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Predicting the efficacy of surgery for pain relief in patients with alcoholic chronic pancreatitis

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ABSTRACT

Background: Recurrent pain is the most disabling complication in patients with chronic pancreatitis. Pancreatic surgery is currently considered as last-resort therapeutic option. The aims of this study were to assess pancreatic surgery performance for chronic pain in patients with alcoholic chronic pancreatitis and to determine factors predictive of therapeutic response.

Methods: All patients with chronic pancreatitis who underwent pancreatic surgery for chronic pain were included and divided into 2 groups according to the cause of chronic pancreatitis: alcoholic and any other chronic pancreatitis causes as the control group. Alcohol, tobacco, and painkiller intake, quality of life data 6 months and 1 year after surgery, and morphological and pathological features were analyzed.

Results: Fifty patients were included in the alcoholic chronic pancreatitis group and 16 patients in the control group. Smoking cessation before pancreatic surgery was achieved in 40% of the alcoholic chronic pancreatitis group compared with 73% of the control group ($P = .005$). Histological analysis revealed a higher prevalence of hypertrophic nerves and perineural inflammation in the alcoholic chronic pancreatitis group than in the control group ($P = .03$ and $P = .04$ respectively). In multivariate analysis, in the alcoholic chronic pancreatitis group, factors predictive of 6-month narcotic use cessation were surgery performed within a maximum of 2 years after chronic pancreatitis diagnosis (odds ratio = 4.228 [1.04–17.17]) and postoperative smoking cessation (odds ratio = 3.561 [1.021–12.41]); at 1 year, only smoking cessation was predictive of narcotic use cessation (odds ratio = 11.33 [2.677–47.98]).

Conclusion: In patients with alcoholic chronic pancreatitis undergoing surgery for chronic pain, narcotic use cessation and improved quality of life depend on early surgery and complete smoking cessation.

Nearly 90% of patients with chronic pancreatitis (CP) report disabling pancreatic pain, which is the main cause of hospitalization.[1] Pain can lead to weight loss, depressive syndrome, addiction to painkillers or drug misuse, as well as impairment of quality of life.[2] A permanent pain characteristic seems to have a more deleterious impact on quality of life than the intensity of the pain itself.[3]

Several studies highlighted great variability regarding the duration of pain evolution during CP natural history and a lack of correlation with its intensity.[3,4] After a median follow-up of 11 years, fewer than 1 in 2 patients (47%) reported a decrease in pancreatic pain over the CP course.[5]

Chronic pain genesis has long been reduced to a pure mechanistic theory, related to hyperpressure caused by pancreatic duct obstruction. It is now well known that pain genesis is multimodal, which explains some therapeutic failures when the choice of treatment is based only on morphological abnormalities. The main components inducing chronic pain are pancreatic and extrapancreatic visceral nociceptive neuronal activation, peripheral and central neurological impairments, and peri-pancreatic complications such as pseudocysts.[6]

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Neuronal plasticity corresponding to the increase in number and size of nerves within the pancreas was described.[7] After peripheral nerve lesions, central neurological sensitization, at both the medullary and cortical levels, might maintain pain.[4,8,9]

The therapeutic strategy commonly applied is a step-up approach, which combines dietary restrictions, focused mainly on ending exposure to risk factors (alcohol and tobacco), with an optimized analgesic medical treatment.[9] Medical treatment can combine analgesics of the 3 levels of the WHO classification with adjuvant treatments such as pregabalin and antioxidants. Pregabalin represents a key treatment for chronic pain because of its neurological action, both central and peripheral. Randomized trials highlighted significant improvements in pain rating scales (ie, Izbicki score) and a morphine sparing effect related to the use of pregabalin (compared with placebo), after only 3 weeks.[10,11]

Oxidative stress is known to be implicated in the pathogenesis of chronic pancreatitis. Among adjuvant therapies, antioxidants have been studied through randomized trials and appear to have a benefit in pain reduction for patients with chronic pancreatitis.[12-14] In a meta-analysis, Rustagi et al.[12] found that patients who received antioxidant therapy had significant reductions in the number of painful days per month and in the number of analagesics consumed per month.

Pancreatic surgery currently appears to be the last resort of the therapeutic strategy, especially after endoscopic treatment failure.

