

A Comparative Study into Pain Treatment in Chronic Pancreatitis between Non Operative Conventional Treatment and Those Treated With Antioxidants

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Abstract: Aim Of The Study: To study the role of antioxidants in controlling pain in patients with chronic pancreatitis and its comparison with non operative conventional treatment.

Background: Chronic pancreatitis is a commonly encountered condition in the surgical wards. In our country most of the patients suffering from pain due to chronic pancreatitis are unable to afford or are not eligible candidates for higher end endoscopic and surgical interventions and hence rely heavily on conservative management for symptomatic pain relief. Such patients may benefit from additional strategies for better pain management and an improved lifestyle. The objective of the present randomized (single- blind) controlled trial was to study the role of antioxidant supplementation for relief from pain in patients with chronic pancreatitis.

Key Words: Antioxidants, chronic pancreatitis, pain.

I. Introduction:

Chronic pancreatitis is a chronic inflammatory condition that is multifactorial in its aetiology, highly variable in its presentation, and a challenge to treat successfully. Population studies suggest a prevalence that ranges from 5 to 27 persons per 100,000 population, with considerable geographic variation.^{1,2} Differences in diagnostic criteria, regional nutrition, alcohol consumption, and medical access account for variations in the frequency of the diagnosis, but the overall incidence of the disease has risen progressively over the past 50 years³.

Clinically, patients with chronic pancreatitis present with abdominal pain in early stage and with diabetes and maldigestion in late stage due to endocrine and exocrine insufficiency, respectively.⁴ Pain is the major problem in 90% of the patients with chronic pancreatitis.⁵ Although the mechanism of pain is not well understood, pancreatic ductal hypertension, pancreatic inflammation, and consequent pancreatic perineural infiltration by immune cells have been suggested to be important causes of pain in chronic pancreatitis.⁶ There is no effective medical therapy for relief from pain of chronic pancreatitis.⁷ Endoscopic treatment and surgery are indicated in patients with pain and dilated pancreatic duct, with the intent of decompressing the obstructed pancreatic ductal system that results from stones and/or stricture.^{8,9} Both are invasive forms of therapy and their results are not satisfactory.

Oxidative stress has been implicated in the pathophysiology of chronic pancreatitis.^{10,11,12} A few reports have shown an increased oxidative stress in patients with alcoholic and idiopathic chronic pancreatitis^{13,14,15} Although two studies with a small sample size had reported some benefit of antioxidants in patients with chronic pancreatitis,^{16,17} data are insufficient to show whether supplementation with antioxidants will decrease oxidative stress and relieve pain in patients with chronic pancreatitis. Convincing evidence is thus lacking to recommend antioxidants for the treatment of patients with chronic pancreatitis. The objective of the present randomized (single- blind) controlled trial was to study the role of antioxidant supplementation for relief from pain in patients with CP.

II. Materials & Methods:

Study type: Interventional, Randomized, Placebo controlled Prospective study.

The study was conducted in the General Surgery Department of NEIGRIHMS, Shillong from January 2010 to December 2012. A total of 60 cases of Chronic Pancreatitis (CP) were included in the study. Odd number of patients was taken as CASES whereas Even numbers were assigned as CONTROLS.

The cases were given Antioxidant medications (Selenium 600 microgram and Vitamin C 500 mg) to be taken daily for a period of 6 months along with Proton Pump inhibitors and Pancreatic enzymes. The controls were given only PPIs and Pancreatic enzymes. Analgesics were given in both groups whenever necessary.

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Pain was evaluated using three scores: Numerical Pain Scoring system (by the patient), Faces rating scale and Behavioural rating scale (by the investigators) when patient presented in our hospital. The scores were given a maximum of ten points and a minimum of zero point. Pain was evaluated on the first day of visit and as part of follow up after being given appropriate medications.

The two groups were studied prospectively for reduction in the intensity of pain and hospitalization due to pain over the next six months. The two groups were also assessed subjectively regarding improvement in their lifestyle over the six month treatment strategy.

The study tools included: a) data collection, b) serial clinical examination, c) blood sampling and radiological findings and d) pain score.

