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Review Article

SURGICAL TREATMENT OF CHRONIC PANCREATITIS WITH FREY PROCEDURE: CURRENT SITUATION

Tratamento cirúrgico da pancreatite crônica com a técnica de Frey: panorama atual

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ABSTRACT - ***Introduction*** - Chronic pancreatitis is a progressive inflammatory disorder characterized by irreversible destruction of pancreatic parenchyma and may be associated with disabling chronic pain and permanent loss of endocrine and exocrine function. Main indication for surgery is intractable abdominal pain and choosing the best technique to be used for a patient remains a challenge. The technique described by Frey combines the effectiveness of pain control characteristic of resection surgery with low mortality and morbidity of derivative procedures. ***Aim*** - To compare and discuss the results of surgical treatment of chronic pancreatitis with Frey procedure. ***Methods*** - A literature review of scientific articles available in Medline/Pubmed database and the national theses descriptors with terms chronic pancreatitis, surgical treatment and Frey procedure. It was selected the most important articles and that reported more experience with this surgical option. ***Conclusions*** - Frey procedure proves to be an option with high effectiveness in controlling abdominal pain secondary to chronic pancreatitis in the long term in patients with abdominal pain and enlarged pancreatic head, with lower rates of morbidity and mortality. The studies showed little interference of technique in the deterioration of endocrine and exocrine pancreatic functions.

HEADINGS - Pancreatitis. Chronic disease. Pancreas, surgery. Abdomen, surgery. Pancreatojejunostomy.

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RESUMO - ***Introdução*** - A pancreatite crônica é desordem inflamatória progressiva caracterizada pela destruição irreversível do parênquima pancreático, podendo estar associada à dor crônica incapacitante e perda permanente da função endócrina e exócrina. A principal indicação cirúrgica é a dor abdominal intratável e a escolha da melhor técnica a ser empregada permanece um desafio. A técnica descrita por Frey conseguiu combinar a eficácia no controle da dor das operações de ressecção com as baixas taxas de mortalidade e morbidade das derivativas. ***Objetivo*** - Comparar e discutir os resultados do tratamento cirúrgico da pancreatite crônica com a técnica de Frey. ***Métodos*** - Revisão bibliográfica de 276 artigos científicos disponíveis no Medline/Pubmed e no banco de dados de teses nacionais com os descritores pancreatite crônica, tratamento cirúrgico e cirurgia de Frey. Foram selecionados os 30 artigos de maior importância e que relataram maior experiência com esta opção cirúrgica. ***Conclusões*** - A técnica de Frey demonstra ser opção de alta efetividade no controle da dor abdominal secundária à pancreatite crônica no longo prazo naqueles pacientes com dor abdominal incapacitante e aumento volumétrico da cabeça pancreática, com menores taxas de morbidade e mortalidade. Os estudos demonstraram pequena interferência da técnica na deterioração das funções endócrina e exócrina.

DESCRITORES - Pancreatite. Doença crônica. Pâncreas, cirurgia. Abdome, Cirurgia. Pancreatojejunostomia.

INTRODUCTION

Chronic pancreatitis (CP) is a progressive inflammatory disorder characterized by irreversible destruction of pancreatic parenchyma and may be associated with disabling chronic pain and permanent loss of exocrine and endocrine function[1]. The patients with this condition remain a challenge today due to the limited understanding of the pathophysiology of the disease, the unpredictability of clinical evolution and the controversies between the diagnostic criteria and treatment options [27].

A number of factors have been directly related to the causes of

the CP. Alcohol intake is a major risk factor for their development, and its action is dependent of dose and time[27]. Smoking also plays important role and is an independent risk factor [29].

The goal of treatment is the pain relief so that it does not interfere with work activities and family life. As a general rule, the control should follow the sequential and phased approach, starting with the elimination of toxic exogenous factors such as alcohol and tobacco, followed by pancreatic enzyme supplementation and judicious use of analgesics. Abstinence from alcohol is essential, especially when this is the pillar of the cause of the CP, since the maintenance of excessive alcohol consumption exacerbates the pancreatic damage and increases mortality[27].

Patients with persistent symptoms after this initial approach may be candidates for more invasive treatments. It is estimated that up to 50% of patients develop progressive or intractable symptoms; they become therefore candidates for surgical treatment

The main indication for surgery is intractable abdominal pain. The choice of surgical treatment is based on CP complications such as pseudocysts, pancreatic fistulas, stenosis, involvement of adjacent organs or suspected malignancy.