There are no clear predictive markers for the evolution of chronic pain or the response to different treatments during CP. Only one study identified 3 risk factors for surgical treatment failure: long-term morphine intake, prolonged chronic pain, and a history of more than 5 endoscopic treatments.[15]

The main objective of this study was to evaluate the efficacy of analgesic pancreatic surgery in patients with alcoholic CP and to determine the clinical, morphological, and histological factors predictive of the therapeutic response.

Methods

Patients

A retrospective monocentric study was performed at Beaujon Hospital (France). All files of patients with CP who underwent pancreatic surgery, regardless of the indication, were analyzed to determine their eligibility. All patients monitored for CP and operated on for recurrent pain between 2008 and 2015 were included.

Inclusion criteria

1. Two groups were studied and compared: The first group comprised patients with alcoholic CP. The second group, the control group, comprised patients with non-alcoholic CP. The causes of CP were genetic (mutations of the PRSS1, CFTR, CTRC, or SPINK1 gene), autoimmune (pathological confirmation), or idiopathic after an exhaustive workup.
2. All patients presented with chronic or recurrent acute bouts of pain, and pancreatic surgery was carried out with the intent of relieving pain in all cases. Surgical procedures included pancreatic resections and drainages. Resections included the Frey and Whipple procedures and left (LP) and median (MP) pancreatectomies. The drainage surgery consisted of a longitudinal opening of the main pancreatic duct (MPD) with Wirsungo-jejunal anastomosis.
3. All patients included had a preoperative pancreatic computed tomographyscan.
4. All surgical specimens were available in the Department of Pathology.

Exclusion criteria

1. Patients with suspected pancreatic tumors or in whom pancreatic cancer was diagnosed within 1year following surgery were excluded.
2. In the control group, all patients with chronic alcoholic consumption above World Health Organization (WHO) recommendations were excluded (>30 g/day for men, >20 g/day for women).

Definitions

Chronic pancreatitis diagnosis was based on a set of clinical and morphological data, with histological confirmation for all patients.

The alcoholic origin of the CP was defined as consumption of >80 g/day alcohol during and more than 10 years.[16] Exocrine pancreatic insufficiency (EPI) was defined by the existence of steatorrhea, need for oral pancreatic enzyme supplementation, or a fecal elastase-1 <100 µg/g stool.

Consumption of analgesics was reported according to the levels set by WHO (1–3) and the mean daily dose. A specific conversion for each analgesic was performed so that all results would be expressed as oral morphine equivalents (OMEs) corresponding to the dose of morphine sulfate taken per day (see Supplementary Data, Appendix 1).

We assessed quality of life with objective data for all patients including analgesic use (1 to 3 levels set by WHO and mean daily dose), pain frequency (daily, weekly, monthly), and weight. All these data were part of our flowchart consultation procedures and were systematically reported in a standardized manner. The quality of life of the patient was rated as good (absence of pain or fewer than one pain episode per week and a normal food intake), average (weekly pain requiring analgesics and/or restriction of diet without sickness), or poor (daily pain requiring daily intake of analgesics and/or a restriction of diet responsible for weight loss).

Radiological analysis

All included patients had a preoperative abdominal CT scan. A senior radiologist expert in the pancreatic field, blinded to clinical and pathological findings, reviewed all exams.

Pathological analysis

All slides were reviewed by 3 authors (B.B., A.C., and V.R.), blinded to the clinical and radiological results. For each patient, all archived HES (hematoxylin-eosin-safran)-stained slides, representative of the entire surgical specimen, were analyzed.

All immunohistochemical techniques were carried out on the same automaton (Nexes GX, Ventana, Tucson, AZ, USA) within the Department of Pathology at Beaujon Hospital. The immunolabeling was carried out after selection of the most representative block from analysis of the HES-colored slides. Sections of 4 µm were made in the tissue blocks included in paraffin. The slides were immunolabeled with monoclonal antibodies against CD56 (clone 1B6, dilution 1/50, Leica Biosystems [formerly Novocastra], Nussloch, Germany); CD8 (clone C8/144B, dilution 1/50, DAKO, Carpinteria, CA) and tryptase (dilution 1/1000, Leica Biosystems). The paraffin sections were immunolabeled after dewaxing and rehydration of the slides. Antigen unmasking was performed following pretreatment at high temperature. Substitution of the primary antibody with phosphate-buffered saline was used as a negative control. The positive controls consisted of cellular elements always stained by the antibodies used: normal nerves for CD56, lymphocytes for CD8, mast cells for tryptase. After staining, the slides were scanned using a computer-controlled image capture device (Aperio, Leica

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