed for this outcome ($I^2 = 17\%$, $P = 0.30$).

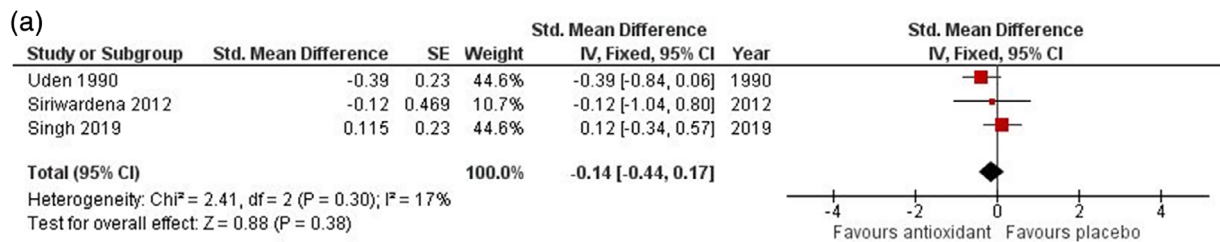
Subsequently, a meta-analysis was performed on the basis of number of pain-free participants reported in studies, receiving either a placebo or antioxidant. This outcome was reported in a total of three of the four studies.^{17,18,29} There was no significant increase in the number of pain-free participants with the use of antioxidants (OR = 1.59 [0.97–2.59]; $P = 0.06$) (Fig. 2b). No significant heterogeneity was observed among the studies included in this analysis ($I^2 = 46\%$, $P = 0.16$), and a fixed-effects model was used.

An analysis of reduction of VAS and pain-free participants using some of the excluded studies was also performed, but there was no significant change in the result (Figure S1, Supporting information). These studies were chosen as they met our inclusion criteria but had been excluded to keep the data homogenous and improve the quality of studies in the review.

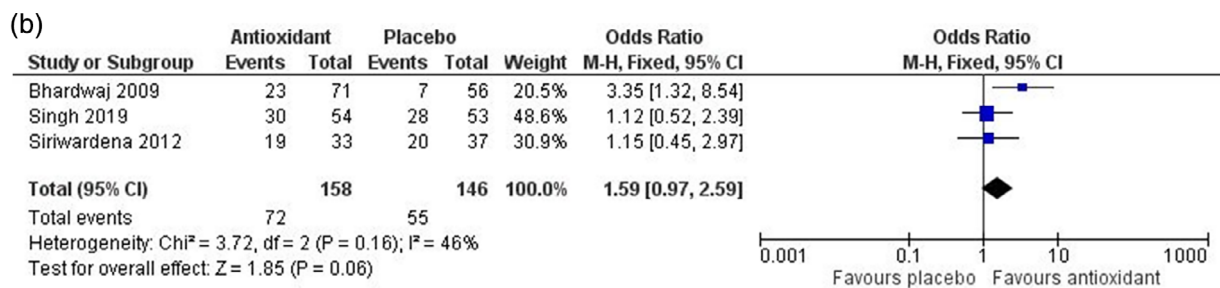
Adverse events. All the included trials reported adverse effects.^{17,18,28,29} Overall, 30 (16.6%) of the 181 participants in

the antioxidant arm reported adverse events compared to 14 (8.3%) of the 169 in the placebo group. Antioxidant use was not associated with a higher rate of adverse events than the placebo (OR = 2.59 [CI = 0.77–8.63]; $P = 0.12$) (Fig. 3). Significant heterogeneity among the studies included was noted ($I^2 = 52\%$, $P = 0.10$), and the random-effects model was used. Most adverse events were minor and included nausea, headache, and gastrointestinal intolerance. Only two patients with significant side effects were described. One developed seizures as a result of hepatic encephalopathy.²⁹ The patient's side effect cannot clearly be attributed to use of antioxidants. Another patient developed swelling of the face and eyes (in one of the excluded studies).²⁵ No trials reported mortality.

Quality of life. QoL was reported in three of the included studies, and different parameters were used for assessment. In view of this, only a systematic review was performed and not a meta-analysis. For this outcome, we also included data from Kirk *et al.*²³ and Banks *et al.*²⁵ Two studies showed an improvement

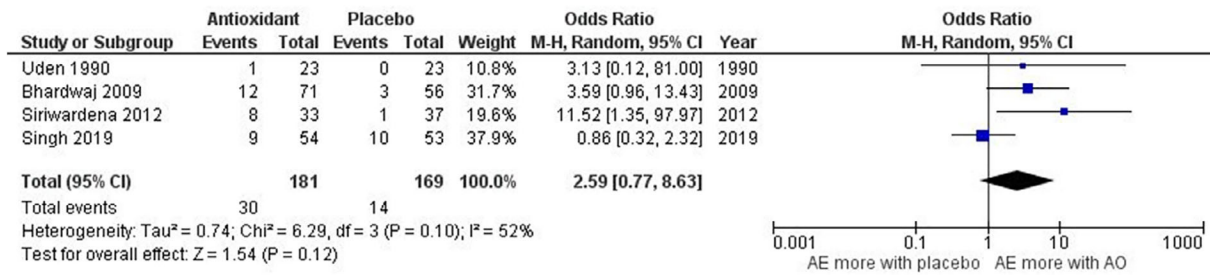


Effect of antioxidants on pain in patients with CP as measured by visual analogue scale (VAS)



Effect of antioxidants on pain in patients with CP as measured by pain free participants

Figure 2 Forest plot showing effect of antioxidants on pain in patients with chronic pancreatitis as measured by visual analog scale (a) and as measured in terms of pain-free participants at end of study period (b).