METHODS

Literature review conducted in Medline/ Pubmed database and the national thesis with the headings CP, surgical treatment and Frey surgery, selecting 276 scientific articles. Thirty papers were chosen, the most important and the ones reporting large experience with this surgical option.

Development of the technique

During the last century, due to the multifactorial cause of pain and little understanding of the pathophysiology of this process, several surgical options have been developed. Historically, the procedures have been classified into three categories: ductal decompression, denervation and pancreatic resection - proximal, distal or total pancreas. The strategies of pancreatic denervation proved ineffective or unfeasible as treatment of choice, which ended the discussion focusing on the dichotomy between surgical decompression versus resection.

In recent decades, however, emerged new hybrid procedures, which combine the two modalities (resection and decompression) and that have proven safe and effective as it had the benefit of remission of pain in long-term surgical resection associated to low rates of morbidity and mortality of decompression procedures.

Although pancreatojejunostomy laterolateral in Roux-en-Y (Puestow surgery or Partington-Rochelle) has become the procedure of choice for ductal decompression for about 40 years, it is clear that this was not the technique that would solve all CP cases, especially those non-dilated pancreatic duct. In addition, articles began to appear showing that despite a remission rate of pain about 80% in three years, approximately 30% of patients had recurrent pain with this technique after this period[7]. Later, it was well established that the main cause of failure of the Partington-Rochelle procedure is the absence of adequate decompression of the proximal main pancreatic duct, and uncinate process and secondary ducts of pancreas[11].

Given to these observations, the partial or total resection of the pancreas appeared to be an attractive solution for the definitive resolution of the pain caused by the disease, since even if the pain was caused by an inflammatory process that affects the nerves, for ductal hypertension or chronic ischemia, surgical removal of pancreatic injured tissue would heal it. In contrast, the more pancreatic tissue is removed, the greater the risk of developing endocrine and exocrine insufficiency, accompanied by their morbidities.

In the primary thought of eliminating the pain, the total pancreatectomy have been proposed for the treatment of CP. Priestley described the first total pancreatectomy in 1944. Over the years, it was realized that they did not produce better pain relief than the duodenopancreatectomy, and still had metabolic tragic consequences when not followed by islet cell transplantation. For all these reasons, total pancreatectomy was practically abandoned after 1970. In recent years, however, this procedure was again employed due to its association with the pancreatic islet transplantations

The operation most used in the treatment of CP is duodenopancreatectomy since 1950, which proved to be effective in controlling pain and complications from [18,25,26]. The three largest current studies on the treatment of CP with the Whipple operation show pain remission in four to six years between 71% and 89% of patients. Although effective in controlling pain and eliminate the main cause of recurrence of the pain of derivative operations resection of the head, keep duodenopancreatectomies mortality rates up to 5% and morbidity 40% even in referral centers[18]. Another factor that contributes to dissatisfaction with the results of resection are the high rates of glandular dysfunction, which affects early half of the patients[2]. Furthermore, persists dissatisfaction with resection of the distal common bile duct and duodenum. Therefore, the natural evolution of surgical treatment was the development of a technique that preserves the duodenum, the pancreatic head and spare enough to maintain

satisfactory exocrine and endocrine functions, even with low morbidity and mortality.

The Beger operation[5] met the wishes expected on duodenal preservation, maintenance of good results and glandular function. The results showed remission of pain in more than 80% of patients, changes similar to those of the exocrine failure patients without surgical intervention and the incidence rate of new diabetes from 8% to 21%[5,20]. The most feared complication of this surgical technique is the duodenal ischemia due to inadequate perfusion or non-preservation of the posterior branch of the gastroduodenal artery. Another factor of concern is the presence of two pancreaticojejunal anastomoses, but the incidence of fistula and other complications, such as delayed gastric emptying, ileus, are similar to the Whipple operation. In a prospective randomized study comparing the two techniques in 40 patients Buchler et al.[8] Showed postoperative morbidity 15% to 20% and hospital stay from 13 to 14 days. A retrospective comparative study[3], showed that the rate of major complications in Whipple operation was 40% compared with 25% in the Beger, with a rate of fistulas of 10% and 25% respectively.

