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BRIEF ARTICLE

Quality of life assessment in patients with chronic pancreatitis receiving antioxidant therapy

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Abstract

AIM: To undertake a baseline study comparing quality of life (QoL) in patients with chronic pancreatitis (CP) on Antox to those with CP, matched for disease duration, who were not on this medication.

METHODS: CP was defined according to the Zurich classification. Sixty eight consecutive patients with CP who were taking Antox (antioxidants) were compared with 69 consecutive control CP patients not on Antox. European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core questions 30 and Pancreatic Modification (28 questions) were used to assess QoL. Out of a total of 137 patients 28 in each group were matched for disease duration (within 12 mo). Median disease duration was 8 (1-22) years in the Antox group and 7 (1-23) years in the Non-Antox cohort (P = NS, Mann-Whitney U-test). Other parameters (age, gender, etiology, endocrine and exocrine insufficiency) were similar between groups.

RESULTS: Median visual analogue pain score in the Antox group was 3 (0-8) compared with 6 (0-8) in the Non-Antox group ($P < 0.01$). Perceptions of cognitive, emotional, social, physical and role function were impaired in the Non-Antox group compared to Antox patients ($P < 0.0001$, $P = 0.0007$, $P = 0.0032$ and $P < 0.005$ and $P < 0.001$, respectively). Analgesics and opiate usage was significantly lower in the Antox group ($P < 0.01$). Overall physical health and global QoL was better in the Antox group ($P < 0.0001$, 95% CI: 1.5-3).

CONCLUSION: Contemporary quality of life assessments show that after correction for disease duration and cigarette smoking, patients with CP taking antox had better scores than non-antox controls.

Key words: Chronic pancreatitis; Antioxidants; Quality of life; Assessment; Management

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INTRODUCTION

Chronic pancreatitis (CP) is a chronic inflammatory con-

dition of the pancreas characterized histologically by loss of normal pancreatic parenchymal architecture with varying degrees of fibrosis and inflammatory infiltration[1]. Clinically, CP presents a spectrum of disease most often marked by chronic or recurrent abdominal pain together with varying features of pancreatic exocrine deficiency, most typically fat-related, resulting in steatorrhea, and manifestations of pancreatic endocrine deficiency, such as diabetes mellitus[1].

Although there are no national incidence registries, population-based data indicate a frequency of 8.6/100000 per year[2] with similar incidence being recognized in the United States[3] and other Northern European countries[4,5]. The clinical course of CP can be characterized by variable background abdominal pain with episodic exacerbations. Although the later stages of the illness are marked by pancreatic exocrine and endocrine insufficiency, abdominal pain is the dominant symptom for many sufferers.

Until now there has been no specific therapy for CP. Rose *et al*[6] demonstrated that CP arose as a result of pathological exposure of the pancreatic acinar cells to short-lived oxygen free radicals - a process termed oxidative stress. The peripheral blood samples taken from patients with clinical CP have shown that antioxidants (the term given to inhibitors of the oxidative stress response), their precursors and co-factors in physiologic antioxidant pathways are depleted during the course of this illness[7]. In addition, there is elevation of peripheral blood markers of oxidative injury. Braganza *et al*[8] reasoned that exogenous supplementation with antioxidants or precursors for antioxidant pathways may augment these deficient pathways and help to quench ongoing acinar injury. From a series of exploratory studies they concluded that co-factors of the endogenous glutathione peroxidase pathway were key components for supplementation. Selenium, vitamin C (ascorbic acid) and methionine were proposed as key antioxidants[8-10]. A commercially-available formulation, Antox (Pharma Nord, Morpeth, UK) was developed comprising vitamin C, vitamin E, β-carotene, selenium and methionine.

There is anecdotal evidence from small, underpowered, randomized trials that oral antioxidant therapy reduces the frequency and severity of episodes of pain[11,12]. More recently, a well-conducted randomized trial from India demonstrated that oral antioxidant therapy was associated with a reduction in hospital admission and "pain days"[13].

In contemporary healthcare terms, perhaps the critical issue in the treatment of CP is assessment of the effect of intervention on quality of life (QoL). In this regard, formal, well-validated questionnaire-based QoL scoring systems are now available for assessment of patients with CP[14].

