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Antioxidants and Pain Control in Patients with Chronic Pancreatitis: A Never-Ending Story

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Abstract: Chronic pancreatitis is a benign disease often characterized by recurrent episodes of abdominal pain accompanied by progressive pancreatic exocrine and endocrine insufficiency; it sometimes requires multiple hospitalizations. This disease is frequently the result of chronic alcohol abuse, even if other factors such as genetic alterations, autoimmune disorders, and obstructive disease of the biliary tract and the pancreas may cause the disease. The pain can be considered the most important symptom; it significantly modifies the quality of life of patients with chronic pancreatitis and its control represents a challenge in the treatment of the disease. Among the several modalities for controlling the painful symptomatology, in addition to the use of high doses of analgesics, adding antioxidant substances to the patient's diet has been attempted. In this paper we review the most recent literature data about the use of antioxidants in alleviating the pancreatic pain.

Key Words: Antioxidants, pancreatitis, chronic, pain, analgesia

Antioksidanlar ve Kronik Pankreatitli Hastalarda Ağrı Kontrolü: Bitmeyen Hikaye

Özet: Kronik pankreatit pankreasın ilerleyici ekzokrin ve endokrin yetmezliği ve tekrarlayan karın ağrısı atakları ile karekterize benign bir hastalıktır ve sık sık hastaneye yatırılmayı gerekli kılar. Genetik değişiklikler, otoimmun hastalıklar ve safra yolları ve pankreasın tıkayıcı hastalıkları sonucunda da oluşabilirse de sıklıkla kronik alkol kullanımı sonucunda oluşur. Kronik pankreatitli hastanın yaşam kalitesini de etkileyen en önemli semptom ağrıdır ve ağrının kontrolü tedavideki en önemli basmaktır. Ağrıyı kontrol etmek için yüksek doz analjeziklerin kullanımına ek olarak, hastaların diyetlerine antioksidanların eklenmesi de denenmiştir. Bu makalede pankreatik ağrının kontrolünde antioksidanların kullanımı ile ilgili literatürdeki son çalışmalar gözden geçirilmiştir.

Anahtar Sözcükler: Antioksidanlar, pankreatit, kronik, ağrı, analjezi

Introduction

Chronic pancreatitis is a benign disease often characterized by recurrent episodes of abdominal pain accompanied by progressive pancreatic exocrine and endocrine insufficiency (1); it sometimes requires multiple hospitalizations. This disease is frequently the result of chronic alcohol abuse, even if other factors such as genetic alterations, autoimmune disorders, and obstructive disease of the biliary tract and the pancreas may cause the disease (2). The pain can be considered the most important symptom and it significantly modifies the quality of life of patients with chronic pancreatitis (3). Its control represents a challenge in the treatment of the disease. Thus, the search for a new medical approach is under investigation.

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Pathophysiology of Pancreatic Pain

There are two main hypotheses regarding the origin of pain in chronic pancreatitis. The first hypothesis, still under debate, claims that there is a correlation between pancreatic pain and pancreatic duct changes or pressure in the duct system (4-8). The second, also called the 'neurogenic inflammation' hypothesis, is the least convincing theory; immunohistological reports have shown that the number of neurotransmitters, such as substance P and its receptor, calcitonin gene-related peptide and other

neurotransmitters, are increased in afferent pancreatic nerves, and a correlation between pain and immune cell infiltration of the nerves has been reported in chronic pancreatitis (9).

Current Treatment Approaches

Medical therapy is the treatment of choice for most patients and it is based on substitutive therapy for either exocrine or endocrine insufficiency and on analgesics for pain control. In the presence of intractable pain, several therapeutic options have been applied in clinical practice in recent years. They include endoscopic therapy (10), thoracoscopic splanchnicectomy (11,12) and extracorporeal shockwave lithotripsy (13), even though, in case of failure of the previous approaches, surgical management remains the main option (14).

Medical Approaches Under Investigation: The Antioxidant Option

Among the several modalities for controlling the painful symptomatology, in addition to the use of high doses of analgesics, adding antioxidant substances to the patient's diet has been attempted (15).

A series of clinical studies beginning in 1983 in England in patients suffering from chronic pancreatitis have raised hope that antioxidant supplementation may be a step forward (15). Reviews of developments until 1996 (15,16) led to the conclusion that dietary insufficiency of methionine and vitamin C, aggravated by selenium deficiency, lays the groundwork for the disease when the oxidant load increases upon regular exposure to environmental chemicals which induce cytochrome P-450 mono-oxygenases (17). Comparing 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 (18-22), while it was noted that patients with severe pain had the lowest values of serum selenium (21). Further, 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 (23). In 2001, Uomo et al. (24) reported the usefulness of antioxidant therapy in a non-controlled study based on three patients affected by hereditary chronic pancreatitis. The two-year study was divided into four six-month periods. In the first and third periods, an oral analgesic drug was administered on demand, whereas in the second and fourth periods, oral antioxidant therapy was administered. The therapy consisted of SAMe (800 mg per day), vitamin C (180 mg per day), vitamin E (130 mg per day), vitamin A (2400 µg per day), and selenium (75 µg per 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. The authors concluded that oxidative stress is one of the main factors determining pain in hereditary chronic pancreatitis and that oral administration of antioxidants seems to be effective in the control of the pain.

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. Japanese authors (25) have suggested that the extract of the 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. However, curcumin is poorly absorbed following oral administration (26). Absorption can be improved by the co-administration of piperine (from black pepper) increasing the bioavailability by 2000% in rats and humans, without precipitating any adverse effects (27). Based on these assumptions, Indian authors have undertaken a pilot study 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 (28). They studied 20 consecutive patients with tropical pancreatitis randomized into two groups. 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) were evaluated. There was a significant reduction in the 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 which arises from the studies of Uomo et al. (24) and Durgaprasad et al. (28) is why such differences exist in pain control using antioxidant treatment. One possible explanation is that the SAMe and the selenium were not used in the Indian study and this may have, in some way, modified the pain control which clearly improved in the Italian study (24). This hypothesis is supported by the study carried out in England and performed using the Antox 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 methionine (29). In this randomized, double-blind, placebo-controlled crossover trial, the efficacy of a combined antioxidant preparation in the management of chronic pancreatitis was evaluated. 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 a further 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. The treatment with antioxidants seems to confirm the data obtained by Uomo et al. (24) in reducing pain in patients suffering from chronic pancreatitis.

Conclusions

Antioxidant treatment may become a useful tool in preventing and curing the pain in patients with chronic pancreatitis. However, large randomized studies are needed in order to definitively assess the usefulness and the best combination of antioxidants in patients with chronic pancreatitis; moreover, it must be kept in mind that the quality of life of the patients who receive such treatment should also be carefully and objectively measured.

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