Non-operative Risk Factors and the Implications of Sandostatin for Postoperative Pancreatic Fistula in Malignant Pancreatic Surgery

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Pancreatic fistula is the most frecquent and severe postoperative complication after pancreatic surgery, with impressive implications for the quality of life and vital prognosis of the patient and for these reasons it is essential to identify risk factors. In the current study, who included 109 patient admitted to a single university center and who underwent pancreatic resection for malignant pathology, we assessed the following factors as risk factors: age, sex, preoperative hemoglobin value, preoperative total protein value, obesity and postoperative administration of sandostatin. Of the analyzed factors, it appears that only obesity and long-term administration of sandostatin influences the occurrence of pancreatic fistula.

Keywords: risk factors, pancreatic resection, sandostatin, obesity

Since 1909 when the first pancreatic resection was successfully performed in humans, surgical techniques have been improved in order to reduce postoperative mortality and morbidity, which remain high (5% respectively 40%)[1,2]. With an incidence between 2% and 30%, pancreatic fistula is the most frequent and severe postoperative complication with impressive implications for the quality of life and vital prognosis of the patient[3- 6].

Reducing the occurrence of postoperative pancreatic fistula still remains a challenge for surgeons, so it is essential to identify risk and protection factors. Factors that seem to influence the incidence of pancreatic fistula are: obesity, age, diabetes history, intraoperative blood loss and operative time, preoperative serum albumin levels, preoperative blood tranfusion and the factors related to pancreas texture, such as soft pancreas, a small Wirsung duct size, types of stump closure and extended limphadenectomy [7-10]. The role of sandostatin in reducing the occurrence of postoperative pancreatic fistula remains uncertain. While some European studies have shown the protective role of Sandostatin, the routine administration of Sandostatin in the USA has been abandoned because there has been no decrease in the incidence of pancreatic fistulas[11-14].

Experimental part

Materials and methods

We retrospectively reviewed all patients admitted to a single university center between 1 January 2008 and 1 July 2017 and who underwent pancreatic resections. Of these patients, only those with malignant pathology were selected. For those 109 patients who met the criteria for inclusion in the study, medical records, postoperative follow-up, preoperative values of hemoglobin and total proteins, postoperative medication were analyzed.

Pancreatic fistula diagnosis was established in patients with amylase values greater than 300 in the peripancreatic drainage tube fluid. The classification of pancreatic fistula was made according to ISGPF (International Study Group of Pancreatic Fistula), in 3 degrees: A, B and C. Fistula classified as grade A is asymptomatic and treated conservatively, grade B fistula is symptomatic and requires antibiotic therapy with or without percutaneous drainage, and grade C fistula is the most serious, causing severe complications, shock, haemorrhages or intraabdominal infections and often involves surgical treatment[4,8, 15,].

The data obtained were processed using IBM SPSS Statistics for Windows, and the Mann-Whitney-U test, Anova, independent T-test were use to compare the means and the differences between two independent groups on the same continuous, dependent variable, and the chi-square test, odds ratio and Fisher exact test were used to determine the difference between two groups or if there is a relationship between two categorical variable. The obtained results were considered statistically significant at a $p < 0.05$.

Of the 109 patients, 61 were women and 48 men, aged between 35 and 79 years, with an average of 59 years. As seen in table 1, were performed 74 pancreaticoduodenectomy (DPC) , most of them for pancreatic neoplasm (38) and ampulomas (26), 13 distal pancreatectomy (SPC), 3 enucleetions and 19 pancreatic biopsies.

		operation				Total
		DPC	SPC	Enucleetion	Pancreatic biopsie	
diagnostic	Pancreatic neoplasm	38	8	0	17	63
	ampulomas	26	1	0	0	27
	Neuroendocrine tumors	3	4	3	2	12
	neoplasm coledoc	7	0	0	0	7
Total		74	13	3	19	109

Table 1

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Figure 1 shows the grouping of patients based on anatomopathological diagnosis.

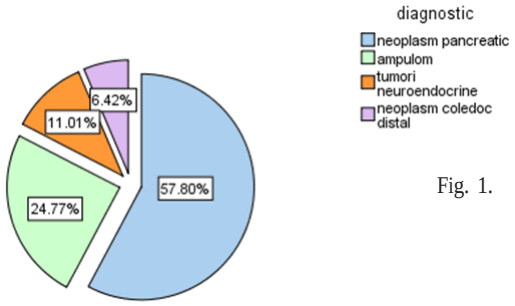

Fig. 1.

Results and discutions

Of total of 109 patients, 17 patients (15.59%) developed postoperative fistula, most of them after pancreaticoduodenectomy (table 2). An explanation of an incidence of only 15.59% of the pancreatic fistula may be due to the fact that our study group was performed only on patients with malignant pathology. There are studies concluding that malignant tumors are associated with a low risk of fistula [7, 8].

In the current study, we assessed the following factors as risk factors: age, sex, preoperative hemoglobin value, preoperative total protein value, obesity and postoperative administration of sandostatin.

For our group of patients, statistical data showed that age is not a risk factor (with an average age of 59.93 years for those without fistula and 53.29 for those with fistula, p = 0.173) Also in a meta-analysis performed on 10 large patient trials, only one study found an increase incidence of pancreatic fistula in older patients [7].

Neither the sex of the patients appears to be a risk factor (p=0.796), the gender distribution being uniform.