Appropriate Ethical Clearance and also Informed Consent were obtained. The various inclusion/exclusion criteria were as follows:

Inclusion Criteria:

Patients presenting with history of Chronic Pancreatitis with significant pain having

At least one episode of pain in a month requiring oral analgesics

OR

One episode of severe pain in last three months requiring hospitalisation.

Exclusion Criteria:

Painless disease

Current pain more likely due to non-pancreatic origin

If the patient already has an intervention in the form of decompressive therapy i.e., surgery or endoscopic sphincterotomy/stenting or ESWL

Systemic conditions like CRF, malignancy, hypertension, and pregnancy

Complications like pseudocyst, pancreatic abscess

Patients who would have received antioxidants in the preceding 4 weeks

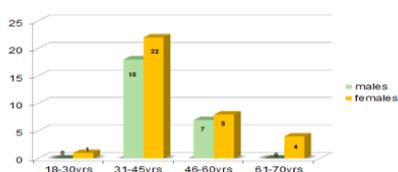
Narcotic addicts

Uncontrolled diabetes

Comorbid conditions like liver diseases

Datas were analysed using ANOVA and the test of Comparison of Proportions.

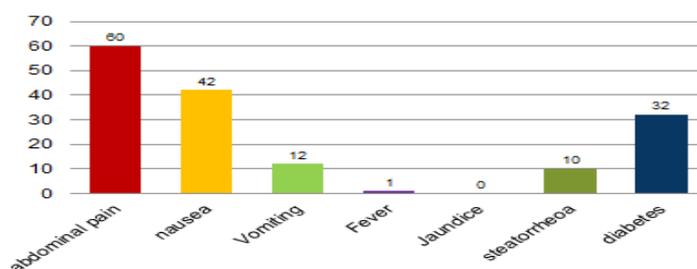
Sex and Age distribution:



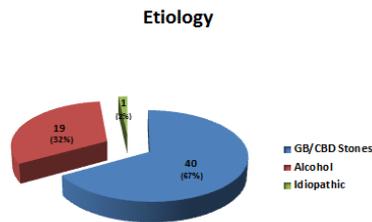
III Results and Analysis:

The Mean Age for Cases is 46.5 years and for Controls is 45.53 years.

Presenting Complaints:



All our patients came to the hospital with complain of abdominal pain. About 53.33% of our patients had Diabetes.

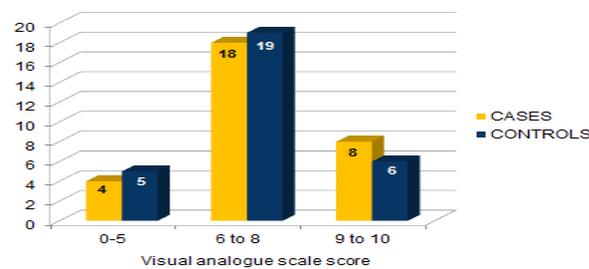


Gall stone was the commonest cause followed by alcohol.

Similarities between Cases and Controls:

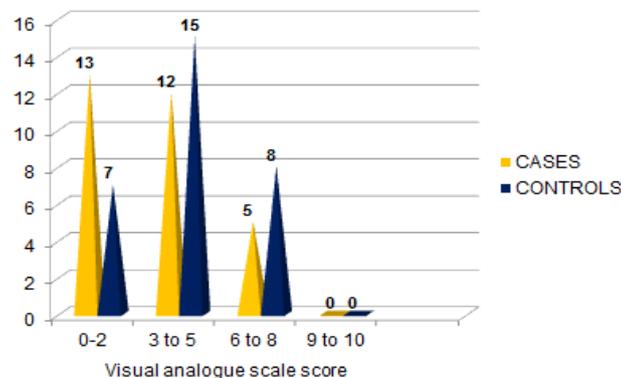
Description	Cases	Controls
Mean age in years	46.5	45.53
Males	12	13
Females	18	17
Abdominal pain	30	30
Diabetes	18	14
Steatorrhea	4	6
CBD/ Gall stones	22	18
Alcohol	7	12
Idiopathic	1	0

Pain Score on 1st day:



