Resource Management In Fistulae Treatment

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Abstract

Background: Gastrointestinal and pancreatic fistulae are characterized as serious complications following abdominal surgery. Fistula formation results to prolonged hospitalization, increased morbidity and mortality and higher treatment costs. Conservative and surgical approaches are both accepted in their management. The purpose of this study was to assess, evaluate and compare the potential clinical benefit of pharmacotherapy and its cost-effectiveness. Both methods involve the use of somatostatin (SMS) and its analogue, octreotide.

Patients and methods:Fifty-one patients with gastrointestinal or pancreatic fistulae were randomized, 19 receiving 6000 iu/day of somatostatin intravenously, 17 receiving 100 μG three times daily (tid) of octreotide subcutaneously and 15 receiving only standard medical treatment.

Results: The fistula closure rate was 84% for the SMS group, 65% for the octreotide, and only 27% for the control group. Differences between pharmacotherapy and the standard group were of statistical significance (p = 0.007). Overall, the mortality rate was less than 5% and statistically significant differences between the three subgroups could not be established. In regards to cost-effectiveness, this was overall in favor of the SMS and octreotide groups versus the control, and better for SMS than the octreotide group. The average hospital stay was 21.6, 27.0 and 31.5 days for the SMS, the octreotide and the control group, respectively.

Conclusions: These data suggest that pharmacotherapy reduces the costs involved in fistulae management (by reducing hospitalization) and also offers an increased, spontaneous closure rate. Further prospective studies focusing on the above parameters are needed in order to demonstrate the clinico-economic benefits.

INTRODUCTION

External fistula formation is a serious complication of gastrointestinal and pancreatic surgery since mortality ranges between 5 and 30% in the case of enterocutaneous and between 5 and 10% in the case of pancreatic fistulae[1,2,3]. Spontaneous fistula closure occurs in most cases when essential treatment principles are followed, such as elimination of sepsis, adequate drainage, proper nutritional support, correction of fluid and electrolyte disturbances, and skin care. However, significant morbidity and mortality rates, increased length of hospitalisation, the cost and the psychological consequences to the patient render the conservative medical treatment insufficient[1,4].

Somatostatin (SMS) and its synthetic analogue, octreotide (SMS 201-995, sandostatin), are known vasoactive drugs that reduce gastrointestinal, biliary and pancreatic secretions[5,6,7]. These properties render them good candidates for the treatment of gastrointestinal and pancreatic fistulae. Their effectiveness has been examined in several clinical trials[7,8,9,10,11,12,13,14]. The results, though, have been rather inconclusive. This study was conducted in order to evaluate the potential benefit from the administration of these two agents to patients with gastrointestinal and pancreatic fistulae, as well as to compare them to conservative treatment with total parenteral nutrition (TPN) alone.

PATIENTS AND METHODS

In this prospective, randomised controlled study, 51 consecutive patients with gastrointestinal (38 patients, 74.5%) or pancreatic fistulae (13 patients, 25.5%) were included. All patients were treated in the surgical clinic at hippocration hospital, athens medical school, greece, between december 1995 and april 1999. They received

standard medical treatment (TPN, skin care, infection control) plus SMS (16 patients), or octreotide (17 patients), or standard medical treatment only (control group, 15 patients). SMS was given by continuous intravenous infusion at a dose of 6000 IU/day, while octreotide was given at a dose of 100 μg three times a day (tid), subcutaneously. The local ethics committee approved the design of this study.

Demographic and clinical characteristics were recorded for all our patients (table 1). The diagnosis of fistula origin was done, when necessary by ct-scan or fistulography (Table 1). The classification of the fistulae was done according to the type, pancreatic or enteric. Enterocutaneous fistulae were further subdivided by origin (Table 1). Fistulae were also classified as high or low output on presentation (Table 1). Enterocutaneous fistulae were classified as high-output fistulae when the daily output on presentation exceeded 500 ml, while pancreaticocutaneous fistulae were considered as high-output fistulae when the daily output exceeded 200 ml[12,15].

