Background & objectives: Oxidative stress occurs in association with painful exacerbations of chronic pancreatitis and antioxidant supplementation appears to benefit this condition. Curcumin, the active constituent of turmeric, is known to exhibit antioxidant activity. This pilot study was therefore undertaken to evaluate the effect of oral curcumin with piperine on the pain, and the markers of oxidative stress in patients with tropical pancreatitis (TP).

Methods: Twenty consecutive patients with tropical pancreatitis were randomised to receive 500mg of curcumin with 5mg of piperine, or placebo for 6 wk, and the effects on the pattern of pain, and on red blood cell levels of malonyldialdehyde (MDA) and glutathione (GSH) were assessed.

Results: There was a significant reduction in the erythrocyte MDA levels following curcumin therapy compared with placebo; with a significant increase in GSH levels. There was no corresponding improvement in pain.

Interpretation & conclusion: Oral curcumin with piperine reversed lipid peroxidation in patients with tropical pancreatitis. Further studies with large sample are needed to define its effect on the pain and other manifestations of tropical pancreatitis.

Key words: Antioxidants - chronic pancreatitis - curcumin - glutathione - lipid peroxidation - malonyldialdehyde - oxidant stress - treatment

Chronic pancreatitis, a disease characterized by progressive, irreversible destruction of pancreatic tissue, is associated with significant morbidity and mortality. Severe abdominal pain is the most common presentation, and diabetes mellitus and steatorrhoea often result from long-standing disease. Currently available forms of therapy are aimed at relief of symptoms (e.g. analgesics for the pain) and complications. The benefits of oral pancreatic enzyme supplementation are inconclusive and surgery is possible or effective only in a small proportion of patients.

Oxidative stress has been shown to play a key role in causing tissue damage in acute pancreatitis as well as in the painful exacerbations of the chronic disease. Low levels of antioxidants have been demonstrated in the diet, and the sera of patients with pancreatitis, and supplementing these appears to be beneficial for the recurrent or persistent pain in such patients.

Curcumin, the active constituent of turmeric (Curcuma longa), exhibits strong antioxidant activity comparable to that of vitamins C and E. However, it is
poorly absorbed following oral administration\(^{11}\). Absorption can be improved by co-administration of piperine (from black pepper) increasing the bioavailability by 2000 per cent in rats and humans, without precipitating any adverse effects\(^{12}\). This pilot study was designed to evaluate the effect of oral intake of curcumin with piperine on the pain, and the markers of oxidative stress in patients with tropical pancreatitis (TP).

**Material & Methods**

**Study design and patients:** The study was single blind, randomized and placebo-controlled. Twenty consecutive patients with TP between the ages of 18 and 65 yr (mean ± SD 25.5 ± 14.3) attending the Gastroenterology Clinic of the Kasturba Hospital, Manipal over an 18 month period from February, 2002 were enrolled. CP was diagnosed based on the clinical features, and findings of imaging of the pancreas. Presence of calcification in the organ, or ductal changes on endoscopic retrograde cholangiopancreatography (ERCP) was essential for diagnosis. Patients with complications of pancreatitis (e.g., bile duct stricture, psuedocyst, ascites), or other gastrointestinal or systemic diseases that might explain the abdominal pain (peptic ulcer, drug induced gastric erosions, biliary diseases) or contribute to lipid peroxidation (such as diabetes mellitus) were excluded. Those with a history of alcohol consumption prior to the onset of symptoms were also excluded. The patients were randomly assigned to receive the study drugs or placebo.

**Drugs and dose:** Capsules of the drugs - 500mg of pure extract of curcumin (95%) with 5 mg of piperine (Synthite Chemicals, Cochin), and of placebo (lactose) were prepared at our hospital manufacturing unit under strict hygienic conditions. Patients were advised to take one capsule of drug or placebo as appropriate three times per day after food for 6 wk. Compliance was monitored by counting the number of capsules returned. Return of more that 10 per cent of the capsules constituted non-compliance. No other medicines were allowed except for antidiabetic medication as necessary, and ketorolac with or without piroxicam orally up to three times a day as needed for the abdominal pain.

**Assessment of adverse drug effects:** Patients were encouraged to report any unwanted symptoms at the earliest. Also complete blood count, liver function tests, and renal function tests were done before and after the treatment.

**Biochemical investigations:** Levels of malondialdehyde (MDA) and glutathione (GSH) in the erythrocytes were estimated before and after treatment. MDA reacting with thiobarbituric acid (TBA) gave a pink chromogen that was read at 532 nm and was expressed as TBARs\(^{13}\). Glutathione, the major non-protein sulphhydryl group in RBCs, is in the reduced form. 5,5′ dithiobis (2-nitrobenzoic acid) (DTNB) is a disulphide chromogen that is readily reduced by sulphhydryl compounds to an intensely yellow compound. The absorbance of this chromogen measured at 412 nm is directly proportional to the GSH concentration\(^{14}\).