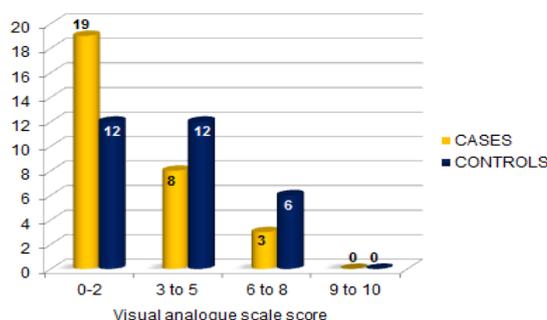
The Mean for Pain Score on the 1st day for Cases: 7.3 points and for Controls: 6.6 points

Response to treatment and pain relief at 3 months:



The Mean on the 3rd Month for Cases: 3.03 points and for Controls: 3.87 points

Response to treatment and pain relief at 6 months:



The Mean on the 6th Month for Cases was: 1.83 points and for Controls: 2.9 points

About 3 patients in Cases and 8 patients in Control Groups had more than 4 hospital visits in 6 months. By the test of Proportions we found out that



Difference = 16.70%

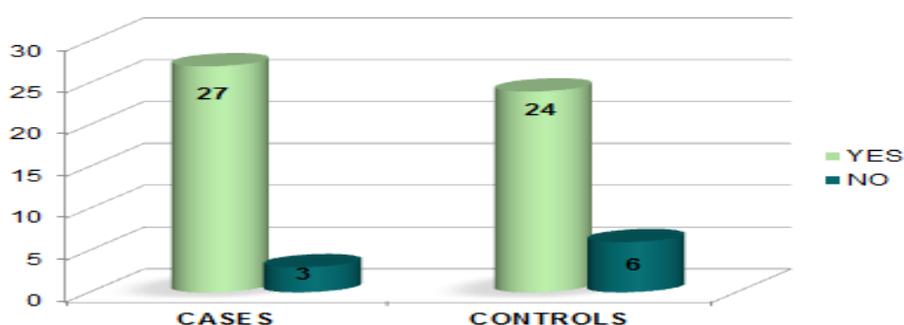
95% C.I.= - 3.30 to 35.62

Chi Square= 1.78

d.f.=1

p value= 0.18

Comparison of improved lifestyle among cases and controls at 6 months:



Applying Odd's Ratio we found that the feeling of betterment between cases and controls as being:

Odd's Ratio= 1.63

95% C.I.= 0.41 to 6.47

III. Discussion:

Upper abdominal pain is the most common symptom in the clinical course of chronic pancreatitis. The mechanisms of pain in CP are not well understood. However, multiple factors are hypothesized including increased ductal and parenchymal pressure from strictures/stones, oxidative injury from free radicals, recurrent ischemia, neuropathic (both peripheral nerve injury due to gland inflammation and a heightened central nervous

component of pain due to hypersensitivity of pain perception), and hormonal (increased cholecystokinin production from duodenum leading to increased pancreatic stimulation). Finally, complications of CP, such as pancreatic cancer or pseudocysts, may be additional sources of pain.

Oxidative stress has been proposed as a potential important mechanism of pathogenesis in both acute and chronic pancreatitis. Oxidative stress can be defined as an imbalance between pro-oxidants and antioxidants leading to free radical formation. Despite the endogenous antioxidant system being quite efficient, increased exposure to pro-oxidants or reduced antioxidant capacity can lead to an imbalance and hence oxidative stress (18). Numerous enzymatic processes result in the generation of free radicals such as reactive oxygen species (ROS) and reactive nitrogen species (RNS), which can oxidize a wide range of biomolecules. Moreover, they can turn-on many stress-activated pathways (19). The oxidative stress can be self-perpetuating leading to recruitment of ROS-generating inflammatory cells to the pancreas, which worsen the oxidative burden leading to further injury (19).