The European Organization for Research and Treatment of Cancer (EORTC) QoL study group has developed a modular approach to the development of QoL instruments designed for use in clinical trials[15]. A 30-item core cancer questionnaire; the EORTC Quality of Life Questionnaire (QLQ) Core questions 30 (C-30) was developed. It was initially developed and validated for use in patients with non small cell lung cancer[16]. The 30-item core questionnaire is intended to be supplemented by additional questionnaire modules to assess disease symptoms and treatment side-effects. The EORTC QLQ Pancreatic Modification (26 questions) (PAN-26) was developed and mainly used for pancreatic cancer[17]. During the development of the QLQ PAN-26, interest was expressed in the feasibility of using this assessment system in patients with CP[14].

Two questions have been added to PAN-26 to produce a questionnaire for use in CP, the QLQ PAN (CP)-28[17].

The aim of this study is to compare QoL, using an appropriately validated, disease-specific questionnaire-based approach in a cohort of patients with CP receiving oral antioxidant therapy to individuals with CP who are not receiving this medication.

MATERIALS AND METHODS

Study design

This is a prospective, single-centre clinical study comparing QoL as assessed using validated, disease-specific EORTC questionnaires[17] in a group of patients with a clinical diagnosis of CP receiving oral antioxidant therapy in the form of Antox (Pharma Nord, Morpeth, UK) to a cohort of patients with CP from the hepatobiliary and gastroenterology services of the same hospital who were not receiving oral antioxidant supplementation.

Patients and treatment algorithm

The terminology advocated by the Zurich International Workshop was used to define alcohol-related CP[18]. All patients had radiological evidence of CP on either computed tomography or magnetic resonance imaging; in addition some patients had supplementary evidence from endoscopic retrograde pancreatography or endoscopic ultrasonography. Routine monitoring of blood glucose was undertaken in the outpatient setting. Pancreatic exocrine function testing was not routinely employed in patients in this study. In general, antioxidant therapy was offered for the treatment of patients with a diagnosis of CP if there was no evidence of a pancreatic lesion potentially requiring surgical intervention, or if there was no marked pancreatic ductal dilatation amenable to endoscopic or surgical drainage. Thus, for the purposes of this study, patients were categorized into those taking Antox and those not taking this medication. Clinical characteristics of these 2 groups are shown in Table 1.

Administration of questionnaire, data registration and analysis

Patients completed the EORTC QLQ C-30 and QLQ PAN-28 questionnaires in the presence of an interviewer as part of a dedicated interview. Pain was assessed using a visual analogue score (VAS), where 0 is no pain and 10 is the maximum (scale 0-10). All interviews were undertaken by the same interviewer (NS). Interviews were conducted

Table 1 Profile of patients with chronic pancreatitis matched for similar disease duration

	CP patients on Antox (n = 28)	CP patients NOT on Antox (n = 28)	P-value
Age (yr), median (range)	53 (24-82)	53 (31-74)	0.30 (Mann-Whitney U-test)
Etiologies	Alcohol: 13 (46%) Idiopathic: 13 (46%) Others: 2 (8%)	Alcohol: 17 (61%) Idiopathic: 11 (39%)	
Gender (male:female)	16:12	18:10	0.79 (Fisher's exact test)
Duration of disease (yr), median (range)	8 (1-22)	7 (1-23)	0.85 (Mann-Whitney U-test)
Current cigarette smoking	8 (27%)	18 (62%)	0.01 (Fisher's exact test)
Alcohol before diagnosis of CP	118 (48-240) g/d per person	160 (28-240) g/d per person	< 0.01 (Mann-Whitney U-test)
Alcohol intake, current mean (range)	25 (0-48) g/d per person	33 (0-96) g/d per person	0.63 (Mann-Whitney U-test)

CP: Chronic pancreatitis.

with patients attending the Hepatobiliary and Gastroenterology clinics in this hospital during the study period February 2007 to February 2009. The interviewer was a clinical research fellow and not involved in the clinical care of any of the patients. Questionnaires were completed prospectively but analyzed retrospectively as a batch after completion of the study. Questionnaire results were not used to inform clinical decision-making. Questionnaire results were transcribed onto an electronic database (Microsoft Excel, Microsoft, Redmond, Washington, USA) for subsequent analysis. The interviews were conducted on a single time point basis: no patients underwent repeat interview. All patients in the Antox group had been receiving therapy for at least 6 mo. No patients had undergone surgery in the 6 mo prior to interview.