The parameters recorded in order to evaluate the results from the administration of these two agents were: length of hospital stay, days until restoration of regular per os nutrition, complications, fistula outcome on discharge (spontaneous closure or surgical/other treatment), days until fistula closure and outcome on discharge. Length of hospital stay, time until restoration of per os nutrition and time to fistula closure, were recorded from the day of fistula onset for patients with a fistula of recent onset (41 patients, 80.4%) and from the day of admission for patients with a fistula of non-recent onset, respectively (more than 8 days prior to admission, 10 patients, 19.6%). The total cost for treatment was calculated based on data provided by the administrative department of our hospital. The figures provided included the total cost of the admission to the health insurance agency.

The statistical tests used were the chi-square test for categorical data and the Kruskal Wallis test for numerical data, while a p of less than 0.05 was considered to indicate statistical significance. All tests were double-sided.

RESULTS

The three patients' groups that were recruited in this study did not actually have the same demographic characteristics. Age varied significantly among the three groups (Kruskal Wallis test, p = 0.049, Table 1), the patients in the standard medical treatment group being older (median age 72 years), followed by the patients in the octreotide group (median age 70 years) and in the SMS group (median age 61.5 years). Due to the relatively small number of patients in each subgroup and the p--value of 0.049 being close to the border of 0.05 this statistically significant result was not considered to reflect non-homogeneity between our groups. Accordingly, the subgroups were well matched for gender (chi-square = 0.671, p = 0.715, Table 1).

The clinical characteristics of the three subgroups in our study were similar. Enterocutaneous fistulae outnumbered pancreatic ones in all groups and no differences could be established between the three groups (chi-square = 2.8, p = 0.253, Table 1). The low- to high- output ratio was approximately 1:1 in all groups, and again no statistically significant differences could be established (chi-square = 1.245, p = 0.537, Table 1).

Figure 1

Table 1: Demographic and clinical characteristics of 51 patients with enterocutaneous or pancreaticocutaneous fistulae, treated with somatostatin, octreotide or standard medical treatment only

	Somatostatin	Octreotide	Standard medical treatment	Total
Patients	19 (37.3%)	17 (33.3%)	15 (29.3%)	51(100%)
	Kruskal Wallis test = 6.0, DF = 2, *p* = 0.049			
Age				
Median (SD)	61.5 (16.9)	70.0 (11.1)	72.0 (13.0)	67.0 (14.7)
Gender	Chi-square = 0.671, *p* = 0.715			
Male	12 (38.7%)	9 (29.0%)	10 (32.3%)	31 (60.8%)
Female	7 (35.0%)	8 (40.0%)	5 (25.0%)	20 (39.6%)
Diagnostic methods				
CT-scan	3 (50.0%)	2 (33.3%)	1 (16.7%)	6 (12.5%)
Fistulography	11 (30.6%)	13 (34.5%)	12 (36.1%)	36 (75.0%)
Other	5 (55.5%)	2 (22.2%)	2 (22.2%)	9 (17.6%)
Fistula type	Chi-square = 2.752, DF = 2, *p* = 0.253			
Enteric	12 (31.6%)	12 (31.6%)	14 (36.8%)	38 (74.5%)
Pancreatic	7 (53.8%)	5 (38.4%)	1 (7.7%)	13 (25.5%)
Fistula origin				
Stomach	1 (25.0%)	2 (50.0%)	1 (25.0%)	4 (8.3%)
Small intestine	6 (31.6%)	7 (36.8%)	7 (36.8%)	19 (39.6%)
Large intestine	5 (38.5%)	2 (15.4%)	6 (46.2%)	13 (27.1%)
Bile duct	3 (37.5%)	4 (50%)	1 (12.5%)	8 (16.7%)
Other	1 (33.3%)	2 (66.7%)	--	3 (6.3%)
Output category	Chi-square = 1.245, DF = 2, *p* = 0.537			
Low	9 (33.3%)	8 (29.6%)	10 (37.0%)	27 (56.3%)
High	10 (41.7%)	9 (37.5%)	5 (20.8%)	24 (47.1%)

Median length of hospital stay was 20 days (Table 2) and was 15, 24 and 28 for the somatostatin, the octreotide and the standard medical treatment group, respectively. The difference was of statistical significance (Kruskal Wallis test = 7.42, p = 0.024, Table 2.

