PANCREAS NEWS

Antioxidants for Intractable Pain in Chronic Pancreatitis Patients. Is the End of the Story?

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The clinical course of chronic pancreatitis is characterized by frequent painful episodes in the early stages of the disease; the pain tends to disappear during the natural course of the disease or after a period of time ranging from a few years to a maximum of 10 years after the onset of the disease [1]. The pain significantly decreases the quality of life of chronic pancreatitis patients and sometimes leads to severe malnutrition [2, 3].

Among several modalities for controlling the pain, the addition of antioxidant substances to high doses of analgesics has been attempted [4]. In fact, it has been suggested that patients suffering from chronic pancreatitis may need antioxidant supplementation [4]. Subsequently, other studies [4, 5] led to the conclusion that dietary insufficiency of methionine and vitamin C, aggravated by selenium deficiency, laid the groundwork for the disease when the oxidant load increased upon regular exposure to environmental chemicals which induced cytochrome P-450 mono-oxygenases [6]. Evaluating the clinical and biochemical data from three consecutive 20-week placebo-controlled double-blind switchover trials using different treatments, the combination of methionine or sulphadenosyl-methionine (SAMe) and vitamin C was identified as the key to success [7, 8, 9, 10, 11]. The potential usefulness of the same approach in patients with hereditary pancreatitis was raised when affected family members were found to have poorer antioxidant blood profiles than their asymptomatic counterparts [12]. In 2001, the usefulness of antioxidant therapy in a non-controlled study based on three patients affected by hereditary chronic pancreatitis was reported [13]. The two-year study was divided into four six-month periods. In the first and the third periods, an oral analgesic drug was administered on demand whereas, in the second and the fourth periods, oral antioxidant therapy was administered. The therapy consisted of SAMe (800 mg/day), vitamin C (180 mg/day), vitamin E (130 mg/day), vitamin A (2,400 µg/day), and selenium (75 µg/day). Patient compliance to the treatment was satisfactory and no side effects were observed; the treatment with antioxidants brought about a meaningful reduction in the number of days of pain in both periods of antioxidant treatment and a meaningful reduction of daily analgesic consumption. Even if the cost of this therapy is not excessively high, the search to achieve a cost reduction in less economically developed countries has led to the identification of natural extracts having the same power as commercially available antioxidants. It has also been reported that the extract of *Curcuma Longa*, a perennial herbaceous plant which can grow as high as one meter and constitutes a part of curry, named curcumin, exhibits strong antioxidant activity comparable to that of vitamins C and E [14.]. However, curcumin is poorly absorbed following oral administration [15]; its absorption can be improved by the co-administration of piperine extracted from black pepper; thus, this approach increases the bioavailability by 2,000% without causing any adverse effects [16]. A pilot study was carried-out in order to evaluate the effect of the association of curcumin and piperine administered orally on the possible reduction of pain in patients with tropical pancreatitis [17]. In this study, 20 consecutive patients with tropical pancreatitis were randomized into two groups [17]; one group received 500 mg of curcumin and 5 mg of piperine for six weeks and the second group received a placebo for an identical period of time. The effects of the two treatments on the pattern of pain and on the red blood cell levels of malonyldialdehyde (MDA) and glutathione (GSH)

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Abbreviations GSH: glutathione; MDA: malonyldialdehyde; SAMe: sulphadenosyl-methionine

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were evaluated. There was a significant reduction in erythrocyte MDA levels following curcumin therapy as compared to the placebo and a significant increase in GSH levels, but there was no corresponding improvement in pain. The question arising from the studies published is why such differences exist in pain control using antioxidant treatment. One possible explanation is that SAMe and selenium were not used in the Indian study and this may have, in some way, modified pain control which had clearly improved in the Italian study [13]. This hypothesis is supported by the study carried out by English researchers: a Antox® (Pharma Nord, Morpeth, Northumberland, UK) tablet, which contains 75 mg of selenium, 3 mg beta-carotene, 47 mg d-alpha-tocopherol acetate (vitamin E), 150 mg ascorbic acid (vitamin C), and 400 mg of methionine was evaluated [18] in a randomized, double-blind, placebo-controlled crossover trial for assessing the efficacy of a combined antioxidant preparation in the management of pain in chronic pancreatitis patients. Patients with proven chronic pancreatitis were randomized to receive treatment with either Antox® or a placebo for 10 weeks. Each group of patients then switched to receive the alternative treatment for an additional 10 weeks. Markers of antioxidant status were measured by blood sampling whereas quality of life and pain were assessed using the SF-36® questionnaire. Nineteen patients completed the full 20 weeks of treatment. Treatment with Antox® was associated with significant improvement in the quality of life in terms of pain, physical and social functioning, and general health perception.