Disease duration-matched cohort

Interim analysis of the whole cohort data showed that there were significant differences in the median age and disease duration between patients in the Antox group and those in the Non-Antox cohort. In an effort to correct for at least one of these factors, disease duration matching was undertaken. The disease duration was recorded for each patient from the clinical chart. Patients in the Non-Antox group were then matched with corresponding individuals from the Antox group. A disease duration of the same time period ± 12 mo was selected for matching. No patient was included twice and data were paired by searching chronologically according to date of interview from first interviewee to the last.

Ethics committee approval

This study was approved by regional research ethics committee.

Statistical analysis

Continuous data are presented as median (range). Statistical comparisons were by non-parametric test using the Mann-Whitney U-test for 2 group comparisons and Fisher's exact test for contingency tables. The Wilcoxon signed ranks test (two-sided test) was used for comparison of paired data. Statistical significance was at the $P < 0.05$ level. The StatsDirect software program was used for statistical analyses (StatsDirect version 2.6.5, http://www.statsdirect.com).

RESULTS

Entire cohort comparison (NOT matched for disease duration)

Alcohol was the most common etiologic agent in 84 (61%) of patients. The median age of the group taking Antox was 56 (24-82) years compared to 47 (24-74) years in those not taking Antox. This difference was statistically significant. Disease duration and proportion of patients with diabetes mellitus were also greater in the Antox groups (although the difference in incidence of diabetes mellitus was not significant).

Entire cohort outcome (NOT matched for disease duration)

VAS, overall physical health scores and global QoL were significantly better in patients with CP taking Antox. These results are reflected in the significantly lower number of patients in the Antox group taking analgesics and opiates.

Disease-duration matched cohort outcome

Table 1 shows that the disease duration-matched cohort were also similar in terms of age, etiology of CP and gender ratio. There were more smokers in the Non-Antox group, and alcohol intake prior to diagnosis was also greater in this group.

The outcome data in the disease duration-matched patients show that patients taking Antox had lower pain scores and fewer were taking analgesics (including opiates). There was no difference in the proportions of patients who were diabetic or who were taking pancreatic exocrine supplements (Table 2). A significantly greater number of patients in the Non-Antox group had undergone either surgical or endoscopic intervention.

Detailed global outcome data from the disease duration-matched cohort are shown in Table 3. Answers to questions were ranked on a scale of 1 to 4 [(1) not at all affected; (2) a little affected; (3) quite a bit affected and (4) very much affected]. In addition to lesser pain scores (as above) factors which were significantly better in patients

Table 2 Quality of life, pain scores and analgesic usage in disease duration-matched patients with chronic pancreatitis

	CP patients on Antox (n = 28)	CP patients NOT on Antox (n = 28)	P-value
Median visual analogue pain scores (range 0-10)	3 (0-8)	6 (0-8)	< 0.01 (Mann-Whitney U-test)
Patients taking analgesics	16	26	< 0.01
Patients taking opiate analgesics	11	23	< 0.01
Diabetes	10 (36%)	11 (39%)	0.80
Pancreatic exocrine supplements	14 (50%)	16 (57%)	0.60

CP: Chronic pancreatitis.

Table 3 Detailed European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core questions 30 and Pancreatic Modification (28 questions) results in disease duration-matched patients with chronic pancreatitis