The proposed mechanisms of injury from free radicals include direct attack, lipid peroxidation, DNA modification, and enzyme degradation/inactivation (18, 19)

The mechanisms of detoxification include alteration of toxic substances to a more polar state thereby allowing for easier excretion (18). Two types of reactions exist: In Phase I metabolism, enzymes cleave the toxic molecule into products that could be more or less toxic. In Phase II an endogenous molecule is attached to the altered products thereby rendering it more polar and easier to excrete. Phase I enzymes include the CYP450 oxidase system and hydrolyzing enzymes. Phase II involves glucuronidation and glutathione conjugation (18). Pro-oxidants that are implicated in acute and chronic pancreatitis include alcohol, tobacco, environmental and dietary toxins, certain drugs, and transition metal cations in a free state such as iron and copper. Both in-vitro and in-vivo animal studies have suggested that pro-oxidants play a role in both acute and chronic pancreatitis. Xenobiotics are detoxified in the body through phase I and phase II pathways, chiefly in the liver.²⁰ Increased exposure to xenobiotics such as alcohol, nicotine, and petrochemical fumes may overwhelm the capacity of phase I and phase II detoxification pathways and result in oxidative stress.^{21,22} The pancreatic acinar cells are also exposed to oxidative stress.²³ Oxidative stress can cause cell damage either directly by cell membrane destruction, depleting the cells of antioxidants; by toxicity from free radical peroxidation products; or through altering signalling pathways, including redox regulation of genes.^{24,25} Free radical per-oxidation products may act as second messengers and block exocytosis in the pancreatic acinar cells, leading to increased autophagy and crinophagy and thus diverting the pancreatic enzymes into interstitium, causing degranulation of mast cells and resulting in inflammation mediated by chemotaxis and pain.²⁶

The diagnosis of CP is usually made with imaging studies. Patients can be diagnosed with cross sectional imaging such as computed tomography (CT) or magnetic resonance imaging (MRI) showing pancreatic calcifications, pancreatic atrophy, and/or a dilated pancreatic duct. In some patients with early or “small-duct” CP, such imaging may be normal (no dilation of pancreatic duct and no calcifications) and the diagnosis may be much more difficult. In such patients, more sensitive structural testing such as endoscopic ultrasound (EUS) or functional testing with secretin stimulation may be necessary for diagnosis. Medical management consists of abstinence from alcohol and smoking, and removal of other environmental toxins or medications, which could be precipitating superimposed attacks of acute pancreatitis. Vigorous attempts at encouraging abstinence are necessary. Smoking cessation is as important as alcohol cessation, as there is now abundant evidence that smoking is equally injurious to the pancreas (27).

A variety of medications can be utilized for pain management, including NSAIDs, pancreatic enzyme replacement, narcotics, non-narcotic analgesics (such as anti-depressants, pregabalin or gabapentin), antioxidants, and octreotide. Referral to psychiatry or pain management specialists may be necessary in some patients.

For those patients who fail medical therapy, a careful evaluation of pancreatic parenchymal and ductal morphology via good quality cross-sectional imaging is imperative. In general, patients with “big-duct” disease are amenable to decompressive endoscopic or surgical therapy. The choice depends upon many factors such as patient preference, tolerability, availability, and center expertise. Options for endoscopic or surgical therapy, unfortunately, are limited in those with “small-duct” disease.

In patients with small-duct disease, pancreatic acinar cells are suggested to be under constant stimulation by CCK because subnormal delivery of pancreatic proteases into the duodenum allows improved survival of a CCK-releasing peptide from the duodenal mucosa.²⁸ Hence, the following potential treatments have been successfully tested:²⁸ oral pancreatic enzymes (non-enteric coated, two trials), subcutaneous octreotide (one trial), and oral dosing with the CCK-A receptor antagonist loxiglumide (one trial). However, this issue is contentious,^{29,30} and the explanation that these measures “allow the pancreas to rest”²⁸ is at odds with the finding that the exocytosis apparatus is already paralysed in an attack and hindered thereafter.³¹ Other explanations might be that such treatments act by blunting an effect of CCK on pain pathways in the CNS³² or by ameliorating electrophilic stress.³³

Micronutrient therapy is designed to supply methyl and thiol moieties that are essential for the exocytosis apparatus while protecting it against electrophilic attack, as by CYP-derived ROS or reactive xenobiotics species.³¹ Findings from six clinical trials have reported that micronutrient therapy controls pain and curbs attacks in patients with chronic pancreatitis.^{16,17, 34-38} Of these trials, three were Descriptive³⁴⁻³⁶ and three were placebo-controlled.^{16,17,37,38} However, the different ways of expressing outcome precludes a meta-analysis.³⁹ The study with the highest power (80%) to detect a difference between treatment and placebo was from Delhi:³⁸ after 6 months' treatment (which included pancreatic enzymes in all patients) there was a greater reduction in the number of painful days per month and in the use of analgesic tablets in the treatment group than in the placebo group; substantially more patients became pain free, and biochemical markers of electrophilic stress were lowered by active treatment.