A placebo-controlled double blind trial published in 2009 by Bhardwaj *et al*. has also reported good results on pain relief using antioxidant supplementation on a large number of chronic pancreatitis patients [19]. In this study, consecutive patients with chronic pancreatitis were randomized into groups which were given placebos or antioxidants for six months. The primary outcome measure was pain relief; the secondary outcome measures were analgesic requirements, hospitalization, and markers of oxidative stress and antioxidant status. One hundred and twenty-seven patients (86 male, 41 females; 35 alcoholic, 92 with idiopathic chronic pancreatitis) were studied; fifty-six patients were assigned to the placebo group and 71 to the antioxidant group. After six months, the reduction in the number of painful days per month was significantly higher in the antioxidant group as compared to the placebo group. The reduction in the number of analgesic tablets per month was also higher in the antioxidant group. Furthermore, 32% and 13% of patients became pain free in the antioxidant and placebo groups, respectively. Thus, the results of this study seemed to confirm that antioxidant supplementation is effective in relieving pain and reducing levels of oxidative stress in patients with chronic pancreatitis. However, this study has many biases: 1) the study was interrupted in recruiting at 147 patients (71 to the placebo arm and 76 to the antioxidant arm) instead of a sample size of 100 patients in each arm as previously calculated; 2) at the end of the study, 56 patients were evaluated in the placebo arm and 71 in the active arm, suggesting that there was a poor random effect; 3) only two etiologies of the disease were enrolled in this study, mainly being idiopathic (68%); 4) the authors also considered also patients with tropical pancreatitis as having idiopathic chronic pancreatitis. It should be pointed out that tropical pancreatitis patients have a clinical history quite different from other forms of pancreatitis, the pattern being characterized by insulin-dependence, ketosis-resistance, diabetes mellitus and the presence of large pancreatic intraductal calculi [20].

A new trial on antioxidants for the relief of pain in chronic pancreatitis patients has recently been published [21]. The authors performed a double-blind, randomized controlled trial which compared the effects of antioxidant therapy with a placebo in 70 patients with chronic pancreatitis. The patients provided one month of baseline data and were followed for 6 months while receiving either Antox® version 1.2 (2 tablets, 3 times daily) or a matched placebo. Antioxidant supplementation contained active ingredients: 38.5 mg selenium yeast of which 50µg was l-selenomethionine, 113.4 mg d-alpha-tocopherol acetate, 126.3 mg ascorbic acid and 480 mg l-methionine together with secondary ingredients: 285.6 mg microcrystalline cellulose, 14.0 mg croscarmellose sodium, 7.0 mg colloidal anhydrous silica and 3.0 mg magnesium stearate. The coating included 4.2 mg beta-carotene. Placebo supplementation contained: 657.9 mg microcrystalline cellulose, 73.3 mg croscarmellose sodium, 15.0 mg colloidal anhydrous silica and 3.7 mg magnesium stearate per tablet.

The etiology was more balanced (51 alcoholic pancreatitis and 19 idiopathic) than in the study of Bhardwaj *et al*. [19]. Twenty-six patients were enrolled in each arm and 57 seven patients were included in the study, allowing for 10% loss to follow-up; the trial aimed to recruit 57 patients. In addition, at an interim inspection, the independent trial steering committee advised that enrolment would be increased to approximately 90 patients, and 92 subjects fulfilled the inclusion criteria and agreed to participate in the trial. Finally, 70 patients were analyzed: 37 in the placebo arm and 33 in the antioxidant arm. The primary analysis was a baseline-adjusted change in pain score at 6 months, assessed by an 11-point numerical rating scale. Secondary analyses included alternative analyses of clinic and diary pain scores, scores on quality of life tests, such as the EORTC-QLQ-C30, QLQPAN28, EuroQOL EQ-5D, and EQ-VAS, levels of antioxidants, use of opiates and adverse events. An intention-to-treat analysis was carried out. After 6 months, pain scores were reduced by 1.97 from baseline in the placebo group and by 2.33 in the antioxidant group but were not significantly different between groups. Average daily pain scores from diaries were also similar. The measurements of quality of life were similar between

groups as was opiate use and numbers of hospital admissions and outpatient visits. Blood levels of vitamins C and E, beta-carotene and selenium were significantly increased in the antioxidant group. What was the conclusion of the study? In patients with painful chronic pancreatitis of predominantly alcoholic origin, antioxidant therapy did not reduce pain or improve the quality of life, despite causing a sustained increase in blood levels of antioxidants. We believe that this study has definitively shown the ineffectiveness of the use of antioxidant treatment in controlling pain in chronic pancreatitis patients.

Conflict of interest The author has no potential conflicts of interest

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