Scales	Items	CP patients on Antox mean score (n = 28)	CP patients NOT on Antox mean score (n = 28)	P-value	95% CI
Physical Functioning	Q-1-5	1.5	1.97	0.005[1]	-0.8 to 0.1
Role Functioning	Q-6-7	1.84	2.75	0.001[1]	-1.5 to 0.5
Pain	Q-9, 19	2.1	3.1	< 0.0001[1]	-1.5 to 0.7
Fatigue	Q-10, 12, 18	2.05	2.86	0.0001[1]	-1.7 to 0.3
Nausea and vomiting	Q-14, 15	1.5	2.2	0.002[1]	-1.2 to 0.2
Cognitive functioning	Q-20, 25	1.6	2.4	< 0.0001[1]	-1 to 0.5
Emotional functioning	Q-21-24	1.8	2.6	0.0007[1]	-1.2 to 0.5
Social functioning	Q-26, 27	1.8	2.7	0.0032[1]	-1.2 to 0.2
Global quality of life	Q-29, 30	2.6	4.9	< 0.0001[1]	1.5 to 3
Pancreatic Pain	Q-31, 33, 35	1.9	2.9	< 0.0001[1]	-1.5 to -0.7
Digestive function	Q-36, 37	2.14	2.5	0.09[1]	-1 to 0
Jaundice	Q-44, 45	1.1	1.2	0.41[1]	-0.25 to 0
Altered bowel functioning	Q-46, 47	2.1	1.6	0.07[1]	-1 to 0
Body Image	Q-48, 51	1.3	2.5	0.0004[1]	-1.2 to -0.25
Alcohol related guilt	Q-49, 50	1.5	1.4	0.7[1]	-0.25 to 0.5
Satisfaction with health care	Q-55, 56	3.2	3.4	0.44[1]	-0.5 to 0.25
Sexual functioning	Q-57, 58	1.7	2.66	0.0003[1]	-1.5 to -0.5
Dyspnea/shortness of breath	Q-8	1.5	1.6	0.63[1]	-0.5 to 0
Difficulty sleeping	Q-11	1.9	2.9	0.0003[1]	-1.5 to 0.5
Loss of appetite	Q-13	1.8	2.5	0.04[1]	-1.5 to 0
Constipation	Q-16	1.7	1.8	0.86[2]	-1 to 0.5
Diarrhea	Q-17	1.5	1.5	0.03[2]	-1 to 0
Financial problems	Q-28	1.3	1.9	0.02[2]	-1 to 0
Bloated abdomen	Q-32	1.9	2.8	0.002[2]	-1.5 to 0.5
Night pain	Q-34	1.8	3.1	< 0.0001[2]	-2 to -0.5
Taste changes	Q-38	1.2	1.7	0.02[2]	-1 to 0
Indigestion	Q-39	1.7	2.4	0.018[2]	-1 to 0
Flatulence	Q-40	2.0	2.6	0.06[2]	-1 to 0
Weight loss	Q-41	1.2	2.4	< 0.0001[2]	-1.5 to -0.5
Decreased muscle strength	Q-42	1.8	2.3	0.11[2]	-1 to 0
Dry mouth	Q-43	1.6	2.2	0.02[2]	-1 to 0
Treatment side effects	Q-52	1.2	2.0	0.0002[2]	-1 to -0.5
Fear for future health	Q-53	2.4	3.0	0.03[2]	-1 to 0
Ability to plan ahead	Q-54	1.8	2.9	0.0001[2]	-1.5 to 0.5

[1]Wilcoxon signed rank test 95% CI; [2]Wilcoxon t-test. CP: Chronic pancreatitis; Q: Question No. (total C-30 + PAN 28 = 58 questions).

taking Antox were: physical functioning, role functioning and cognitive and emotional functioning. These translated into a significant improvement in global QoL. Digestive function, jaundice and bowel function were not significantly different.

DISCUSSION

This study has examined QoL in patients with CP. Contemporary criteria were used for definition of disease and the Zurich Workshop recommendations were used for assessment of alcohol-related CP[18]. QoL has been evaluated in 2 cohorts of patients: those taking oral antioxidant therapy for CP and those not taking this medication. Specific disease-validated questionnaires were used for assessment of QoL[17].

Antioxidant therapy has been available for the treatment of CP for over 20 years[19]. However, the lack of good-quality randomized trial evidence and the dearth of information about clinical outcome in patients taking antioxidants has meant that this treatment remains on the periphery of practical management.

Thus, the importance of the present study is that it is believed to be the first to utilize specific disease-validated questionnaire methodology to assess QoL in patients with well-defined CP taking oral Antox. Potential sources of bias in these data should be borne in mind when interpreting the results.