Studies from Manchester, UK, suggested that the micronutrient therapy formulation should include methionine and vitamin C,⁴⁰ with the need for selenium assessed by measuring blood concentrations. Vitamin E and β carotene were included in the first trial because there was no commercial preparation that did not include them,³⁷ and three of the other five trials also used this protocol.^{17,34,38} Improvement, as judged by the number of attacks, admission episodes, pain diaries, pain intensity, or permutations and combinations of these factors, occurred by 10–12 weeks.^{17,37,38}

In the UK, the micronutrient therapy preparation Antox (Pharma Nord, Morpeth, UK) is a convenient means of dosing because it contains all the desired items. A starting regimen of two tablets of Antox three times per day provides daily doses of 2.88 g methionine (but up to 4 g might initially be needed in some patients),⁴¹ 720 mg vitamin C, 300 μ g organic selenium, and 210 mg vitamin E (which is unnecessary until steatorrhoea develops).⁴² This treatment has no significant side-effects now that β carotene has been withdrawn because of cosmetic problems:⁴¹ one patient (of >300) developed schizophrenia when on 4 g of methionine daily but, of note, this patient had a strong family history of psychiatric disease.⁴¹

Patients should also be given dietary advice on antioxidant-rich foods to aid the long-term management of the disease. It should be stressed that culinary practices—eg, frying vegetables at high temperature (as in south India⁴³)—could compromise the bioavailability of antioxidants, notably of ascorbic acid.³⁶ Blood monitoring is essential to ensure that plasma and erythrocyte glutathione levels have increased and that concentrations of the prescribed micronutrients are not excessive, because this would compromise the physiological roles of ROS.^{44,45}

Very recent reports indicate the need to keep track of blood homocysteine, and concentrations of vitamins (B6, B12, folic acid) that serve as cofactors of enzymes that govern homocysteine removal—either by facilitating its transmethylation back to methionine, or by ensuring its passage along the transsulphuration pathway towards glutathione.^{31,43,46,47} Of particular interest, elevated homocysteine has been recorded in people at Soweto (South Africa) who drank more than 100 g alcohol per day for many years⁴⁸—a group that is traditionally regarded as being at high risk of chronic pancreatitis.⁴⁹

Treatment for 10 weeks is recommended before any invasive procedure in patients with chronic pancreatitis, to calm the disease process. Full treatment is usually needed for 6 months, followed by a gradual dose reduction guided by biochemical data and patients' symptoms.⁴¹ We recorded treatment failure in 10% of patients, usually because of non-compliance (eg, in patients who misuse alcohol) or a large cyst or pseudocyst;⁴¹ otherwise, symptom control was achieved by choline supplements to boost methyl supply.³¹

Moreover, micronutrient therapy has no effect on painful conditions that might be misdiagnosed as chronic pancreatitis (unpublished); once validated, this finding could form the basis for a therapeutic trial when the diagnosis remains equivocal after full testing. Finally, there is increasing evidence to support the idea that a daily micronutrient supplement might abort the development of chronic pancreatitis in groups or even populations at risk of the disease.^{31, 48}

Micronutrient treatment is better at controlling pain and improving quality of life than conventional treatment.⁵⁰ Moreover, long-term micronutrient treatment might curb disease progression.⁵¹

There have been a number of studies evaluating patients with both acute and chronic pancreatitis demonstrating increased levels of free radicals, oxidative stress, and reduced antioxidant capacity. These observations support the idea that supplementation with antioxidants might have value in mitigating the damage and reducing pain.