Forest plot showing adverse events with antioxidants use in patients with chronic pancreatitis

Figure 3 Forest plot showing adverse events with antioxidant use in patients with chronic pancreatitis.

in the QoL indices.^{18,23} Bhardwaj *et al.* reported a higher reduction in the man days lost per month in the antioxidant group compared to the placebo group.¹⁸ Kirk *et al.* also reported a significant improvement in the antioxidant group's QoL.²³ They reported a quantitative measure with the SF-36 questionnaire and revealed a significant improvement in six of the eight domains assessed in the model.

In contrast to this, three other major studies reported no significant improvement.^{17,25,29} Banks *et al.* reported that there was no improvement in the activities of daily living (ADLs) in the antioxidant arm compared to the placebo.²⁵ The ANTICIPATE trial and the trial by Singh *et al.* both assessed QoL based on validated objective questionnaires in the form of the European Organization for Research and Treatment of Cancer (EORTC) QOL Questionnaire Core questions 30 (EORTC QLQ C-30 version 3.0 [both in English and vernacular language]) and pancreatic modification (28 questions) (QLQ PAN-28 [in English]).^{17,29} In both these studies, questions pertaining to the global health quality of patients were not significantly different between both groups.

To summarize, antioxidants would not improve QoL in all patients of CP. A pattern can be noticed where studies that showed improvement in pain with antioxidants also showed improved QoL, and the studies where no improvement was seen demonstrated no improvement in QoL. Therefore, we need to identify the subgroup that experiences pain reduction with antioxidants as their QoL should also improve.

Additional analysis. Among our included studies for meta-analysis, three used antioxidants for a period of 24 weeks, while one study by Uden *et al.* used it for 10 weeks. To determine if the duration of therapy affected the response, a subgroup analysis was performed with the remaining three studies. To evaluate analgesic effect, pain-free participants were assessed, which had initially been calculated on these studies only, and the results remained the same (Fig. 2b) There was no change in adverse effects as well (OR = 2.65 [0.63–11.15]; I² = 68%) (Figure S2).

Sensitivity analysis was performed based on etiology (alcoholic vs non-alcoholic) and age (<35 years vs >35 years). This could be done for two studies for which individual patient data were available.^{17,18} No statistically significant increase in the number of pain-free participants was observed with antioxidant use in any of the groups based on etiology (non-alcoholic

CP: OR = 1.82 [0.92–3.61]; I² = 0%; alcoholic CP: OR = 1.76 [0.05–61.58]; I² = 84%) or age group (age < 35: OR = 2.21 [0.9–5.45]; I² = 36%, age > 35: OR = 1.43 [0.45–4.52]; I² = 0%) (Figure S3).

Two studies also reported oral analgesic use, and on analysis, we found that antioxidant use did not significantly reduce the number of oral analgesics required per month (Figure S4).

Discussion

In our meta-analysis, we found that antioxidants did not reduce pain in CP. This was true for severity of pain as assessed by VAS and also for number of pain-free participants, which is a more clinically important, as well as more objective, outcome. As freedom from pain was a stringent outcome, we also tried to elicit if analgesic use reduced. We could not demonstrate any reduction in use, although this was limited by data from only two studies, and type of oral analgesic used was not available. Second, there were slightly more adverse effects with the antioxidant, but it was not seen with commercially available combination antioxidants. The effect of antioxidants on QoL was variable across studies.

The included trials each had a small sample size but were all randomized controlled trials and well designed. There was no heterogeneity between the studies that reported VAS score as the outcome measure of pain or when assessing number of pain-free participants. The results from the studies were different. Bhardwaj *et al.* showed a significant improvement in the number of pain-free participants in their study, while the same could not be replicated in the other studies. This could possibly be due to the difference in their baseline pain characters, severity of underlying disease, and prior treatment received. Bhardwaj *et al.* included patients who had pain at least once a month in the last 3 months or had severe pain needing hospitalization even once in the last 3 months. Siriwardena *et al.*, on the other hand, included patients with a baseline pain value of Numerical Pain Rating Scale (NRS) of >5 at least once a week, and most of these patients were difficult to manage. This possibly shows that pain at the time of inclusion and usage of analgesics (including number and type) can affect the response to antioxidants as those on opioid analgesics can also have hyperalgesia and lower pain thresholds and some dependence. This could alter the outcome assessed, and it should be kept in mind when interpreting results.