Finally, in 1987, Frey and Smith[12] described a new technique for the treatment of CP, which consisted of local resection of the pancreatic head with a longitudinal pancreatojejunostomy. The author spared the gland close to the duodenum as a 95% pancreatectomy ("near total") and a posterior layer of the parenchyma of the head, which was excavated in continuity with the longitudinal Wirsung ductotomy, excising both the main duct and Santorini in cephalic portion (Figure 1).

Unlike duodenopancreatectomy and Beger operation this procedure saves the pancreatic neck and the posterior capsule of the pancreatic head. In the operation of Frey, the cervix is preserved intact, along with the body and tail of the organ, which reduces the risks of the operation (Figure 2). Later, Frey and Amikura [11] to reduce the risk of exceeding the head capsule of the pancreas and subsequent drilling the portal trunk, determined as the limit of excavation of the head the same plane as the posterior wall of the Wirsung's duct and Santorini opened in the uncinate process. All the tissue above the plane, including the duct of Santorini is excised. The reconstruction occurs with covering with a loop of jejunum in Roux-en-Y fashion which continues with the main pancreatic duct in the pancreatic body and tail.

Subsequent studies showed remission with the painful operation equivalent to that of Frey or Beger duodenopancreatectomy, but with mortality rates close to zero[16,17,28].

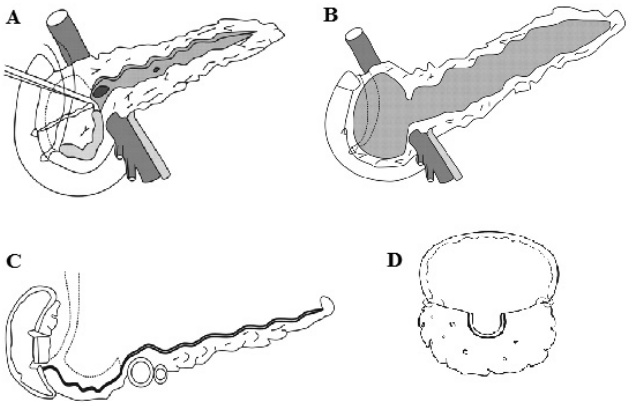

FIGURE 1 - Main steps of the Frey technique where (A) corresponds to the opening of the duct of Wirsung taking out the calculi and removing stenosis; (B) enucleation of the pancreatic tissue of the head and uncinate process of the pancreas in contiguity with the opening of the duct of Wirsung; (C) cross-sectional view which shows the posterior margin of resection of the pancreatic head in contiguity with the main pancreatic duct; (D) reconstruction with pancreatojejunal anastomosis.

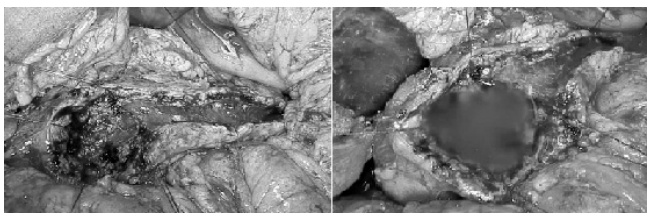

FIGURE 2 - Photographs of the pancreas after enucleation of pancreatic head and uncinate process and longitudinal opening of the main pancreatic duct

RESULTS

Ideally, the appropriate procedure for the patient suffering with abdominal pain secondary to the CP must have low rates of morbidity and mortality, be easy to perform, provide long painful period of remission, correct the complications or the worsening of functions of exocrine/endocrine gland. There is no ideal operation and even the more recently developed, such as the Beger and Frey procedures, meet all the criteria described above. Choosing the best technique to be used remains a challenge and is often based on empirical concepts, largely due to lack of complete knowledge of the pathophysiology of the disease.

The diffusion of the technique of Frey as standard surgical treatment is due to easeness of the procedure and the fact that the basic precept of the technique goes against the main cause. Treatment failure was observed in improper side drainage of the ducts of the head and uncinate process of the

pancreas.

The technique described by Frey managed to combine the effectiveness in controlling pain characteristic of resection operations with low mortality and morbidity eliminating the main cause of the pathophysiology of recurrent painful pancreatojejunostomy side alone. The technique also proved to be easier to perform and with less morbidity than Beger's technique with similar results with regard to pain management in long follow-up [17].