Uden et al⁵² performed a double-blind placebo controlled trial utilizing organic selenium, carotene, vitamin C, vitamin E, and methionine. In this small group of patients with chronic pain and recurrent acute pancreatitis, they found that fewer patients on antioxidant therapy had recurrent attacks compared to placebo ($p=0.032$). The authors concluded that clinical improvement was noted in patients on therapy above and beyond placebo effect.

Another small study by Heaney and colleague⁵³ looked at the role of antioxidant therapy in patients with recurrent acute pancreatitis from familial hypertriglyceridemia. They showed that in a very small group of patients, antioxidants prevented recurrent episodes, despite unchanged triglyceride levels.

A more recent randomized study from India evaluated the antioxidant curcumin (from turmeric) and its effect on patients with tropical pancreatitis⁵⁴. Patients on therapy had decreased markers of oxidative stress compared to placebo. Unfortunately, no improvement of pain was seen.

Another randomized, placebo-controlled cross-over study by Kirk and colleague⁵⁵ evaluated the efficacy of combined antioxidants (selenium, β -carotene, L-methionine, and vitamins C and E) in patients with CP. Only 19 of 36 patients completed the trial. Nevertheless, the investigators found that treatment with combination antioxidants led to significant improvements in quality of life with regards to pain, physical and social functioning, and general health perception.

The largest randomized study to date for relieving pain in CP with antioxidant therapy was published by Bhardwaj and colleagues⁵⁶. In this trial the investigators studied patients with both alcoholic and idiopathic CP. One hundred twenty-seven patients were randomized to receive either antioxidant therapy (n=71) or placebo (n=56) for a 6-month period. The antioxidant supplementation was a combination of 600 mcg selenium, 0.54 g ascorbic acid, 9000 IU β carotene, 270 IU α -tocopherol and 2 g methionine daily in divided doses. The primary outcome was pain relief assessed by reduction in painful days per month as measured by a pain diary. The primary outcome was evaluated by a blinded clinician. Secondary outcomes evaluated were decrease in requirement for oral and parenteral analgesics, decrease in attacks leading to hospitalization, percentage of patients becoming pain free during therapy, days missed from work, and change in serum markers of oxidative stress and antioxidant levels. The results showed that reduction in painful days per month was 3.21 days in the placebo group compared to 7.37 days in the antioxidant group ($p < 0.001$). Additionally, the antioxidant group had statistically significant reductions in the number of monthly analgesics required, need for hospitalization, and number of days lost from work. Interestingly, one-third of the patients in the antioxidant group became pain free compared to 12.5% of the placebo group ($p = 0.009$). Patients with CP had higher levels of markers of oxidative stress and lower antioxidant levels. No adverse events were noted. Although some clinical studies have shown promise in the use of antioxidant therapy, many questions remain about its use in such patients²⁷. Furthermore, what is an appropriate combination of antioxidants? At what point during medical management should antioxidants be introduced and what is an optimal duration of therapy? Finally, some issues have been raised about potential side effects of antioxidants after long-term use. Some studies have suggested increased cardiovascular risk from long term vitamin E use⁵⁷.

IV. Conclusion:

Pain management in CP is frustrating and challenging for patients and physicians alike. The cornerstone of initiating management is removal of offending agents such as alcohol and tobacco. A variety of medical therapies can then be tried before resorting to endoscopic and/or surgical management. Many studies have now shown that oxidative stress is important in the pathophysiology of CP and antioxidants have an attractive potential as adjunctive therapy. The overall effectiveness of antioxidants is not known, and the best mixture of agents and dosages is not clear. At the moment, a trial of a mixture of antioxidants containing vitamin C, vitamin E, selenium, and methionine is reasonable as one component of overall medical management. However the dosage and length of therapy is unclear. In our study we have found that there was a decrease in pain and an improvement in their daily life activities in both cases and controls. Both groups showed a reduction on the number of hospital visits (10% for cases and 26.67% for controls) and a certain degree of betterment after 6 months of treatment. The decrease in pain in the control group could be due to pancreatic enzyme supplementation, abstinence from alcohol and dietary advice regarding intake of adequate macro and micro nutrients. Further well-designed clinical studies are needed to determine the appropriate combination of agents, time of initiation, and duration of therapy.

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