

Prospective randomised pilot study of management of the pancreatic stump following distal resection

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Background

Numerous surgical techniques have been described in the literature for pancreatic stump management following left resection, but there is only one prospective, randomised study. A prospective randomised pilot study was designed to assess five different pancreatic stump management techniques after distal resection in an attempt to identify which was the most effective in terms of complications and ease of execution.

Methods

Sixty-nine consecutive patients were randomly assigned to five different treatment groups: manual suturing, suturing plus fibrin glue, suturing plus polypropylene mesh, pancreaticojejunostomy and suturing with a stapler. All presented a soft residual pancreas.

Results

The overall incidence of pancreatic fistula was 19%, ranging from 7% to 33% in the different treatment groups. None of the techniques significantly reduced the incidence of postoperative complications.

Discussion

On weighing the complications observed against ease and speed of execution, the construction of a pancreaticojejunostomy and closure of the stump with a mechanical stapler may be regarded as the procedures to be tested in future.

Keywords

distal pancreatectomy, pancreatic fistula, pancreatic stump management.

Introduction

The formation of a pancreatic fistula is the most frequent complication following distal resection of the pancreas [1–6]. Although some surgeons [7] claim that the technique used to close the stump has no bearing on the risk of fistula formation, others [2,8–16] have proposed various techniques in an attempt to reduce the incidence of complications. These manoeuvres include the use of mechanical staplers [2,8–10], fibrin glue [11,12] and the injection of prolaminate into the pancreatic duct [13]. Others have used ultrasonic dissectors [14], seromuscular flaps [15] and gastric serosal patches [16]. The results achieved with these various procedures are hard to interpret owing to a lack of homogeneity regarding the underlying pathology, whether chronic pancreatitis or a 'soft' gland, and the definition of pancreatic fistula adopted. Moreover, to the best of our knowledge, no prospective randomised clinical trials have been conducted to date.

We present the results of a prospective randomised clinical pilot study on various techniques used for stump closure after distal resection of a soft pancreas.

Methods

Over the five-year period 1993–97, 69 patients (19 men, 50 women) were recruited to the study from a total of 80 patients undergoing left pancreatic resection. All suffered from pancreatic tumours of the body or tail with a 'soft' residual pancreas. There were 61 left splenopancreatectomies and 8 distal resections with preservation of the spleen. Table 1 gives the definitive diagnoses. Patients were not treated prophylactically with octreotide.

After giving informed consent, patients were randomly assigned to one of five treatment groups. The first group (15 patients) received simple ligation of the main duct with non-absorbable sutures and closure of the

Table 1. Definitive histological diagnosis

Diagnosis	No.
Cystic tumours	30
Neuroendocrine tumours	15
Ductal adenocarcinomas	13
Intraductal mucinous tumours	10
Other	1
Total	69

stump with full-thickness interrupted sutures. In the second group (11 patients) 5 ml fibrin glue (Tissucol) was applied to the stump after closure as in group 1. In the third group (15 patients) a polypropylene mesh (Marlex) was applied to the stump, again after closure as in group 1. The fourth group (14 patients) received an end-to-end pancreaticojejunostomy using a defunctioned (Roux) jejunal loop. Mechanical suturing with a stapler (T.I.A. Multifire TA 60-3.5 Auto Suture) was used in the fifth group (15 patients).

A tube drain was placed next to the cut surface of the pancreas or the anastomosis. Amylase was measured in the drainage fluid on days 5 and 7 and twice weekly over subsequent weeks in patients who developed a fistula. In the standard case the drain was withdrawn on days 3 and 5 and then removed on day 7. Postoperative ultrasonography (US) and/or computed tomography (CT) were performed in all patients before discharge.

The primary end-point of the study was the incidence of pancreatic fistula defined as the loss of at least 10 ml/day of drainage fluid with an amylase content of at least 1000 U/L beyond postoperative day 7. Correlations were also sought between fistula formation and laboratory test indices, body mass index (BMI), the characteristics of the tumour, surgical radicality, preservation of the spleen, operating time and length of hospital stay, as well as mortality and general morbidity rates.