Patients were not randomly allocated to Antox or Non-Antox; those receiving Antox were older and had longer disease duration (Table 1). Although disease-duration matching may have corrected for some of these factors, other confounding factors could persist: there were more smokers in the Non-Antox group and a sequential, multiple interview strategy would have yielded a more accurate reflection of QoL. This is accepted but must be balanced against the inconvenience to patients resulting from completing the lengthy questionnaires involved in this study. Also on a practical basis all patients were interviewed at relatively stable points in their disease with no history of recent surgery or change in medication.

Accepting these likely sources of bias, measures of QoL showed a significant benefit in patients on Antox: pain scores, physical health scores and global QoL together with analgesic (including opiate) intake were significantly better in the Antox group.

However, these findings may simply reflect a more mature population in the Antox group who have had more time to adjust to their illness and in some of whom the disease may be "burnt out"[20].

It is accepted that disease duration in a long-term chronic illness such as CP can be unreliably recalled[21] but prospectively recorded duration data were taken from the patients' charts and thus any error should be similar in both groups. The process of matching for disease duration produces a cohort of 28 pairs who are also reasonably well matched in terms of age, gender and etiology (Table 3). Although alcohol consumption in the Non-Antox group was greater prior to diagnosis, there was no difference after diagnosis.

The outcome data from the disease duration-matched cohort show some striking findings. VAS were significantly lower in the Antox group with a corresponding lower use of analgesics including opiate analgesics. There were no differences in the proportion of patients with diabetes or those taking pancreatic exocrine supplements, suggesting that if Antox modified symptoms in CP, there was no effect on the underlying disease course. Examined in detail, using the full EORTC questionnaires, the study showed improvement in global QoL in patients taking Antox. There were no differences in jaundice and digestive function answers, again suggesting that antioxidant therapy may modify symptoms without affecting disease progression.

These data should be considered together with the results of a recent large randomized trial from India of oral multi-compound antioxidants in painful CP. Although the Indian study did not use QoL measurement and had soft principal end-points in the form of reduction in hospital admission and reduction in "pain days" the study showed benefit from treatment with antioxidants.

In summary, this study has used well-validated, disease-specific questionnaires to assess QoL in patients with well-defined CP and compared a cohort of patients taking Antox to a group who were not. When corrected for differences in disease duration and age, patients on Antox had significantly lower VAS, lower analgesic use and better global QoL. Caution in interpretation is required. We would state that these data support a renewal of interest in the role of antioxidant therapy in CP and favor the conduct of a formal, randomized placebo-controlled trial of Antox in painful CP.

COMMENTS

Background

Chronic pancreatitis (CP) is associated with severe, disabling, frequent abdominal pain. It often leads to endocrine (diabetes) and exocrine (diarrhea and weight loss) disorders. In general, patients with CP have very poor quality of life (QoL) and outcome. No treatment has been found to combat long-term pain and cure.

Research frontiers

There has been anecdotal evidence of upregulation of the oxidative stress response and deficiency in antioxidants levels in patients with CP. The cascade of events due to repeated exposure and non correction leads to pancreatic fibrosis. This in turn leads to severe, chronic abdominal pain and poor QoL. In this study we demonstrated improvement in QoL for patients who were on antioxidant therapy.

Innovations and breakthroughs

Antioxidant therapy for CP was suggested in the mid 1990s. There have been a few studies showing the benefit of antioxidant therapy in CP. However, due to the paucity of data, it has not been universally accepted. This is the first comparative study to report QoL assessment in patients with CP on antioxidant therapy and those NOT on antioxidant therapy.

Applications

The study has renewed interest in antioxidant therapy for CP. The data lack randomization. This report supports the progression to a formal randomized double-blind trial of antioxidant therapy assessing QoL and outcome in patients with CP.

Terminology

Antioxidants is the term given to inhibitors of the oxidative stress response. They are typically selenium, vitamin E, methionine and ascorbic acid. European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core questions 30 and Pancreatic Modification (28 questions) (PAN-28) (EORTC, QoL core questionnaire and its pancreatic modification, PAN-28) are the QoL assessment tools validated and used for patients suffering from CP. Such a methodology is important and vital in measuring the outcome in chronic diseases.

Peer review

In general, this study by Shah *et al* has high originality and is interesting because they revealed the effectiveness of antioxidant treatment for CP which focused on QoL.

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