The rate of postoperative complications reported in international literature varies from 0% to 42%; comprehensive national study presented by Gestic had postoperative morbidity of 28.7%[10,11,13,15,16,17,22,23]. Most of these complications are due to infectious complications, mainly pneumonia[23]. This result seems to be associated with a high prevalence of smokers and malnourished contained in this study, reinforcing the association between hypoalbuminemy and infectious complications.

The occurrence of pancreatojejunal anastomotic leaks in the literature ranges from 5% to 11.7%[10,23]; national study showed a prevalence of 6.8%[13].

The length of postoperative hospital stay presented in the literature ranged from 7.5 to 16 days. The operative mortality ranges from 0% to 3.2% and the causes are more often assigned is sepsis (abdominal and lung) and bleeding[10,11,13,15,16,17,22,23].

Several papers of reference centers for surgical treatment of CP reported rates of postoperative bleeding less than 3%, grouping all the techniques employed. Although few randomized controlled trials, there was a trend of Beger and Frey techniques to present the highest rates of this complication (5% to 10%), usually originating from the remnant excavated pancreatic head[8,25].

The average weight of excised pancreatic tissue in surgical patients is an important factor that may influence the results of the technique and reflects the degree of aggressiveness of resection employed. The principle was first described by Frey to dry the largest possible amount of calcified tissue in the pancreatic head to avoid the main cause of failure in derivative operations: inadequate decompression of the pancreatic head tissue. Amikura and Frey[11] described excision of 5, 7 g per patient, range 2 g to 11 g, which is much lower than that reported in Brazil by Gestic[13], with an average of 17.4 g (range 5 g to 78 g). Negi et al. reported an average of 9.5 g enucleation in patients with average size of 6.0 cm pancreatic head[22]. The largest amount of excised tissue could lead to higher incidence of shortcomings but nevertheless, Gestic showed no association between the amount of pancreatic tissue excised and the emergence of new deficiencies (exocrine or endocrine) and not with the time of appearance of these[13]. On the other hand, this more aggressive in the excavation of the pancreatic head can justify higher rate of surgical morbidity when compared with the more recently published series.

Sakata et al.[24] Proposed limited resection of the pancreatic tissue of the head, initially only the pancreatic tissue prior to the duct of Wirsung, and later with excision only zone in the area before the main pancreatic duct, in which the author called minimal resection. The author, who does not describe the amount of tissue enucleated from the pancreatic head in grams, but in an area excised (1.8 cm^2) showed mean follow-up of 48.7 months, painful remission above 84% with worsening function of pancreas in only 6% of patients. Reported as advantages, the preservation of pancreatic tissue, prevention of intra-operative injury to the intra-pancreatic bile duct and portal vein, which joined together in prevalence in this series, 15% of patients. However, this change emphasizes the inability of the technique in cases of large cephalic masses or where compression of the biliary system, which was more common in the Brazilian Gestic sample [13], whose patients had, on average, 6.0 cm pancreatic head (40-10 cm) and 26% were admitted with cholestasis.

Pain Control

The results of most studies on the control of pain after surgical treatment of CP have limitations and interpretation of comparison due to lack of standardization of data collection on this symptom. Also subjective symptom, evaluation of abdominal pain as a criterion for surgical success in postoperative should be taken with caution, since it is influenced by a series of psychological and social factors. The coexistence of mental disorders in alcoholics and patients dependent on opioids may interfere with the results of treatment. For this reason, the service of the authors routinely requires discontinuation of alcohol intake and consumption of cigarettes and narcotics, providing psychosocial support for these patients so that they can deliver better results not only in pain control, but also in global recovery. Thus, it is observed that the operation is only part of a complex and multidisciplinary treatment that begins to prepare the patient for the procedure and should continue throughout the postoperative follow-up.

The largest national study of the technique of Frey showed results of pain management in long-term similar to other published reports of remission of 91.4% in painful mean follow-up of 77 months. The results are consistent with those observed with most published series (Table 1).

Frey and Amikura[11] advocate active surgical

TABLE 1 - Comparison of results in pain remission in postoperative follow-up of patients undergoing the Frey series

	Pain remission at the end of follow-up (%)	Average follow-up (months)	N
Frey and Amikura (1994)[11]	86.7	37	50
Izbicki et al. (1995)[17]	89	17	22
Izbicki et al. (1998)[16]	90	24	31
Ho and Frey (2001)[15]	88	38.4	75
Falconi et al. (2006)[10]	88.8	60	40
Pessaux et al. (2006)[23]	88	15	34
Egawa et al. (2009)[9]	100	46	71
Keck et al. (2010)[19]	62	43	50
Negi et al. (2010) [22]	75	76.8	60
Gestic[13]	91.4	77.0	73

attitude in the early stages of the disease before the start of the vicious cycle of pain, drugs abuse and inability to work. After these, complete recovery, even with good surgical outcome, is almost always incomplete.