A non-parametric analysis of variance (Kruskal–Wallis tests) was used to compare the variables among groups followed, if significant, by the Mann–Whitney *U* test corrected for multiple comparisons. The chi-squared test was performed for analysis of nominal data; in the two-way contingency tables Yates's continuity correction was applied, or Fisher's exact test in the case of small expected frequencies. The SPSS (rel. 7.5 SPSS Inc., Chicago, IL) statistical programme was used.

Table 2. Fistulas observed and operating times in the various treatment groups

Group	Number of patients	Fistulas		Operating times	
		n	(%)	min	(range)
I	15	5	(33)	252	(100–510)
II	11	3	(27)	234	(170–360)
III	15	2	(13)	221	(130–360)
IV	14	1	(7)	258	(180–480)
V	14	2	(14)	212	(125–360)
Total	69	13	(19)		

I, manual suture; II, manual suture + fibrin glue, III, manual suture + polypropylene mesh; IV, pancreaticojejunostomy; V, mechanical suture (stapler).

Results

There were no postoperative deaths. Thirteen patients (19%) developed an external pancreatic fistula during the postoperative period. In 5 patients, the fistula developed within the first week, and in the other eight it followed an initial week that was characterised by an uneventful course and consequent removal of the drain; these delayed fistulas presented as intra-abdominal collections on ultrasound scan. After replacing the drain via the existing fistula tract ($n=4$) or under radiological guidance ($n=2$), six patients were cured by these conservative means. Another two patients (3% of the total) required repeat laparotomy. In all, 11 fistulas responded to non-operative treatment. Table 2 shows the distribution of the fistulas observed in the various treatment groups together with the operating times. No statistically significant difference was found either between the incidence of fistulas and the type of stump management ($p=0.23$) or between the operating times for the various procedures ($p=0.61$).

All the fistulas observed were low-output, the mean daily output being 50 ml (range: 10–200 ml). However, in 10 of the 13 patients the fistula was associated with a serious clinical situation, as demonstrated by the lengthy period of postoperative hospitalisation (mean 31.3 days; range: 13–66 days) and/or by the need to reoperate and/or discharge the patient with the drain still *in situ*. The remaining 3 patients had a shorter mean postoperative hospital stay (21.5 days) than the others with the same complication as well as rapid fistula closure, even though they presented with intra-abdominal collections requiring percutaneous drainage. Regarding other problems, 11 patients developed respiratory complications after distal pancreatectomy, while another

6 had radiological evidence of small asymptomatic postoperative collections, which either reabsorbed spontaneously ($n=4$) or required percutaneous drainage ($n=2$). The drainage fluid was free of amylase. Five patients developed diabetes. Table 3 shows the difference in postoperative hospitalisation times in patients with and without complications.

Other variables considered in the analysis were BMI, serum albumin values, the definitive histological diagnosis, the size of the tumour mass, the presence (if any) of carcinoma at the cut surface, the transfusion requirement during or after operation and, lastly, the preservation or otherwise of the spleen. No statistically significant correlations were found, however, between any of these variables and fistula formation. Among the routine laboratory parameters considered, above normal values were detected for alkaline phosphatase ($p=0.015$ with a cut-off of 90 U/L) in the subgroup of patients with fistulas.

Discussion

It is reasonable to suppose that the occurrence of complications following distal resection of the pancreas depends on various factors, undoubtedly including surgical expertise and experience but also, especially, the consistency of the residual parenchyma. In this latter context, two groups of patients can be identified: a high-risk group with neoplastic disease or trauma and tissue of normal consistency; and a low-risk group with an indurated pancreas as a result of chronic inflammation. In chronic pancreatitis, any outflow obstruction to the main duct could increase the pressure and facilitate fistula formation, thus suggesting the construction of a pancreaticojejunostomy as the procedure of choice in such cases [17]. In this connection, it is interesting

to note that preoperative serum alkaline phosphatase was significantly higher in the patients with postoperative fistula. This finding, which warrants further assessment, could suggest some undetected and perhaps functional papillary disease that favoured the development of a postoperative fistula.

The lower risk of complications in patients suffering from chronic inflammatory disease is extensively confirmed in the literature [17–22], yet many studies of distal pancreatic resection make no distinction between high-risk and low-risk patients [1,11,23,24], which prevents meaningful comparisons. The present group of patients constituted a homogeneous sample in terms of the quality of their residual pancreatic tissue in that chronic pancreatitis was considered an exclusion criterion.