Nor for the preoperative value of hemoglobin and total proteins, statistically significant data were not found. Hemoglobin means for patients who developed postoperative pancreatic fistula (12.11 mg/dL) is close to that of patients without fistula (12.6 mg/dL) and p>0.05. The same can be observed with the preoperative value of total proteins. There are no signficant differences btween two groups (the total protein main for those with fistula is 67 mg/dL and for those without fistula is 69.55 mg/dL) with a p>0.05.

The obesity frequency in our patients group was 18.3% (20 patients from grade I to morbid obesity). There was a major difference between obese and non-obese patients group with regard to the occurrence of pancreatic fistulae. The incidence of pancreatic fistula in obese patients was 53.84%, as opposed to 12.65% in non-obese patients. p = 0.008 indicates a high correlation between the occurrence of fistulae and the presence of obesity.

Calculating a relative risk = 3.125 indicates that obese patients have a 3-fold higher risk of developing pancreatic fistulae. This conclusion is supported too, by the value of OR = 4.253 which confirms that obesity is a risk factor.

Major differences have also been observed between patients receiving or not receiving Sandostatin or analogues in the postoperative period. The incidence of pancreatic fistula was double (20.33%) in patients receiving Sandostatin (59 patients) versus 10% in those who did not receive Sandostatin (50 patients).

Also, the mean of the sandostatin ampoules administered to patients who made the fistula is almost double (18.88 ampoules) compared to patients who did not do the fistula (10.25 ampoules). P=0.021

		fistula		Total
		no	yes	
operation	pancreaticoduodenectomy	61	13	74
	Distal pancreatectomy	12	1	13
	Enucleetion	1	2	3
	Pancreatic biopsie	18	1	19
Total		92	17	109

Table 2

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	7.006[a]	1	.008		
Continuity Correction[b]	5.317	1	.021		
Likelihood Ratio	5.925	1	.015		
Fisher's Exact Test				.015	.015
Linear-by-Linear Association	6.941	1	.008		
N of Valid Cases	109				

Table 3

Group Statistics

	fistula	N	Mean	Std. Deviation	Std. Error Mean
fiolesando	N0	92	10.25	13.215	1.378
	yes	17	18.88	17.645	4.280

Table 4

Table 5

Independent Samples Test

	Levene's Test for Equality of Variances		t-test for Equality of Means						
	F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	95% Confidence Interval of the Difference	
								Lower	Upper
Equal variances assumed	2.416	.123	-2.341	107	.021	-8.632	3.687	-15.942	-1.323
Equal variances not assumed			1.920	19.451	.070	-8.632	4.496	-18.028	.763

The relative risk for patients receiving Sandostatin is RR = 2.03, which means that these patients have a twofold risk of developing pancreatic fistula. The same conclusion is also supported by OR = 2.29 which means that the administration of Sandostatin following pancreatic resection represents a risk factor for the occurrence of postoperative pancreatic fistulas.

Sandostatin is considered as a protective factor that decreases the incidence of pancreatic fistula by its role in decreasing the secretion of pancreatic enzymes [15-17, 18]. Considering this effect of sandostatin and the desire to resolve a serious problem - the pancreatic fistula - many surgeons decided the routine administration of sandostatin after pancreatic resections [17].

In some multicentric studies performed on patients with benign pathology (most patients included being diagnosed with chronic pancreatitis), a significant decrease in postoperative complications was observed in patients receiving octreotide [19].

In another prospective study there was found a low pancreatic secretion in patients with pancreatic adenocarcinoma, and it appears that these patients have a low risk for postoperative complications, unlike other patients with another histological diagnosis [8, 19].

Recent studies have shown that the prophylactic administration of sandostatin and its analogs has a positive effect on the reduction of morbidity and postoperative complications but does not reduce the incidence of pancreatic fistulae [16, 20, 25] In contrast, other studies have shown that administration of sandostatin does not bring improvements in terms of hospitalization days, surgical reinterventions, and mortality rates [16, 21]. It seems that the results are different when using long-term half-life sandostatin analogues such as Pasireotide, whose use leads to a decrease in the incidence of fistulas [11,16].

There are still contradictions between the findings of studies in Europe and those made in the USA. While a decrease in the incidence of pancreatic fistula was observed in Europe in patients receiving postoperative sandostatin, in the United States, lower incidence of fistulas (6-9%) was observed in patients who did not receive sandostatin (placebo group) [17].

From our experience, it appears that administration of sandostatin in patients with malignant pathology does not have a beneficial effect. On the contrary, a doubling of the incidence of pancreatic fistulas was observed in our patients. Perhaps in their production also contributed the decrease of the perfusion pressure of the abdominal viscera (effect produced by sandostatin), but to prove this it is necessary to investigate on experimental models the effects of sandostatin on microvascularization at the level of the production of fistulas.

A study from 2016 who included 202 patients undergoing pancreaticoduodenectomy for cancer, observed that among patiens who had major complications, survivors had a lower visceral fat area and concluded that visceral obesity is an independent predictor of pancreatic fistula [22-24] The same conclusion is sustained by another study made on 539 succesive patients undergoing pancreati-coduodenectomy [4]. The association between obesity and the development of pancreatic fistula can be explained by the fact that peripancreatic fat tissue and visceral obesity make it difficult to expose the pancreas and increase the risk of damage the pancreatic capsule during dissection [4].

Conclusions

Even meta-analyzes performed on studies with large trials of patients have not been able to draw firm conclusions about the role of sandostatin in the occurrence of pancreatic fistulae. However, it seems that obesity and long-term administration of sandostatin are risk factors for the development of pancreatic fistulae.

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