The article of Izbick et al.[17] in 1995 was a prospective, randomized study comparing the Frey and Beger techniques. The authors demonstrated no statistical difference between the two techniques with regard to operative time, weight gain and postoperative pain control (Frey 89% and 94% Beger). In 1998, the same group published a prospective randomized study[16], with 61 patients, mostly due to alcohol (77%), comparing the evolution of Frey technique with duodenopancreatectomy (Traverso-Longmire technique) in the treatment of CP. Patients who underwent Frey technique showed no statistical difference in remission of pain postoperatively compared with those undergoing duodenopancreatectomy. However, had shorter surgical time, less blood transfusion and morbidity (19% versus 53%) and greater weight gain after surgery with a mean of 24 months.

Negi et al.[22] presented results of pain control in 75% of patients at a mean follow-up of 76.8 months and demonstrated as risk factors for failure of surgical treatment, thef opiate use in the preoperative period, a pattern of ongoing pain, symptoms for at least six years, the occurrence of postoperative complications and age above 38 years. The author showed no association of relapse with the return of pain, abuse of ethanol in the postoperative period.

Pancreatic function

Despite the control of abdominal pain being the main and most pursued goal of surgical treatment of CP since the early interventionist approach of this disease, the preservation of exocrine and endocrine functions of the body is becoming increasingly important in the analysis of the results of treatments. In addition to being effective in eradicating the pain, the technique should not accelerate functional deterioration of the gland.

Just at this current approach, emerged the technique of Frey. Gestic[13] presented a population in which 65.7% of patients had normal pancreatic function during surgery, and only 24.3% remained in the same way after five years of monitoring, with rates of 36.7% new cases of diabetes and 49% of new exocrine insufficiency. These results show the inexorable loss of glandular function while sparing surgery for pancreatic parenchyma.

Both endocrine and exocrine pancreatic dysfunction seem to have less influence on late mortality of patients with CP than the continued use of alcohol, narcotics, liver failure, suicide, accidents and recurrent pancreatitis [11]. However, this does not diminish the goal to preserve pancreatic function because they greatly influence the quality of life.

Diabetes is the most important sequel of late CP, is an independent risk factor for mortality in these patients, having been operated or not, and affects the quality of life[20]. The incidence of new cases of diabetes varies in different series[10,11,13,15,16,22,23] 10% to 25%, mean follow-up from 17 to 60 postoperative months. Gestic[13] following 77 months, reported incidence of new diabetes in 36.7%, above the other series.

The loss of function of the pancreatic tissue in patients with CP may result from disease progression or surgical resection. The effect of pancreatic bypass in delaying the development of diabetes is controversial. It is difficult to measure how the progression of the disease or the surgical procedure are responsible for the development of diabetes due to the heterogeneity of the studies.

Malka et al.[20] observed in long-term prospective study with 500 patients that diabetes appears, on average, 4.5 years after onset of symptoms of CP and dependence on exogenous insulin after 6.9 years 20. The study also showed that the surgical technique associated with increased risk of developing diabetes was the caudal pancreatectomy. Risk factors for the development of this complication were: younger age of onset of CP, longer follow-up and postoperative high prevalence of pancreatic calcifications and liver cirrhosis. The study concludes that the elective operation for the CP, except for the caudal pancreatectomy does not influence the risk of diabetes or insulin dependence by 25 years after the beginning of the CP. Moreover, contrary to many studies, noted that duodenopancreatectomy did not influence the risk of diabetes compared with the natural history of disease in patients treated conservatively.

It is controversial to say that the drainage of the main pancreatic duct preserves or improves pancreatic function by the release of the obstruction

to the flow of pancreatic juice. Nealon et al.[21] showed that 13% of patients undergoing ductal drainage evolved with worsening of pancreatic function, to 78% of those treated conservatively. Malka et al.[20] in their study said that more decisive for the evolution of pancreatic function is the degree of parenchymal destruction, not ductal obstruction.