A further obstacle to any uniform analysis of patient outcomes in the literature is the lack of a clear-cut definition of pancreatic fistula (if indeed one is offered at all). A number of investigators include infections, abscesses or, more generically, 'sepsis' among the major complications and report only a minimal incidence of pancreatic fistulas [25,26]. For example Brennan and colleagues [25] report only one fistula in a series of 31 distal resections, but describe 6 patients with collections or abscesses. They do not report the amylase concentration in the drainage fluid from the latter, but it seems likely that at least some of these collections originated from a leakage of pancreatic juice from the stump. By the same token, Fabre and co-workers [26] report only 4 cases of postoperative pancreatic fistula in a multicentre study of 116 distal pancreatectomies (3.4%), yet there was a 27% reoperation rate: 12 of the reoperations were required for haemorrhage and 10 for intra-abdominal 'sepsis'.

If we were to use the same assessment criteria, the incidence of fistula in the series would drop from 19% (13 cases) to 7% (5 cases). Eight of the fistulas originated as collections and/or abscesses that required drainage (beyond postoperative day 7). In all 8 cases, the outcome after this procedure was a fistula with an output > 10 ml/day and an amylase content > 1000 U/L, thus fulfilling the inclusion criteria. By draining these collections, an 'internal' fistula was converted into an 'external' fistula [27].

The definition of fistula used in this study may appear as inclusive as it is pragmatic. In future, it may be necessary to supplement the definition by analysing other clinical criteria such as discharge of the patient with a drain *in situ*, readmission to hospital and length of stay.

Table 3. Postoperative course and discharge

Postoperative course	No. of patients	Postoperative discharge (days)	
		Median	Range
Uncomplicated	27	12.5	(9–15)
Pancreatic fistula	13	29.0	(13–66)
Pulmonary complication	11	13.5	(11–16)
Asymptomatic abdominal fluid collection	6	19.5	(10–27)
Diabetes	5	20.5	(16–29)
Other complication	7	21.0	(13–33)

Uncomplicated patients in our series have hospital stays ranging from 9 to 15 days postoperatively. Several patients who qualified as 'complicated' rapidly return to normal and could be discharged within the same time span as the 'uncomplicated' cases. By contrast, some patients with a subclinical leak later developed troublesome collections or abscesses which, when drained, gave rise to a pancreatic fistula. Hospitalisation times and a prolonged follow-up are therefore indispensable parameters for any realistic assessment of outcome.

As regards the various stump management techniques assessed in this study, there were no statistically significant differences between the five patient groups, although each group contained relatively small numbers of patients. Closure of the stump with interrupted or mattress sutures after elective ligation of the main pancreatic duct (33.5% complication rate) is rapid and simple but should not necessarily be regarded as a routine solution. This procedure may prove unsuccessful either due to ischaemia of the pancreatic remnant induced by the ligation, failure to recognise the main duct or because one of the minor ducts is missed in the suturing procedure. Tissucol has recently been used in pancreatic surgery [28]. It failed to reduce the incidence of fistulas and has in any case been withdrawn from use in Italy during the trial. The novel application of an adequate polypropylene mesh to the cut surface was designed to induce a fibrotic reaction capable of 'walling off' the pancreatic stump and blocking any leak, and the result was satisfactory (13% complication rate).

A pancreaticojejunal anastomosis guarantees drainage of all the pancreatic ducts. Apart from time, its main drawback is the risk of a possible enteric component to any fistula that may form. We achieved excellent results with this procedure (7% complication rate), and the operating time was about 20% longer than the shortest time achieved with the stapler (14% fistula incidence). The stapler offers a combination of safety and speed of execution by virtue of the possibility of 'sealing' the minor ducts as well as the main duct even when the latter can not be identified [2].

This was a pilot study and, to the best of our knowledge, the second prospective randomised investigation of the subject [29]. We are now conducting another trial using the management techniques – mechanical stapling and pancreaticojejunostomy – which may be considered the procedures that deserve further controlled evaluation.

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