Prolonged use is also a common practice in most centers using antioxidants.⁶ Therefore, to keep the results clinically relevant, we did not include trials that had a very short duration of therapy, even though they were well designed.²⁷

It has been proposed previously that oxidative stress may vary according to the etiology of CP, especially for alcoholic pancreatitis.³⁰ However, those results were based on the predominant group in each study and not on individual patient analysis. On analysis of individual patients from the two studies, we could not demonstrate any difference in results during sensitivity analysis of alcoholics *versus* non-alcoholics. Although data from Siriwardena *et al.* were not part of the sensitivity analysis, they included more than 70% of alcoholic patients and therefore were unlikely to alter the results. Another approach was attempted including patients of age < 35 years, most of whom had idiopathic pancreatitis, but the approach demonstrated a similar outcome.

Some hypothesize that antioxidants may be beneficial in the early part of the disease process when the oxidative stress is high. Based on this, more meaningful results may be obtained if antioxidants are used in the early stage of CP or recurrent acute pancreatitis (RAP). This is especially true as some studies that included patients with more refractory pain and had a majority with a history of endoscopic or surgical intervention demonstrated less efficacy of antioxidants compared to studies with more naïve patients.^{18,29} An antioxidant may be less efficacious in more advanced disease, possibly because the pathogenesis of pain in later stages is also contributed to by obstruction (calculi, stricture) and a combined component of neuropathic pain. Other factors that may affect the outcome are smoking, which increases the oxidative stress, and malnutrition, which is more prevalent in idiopathic pancreatitis in Asian countries and may be a marker of reduced natural antioxidant intake. Due to limited data and number of patients, we were unable to control for these factors.

Our meta-analysis is important because the antioxidant used in all studies was similar and was based on a combination of antioxidants that are commercially available and used in clinical practice. This makes the findings of our study relevant to clinical practice. However, our review had its own limitations. First, there was a difference in the antioxidant used in many trials evaluating the use of antioxidants in CP. Because of this, we had to exclude some studies using older molecules, like allopurinol and curcumin, to keep the results relevant to today's clinical practice. Second, there was variation in the method of reporting of pain; subsequently, the analysis had to be performed in two different categories (VAS and pain-free participants). This led to a reduction in the number of patients that could be included in the analysis at one time. Third, there was limited information available for other outcomes like QoL, because of which only a qualitative review was possible. This would be important to assess in future studies in a more objective manner as it is a more holistic goal in a multifaceted disease like CP.

Prior reviews and meta-analyses have assessed the use of antioxidants in CP. One review in 2009 was unable to provide clear conclusions.³¹ Since then, there have been two major trials, in 2009 and 2012, and both had a larger sample size and the advantage of using combination antioxidants.^{18,29} However, both had conflicting results, and this led to another set of meta-analyses, which was carried out in 2014–2015.^{14,32,33} The first meta-

analysis was by Rustagi *et al.*, which demonstrated a benefit of antioxidants; however, they have combined the type of studies and the different types of antioxidants, which contributes to heterogeneity.³⁰ The Cochrane meta-analysis stated that there was some improvement in pain, but clinical significance was doubtful in view of the small effect size.¹⁴ Similar results were given in two other meta-analyses in the same period, and the need for more data was evident.^{32,33} In our meta-analysis, we have included more recent data, which included well-conducted randomized controlled trials, that were not included in the prior reviews and that has resulted in a change in the results. The paper by Singh *et al.* showed no significant reduction in pain and was part of the analysis with VAS, as well as pain-free participants. The previous Cochrane review had shown a marginal benefit, but the recent trial has tilted the scales, and overall, no significant benefit in terms of pain could be demonstrated in our meta-analysis.

To conclude, based on the current evidence and according to this meta-analysis, antioxidant therapy does not reduce pain in all patients with CP. They have few minor adverse effects, but these are not statistically significant and did not appear to improve QoL in all patients. As CP patients are on many medications, the lack of therapeutic benefit is important to consider because it increases the pill burden significantly. This discourages the routine use of antioxidants in CP patients. It may be considered on a case-by-case basis till further subgroups with benefit are identified.

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Supporting information

Additional supporting information may be found in the online version of this article at the publisher's website:

Figure S1. On inclusion of some excluded studies, a forest plot is given showing effect of antioxidants on pain in patients with chronic pancreatitis as measured by visual analog scale (VAS) (a) and as measured in terms of pain-free participants at end of study period (b).

Figure S2. Forest plot showing adverse events with antioxidant use in patients with chronic pancreatitis (studies with intervention duration of 6 months).

Figure S3. Forrest plots showing sensitivity analysis in different subgroups of patients.

Figure S4. Forrest plot comparing reduction of oral analgesic use with antioxidant use compared to placebo.