**Assessment of clinical parameters:** Abdominal pain was scored using the visual analogue scale (VAS) at 0 and 6 wk, i.e. before and after treatment\(^{15}\). The number of analgesic tablets taken during the study period was recorded.

**Statistical analysis:** Data were analyzed by the Mann Whitney U test using the software SPSS.

<table>
<thead>
<tr>
<th>Table I. Characteristics of patients with chronic pancreatitis</th>
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<tbody>
<tr>
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<tr>
<td>Curcumin group (n=8)</td>
</tr>
<tr>
<td>Age range and 18-55 (23.6 ± 12.8)</td>
</tr>
<tr>
<td>Male/female 7/1</td>
</tr>
<tr>
<td>Duration of pain  1-3</td>
</tr>
<tr>
<td>Calcification No. (%)  5 (71)</td>
</tr>
<tr>
<td>Diabetes mellitus No. (%)  4 (50)</td>
</tr>
<tr>
<td>Severity of pain (mild/moderate/severe)  1/2/5</td>
</tr>
<tr>
<td>Erythrocyte MDA (nmol/g Hb)  14.80±1.19</td>
</tr>
<tr>
<td>GSH levels (mg/g Hb)  4.51±0.61</td>
</tr>
<tr>
<td>Visual analogue score (VAS) for pain  5.5±0.56</td>
</tr>
</tbody>
</table>

Values of MDA, GSH and VAS are given as mean ± SE. MDA, malondialdehyde; GSH, glutathione.
The study was approved by the Ethics Committee of the institution and written informed consent was obtained from all subjects.

Results & Discussion

Fifteen (75%) of the 20 patients enrolled returned for evaluation. No adverse events were reported. Compliance with drugs was 100 per cent (Table I).

After treatment, there was a significant reduction in the erythrocyte MDA level \( (P < 0.01) \) in the curcumin group compared to the placebo group (Table II). However, the corresponding increase in the GSH level was not statistically significant. There was no improvement in the pain in either group after treatment. There was no difference between the two groups in terms of intake of analgesics (data not shown).

Our study confirmed earlier reports on the evidence for oxidative stress and lipid peroxidation in patients with chronic pancreatitis. Additionally, it demonstrated a significant improvement in MDA levels after 6 wk of treatment with a combination of curcumin and piperine in a specific form of the disease - tropical pancreatitis. Antioxidants like organic selenium, betacarotene, vitamin C, vitamin E and methionine improve the parameters of oxidative stress as well as relieve pain in patients with chronic pancreatitis. However, in the present study, treatment with curcumin resulted in a statistically significant improvement only in the levels of MDA but not of GSH. The reasons for this disparity are not known. Small number of patients studied could be a limiting factor.

Care was taken to exclude patients with other diseases presenting with abdominal pain and oxidant stress. Despite this there was an unexpected, though statistically insignificant, increase in GSH levels in the placebo group also. This might have masked the beneficial effect of curcumin on this parameter. Also, there was no improvement in pain with therapy. It could be possible that there was no direct relationship between pain and lipid peroxidation in this disease. The causes of pain of CP are not well understood, and are clearly multi-factorial. Studies with large sample size are needed to clarify these issues.

**Table II.** Response of curcumin on lipid peroxidation after oral administration for 6 wk

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Curcumin group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erythrocyte MDA</td>
<td>6.02±0.95</td>
<td>11.46±0.51*</td>
</tr>
<tr>
<td>(nmol/g Hb)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GSH levels (mg/g Hb)</td>
<td>8.31±0.71</td>
<td>5.47±1.54</td>
</tr>
<tr>
<td>VAS for pain</td>
<td>5.81±0.74</td>
<td>6.57±0.52</td>
</tr>
</tbody>
</table>

Values denoted as mean ± SE

*\( P < 0.01 \) compared to placebo. MDA, malonyldialdehyde; GSH, glutathione; VAS, visual analogue score

Turmeric has long been used in the Chinese and Ayurvedic systems of medicine, as an anti-inflammatory agent among other things. Its active component, curcumin, has received considerable attention. Much of the observed activities of *Curcuma longa* seem to be due to curcumin. It is known to relieve pain and inflammation, and is safe when given orally. Several studies have reported the antioxidant property of curcumin, augmenting endogenous antioxidant levels. It also down regulates nitric oxide formation. Whether this action has a role in the beneficial effects of curcumin in TP needs further evaluation. The dose of curcumin used in previous studies varied widely. We chose the dose used in our study based on our preliminary experience.

MDA level in the body indicates the extent of lipid peroxidation. Glutathione is an important water-phase antioxidant, antitoxin and essential cofactor for antioxidant enzymes protecting the mitochondria against endogenous oxygen radicals. Its level reflects the free radical scavenging capacity of the body. GSH depletion leads to tissue damage due to lipid peroxidation.

This pilot study showed that curcumin administered orally with piperine reversed lipid peroxidation in patients with non-alcoholic chronic pancreatitis of the tropics. It also raises interesting questions for future evaluation. These include the role of lipid peroxidation in the pain and other manifestations of CP, and also the dose and duration of therapy for clinical benefit, if any.

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References


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