Exocrine insufficiency is late manifestation of the CP and has a prevalence of 25% to 70% in these patients, which depends largely on the time elapsed between the onset of symptoms and research. In the evolution of the CP, intense steatorrhea leads to cachexia or susceptibility to infection that interferes with the prognosis; the data are not highly valued by the follow-up as are the endocrine function. There is also wide variety of diagnostic methods (fecal fat balance, levels of elastase and chymotrypsin faecal test pancreatolauril, among others) and the normal parameters, which makes comparisons of unequal outcomes.

The discussion proposed by the studies of Nealon et al.[21] regarding the benefit of surgical treatment for the preservation of endocrine function also fits the pancreatic exocrine function. Animal study conducted by Austin et al.[4] showed that the exocrine insufficiency caused by obstruction of the main pancreatic duct of cats for two months was irreversible even after the release of the obstruction.

Cholestasis and portal hypertension

The frequency and intensity of jaundice do not seem to be related to the evolutionary stage of the disease, but depend mainly on the anatomical relationship between the terminal bile duct and pancreatic head. The realization of the bileodigestive derivation associated with the treatment of the pancreas in cases of biliary obstruction is not resolved by the head decompression and is often not a causative factor of postoperative complications.

Another complication often associated with CP is the extra-hepatic portal hypertension, which is defined as hypertension of the portal venous system in the absence of liver cirrhosis. Bloechle et al.[6] studied the impact of the Beger and Frey operations on patients with hypertension and nonocclusive portal CP. The authors found that in patients who had portal hypertension and underwent the Beger had improved blood flow in the splenic and superior mesenteric veins, with a reduction of their sizes, and there was no restoration of normal flow in those subjected to the technique of Frey. Attributed the better outcome of Beger operation due to transection of the pancreas on the portal venous system, which releases the vein fibrosis. However, none of the patients with portal hypertension who suffered Frey and therefore did not restore venous flow appropriately, progressed to clinical outcomes such as gastric or esophageal varices during the follow-up. Thus, the authors conclude that, while not restoring the portal venous flow, the Frey operation should not be ruled out in patients with portal hypertension due to little evidence of clinical impact.

Recurrence of alcoholism and late mortality

An important factor in the evaluation of patients with CP - most of them drink alcohol -, is maintain abstinence in ethanol ingestion. The hope that the relief of abdominal pain, regained weight and improving the quality of life can lead to disappointment of the medical team. In the analysis of Gestic[13], 32.9% of patients returned to excessive alcohol intake, on average, 21.5 months after surgery, and drinking a daily average of 214 g of ethanol. Noteworthy is the fact that among those patients who resumed alcohol abuse, 60.9% did so within the first postoperative year.

Alcoholism exacerbates the continuing dysfunction of the pancreatic parenchyma. To Sakata et al.[24], is considered that the addiction, not surgery, is the main cause of pancreatic dysfunction. Gullo et al.[14] found that both endocrine and exocrine function deteriorated in patients who stopped drinking alcohol or not. However, the incidence of pain, diabetes and exocrine insufficiency were higher in those patients who continued the habit. In addition, the disease complications progress more rapidly in those who continued to drink alcohol.

Thuluvath et al.[30] showed 25% mortality rate, with a mean survival of 8.2 years from onset of symptoms in patients with CP. More alcoholic patients died (35%) than non-alcoholics (10%) and the leading cause of death is cancer. Patients operated for pain control had a mortality rate of 9% versus 34% of those not operated, as well as mortality was higher among those operated on for complications than those who operated for pain.

Frey and Amikura[11] showed a mortality of 5.8% in patients followed on average for 37 months. Deaths were attributed to extra-pancreatic cancer and complications of diabetes. Gestic reported mortality of 16.4% of patients on long-term follow-up. The main causes of death in this national study were neoplasia (non-pancreatic) and complications of liver cirrhosis and diabetes. Showed also to be statistically significant higher survival rate on those who remained abstinent compared to those that returned to alcohol abuse.

CONCLUSIONS

Surgical treatment of CP with anterior resection of the pancreatic head associated with pancreatojejunostomy, technique known as Frey´s, proved to be highly effective in controlling

abdominal pain secondary to this disease in long-term, combined with small interference on exocrine and endocrine function. The technique of Frey should be considered as primary treatment for patients with CP accompanied by abdominal pain and increase in volume of the pancreatic head, because it is safe and easier to perform with less morbidity and mortality than other techniques.

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