Figure 2

Table 2: The comparative evaluation of somatostatin, octreotide and standard medical treatment groups, through several characteristics

	Somatostatin	Octreotide	Standard medical treatment	Total
Patients	19 (37.3%)	17 (33.3%)	15 (29.3%)	51 (100%)
Days to oral nutrition, Kruskal Wallis test = 1.608, DF = 2, p = 0.448				
	19 patients	17 patients	14 patients	
Median (SD)	13.0 (5.7)	13.0 (12.1)	17.0 (11.5)	13(10.2)
Outcome on discharge, Chi-square = 4.591, DF = 2, p = 0.101				
Dead	0	0	2 (100%)	2 (3.9%)
Alive	19 (38.8%)	17 (34.7%)	13 (26.5%)	49 (96.1%)
Complications, Chi-square = 2.116, DF = 2, p = 0.347				
Yes	8 (32.0%)	7 (28.0%)	10 (40.0%)	25 (49.0%)
No	11 (42.3%)	10 (38.5%)	5 (19.2%)	26 (51.0%)
Outcome, Chi-square = 11.6, DF = 2, p = 0.003				
Closure	16 (51.6%)	11 (35.5%)	4 (12.9%)	31 (60.1%)
Other therapy	3 (15.0%)	6 (30.0%)	11 (55.0%)	20 (39.9%)
Days to closure, Kruskal Wallis test = 3.933, DF = 2, p = 0.140				
Median (SD)	10.5 (7.5)	16.5 (16.6)	18.0 (5.3)	16.0 (11.8)
Days in hospital, Kruskal Wallis test = 7.419, DF = 2, p = 0.024				
Median (SD)	15 (12.0)	24 (13.7)	28 (20.4)	20.0 (16.2)

A difference between the two therapy arms was not established (Mann Whitney u-test, z = -1.745, exact p = 0.08). The time interval until restoration of per os nutrition also did not vary significantly between the three subgroups (overall median 13.0 days, Kruskal Wallis test = 1.6, p = 0.448, Table 2). Similar results were obtained when the outcome on hospital discharge was evaluated. Overall death rate was 3.9% (2 out of 51 patients) with both deaths having occurred in the standard medical treatment group. However, this difference was not statistically significant.

Overall complication rate in our series was 49.0% (25 out of 51 patients), while in the standard medical treatment group it was 66.7% (10 out of 15 patients). In the somatostatin and octreotide group, the complication rate was 42.1% (8 out of 19 patients) and 41.2% (7 out of 17 patients), respectively. Even though variation in the complication rate between the three groups was seen, these differences were not statistically significant (chi-square test = 2.116, p = 0.347). Overall closure rate was 60.1% (31 out of 51 patients). In the standard medical treatment group it was 26.7% (4 out of 15 patients), while in the SMS and octreotide group it was 84.2% (16 out of 19 patients) and 64.7% (11 out of 17 patients), respectively, with these differences being statistically significant (Kruskal Wallis test, p = 0.003). Conversely, the difference in closure rate between the SMS and the octreotide group was not statistically significant (fisher's exact test, p = 0.255). The median time for fistula closure was 16 days (Table 1i), while in the standard medical treatment group it was 18 days, in the SMS group 10.5 days and 16.5 days in the octreotide group, respectively. These differences did not reach statistical significance (Kruskal Wallis test, p = 0.140).

The median cost of hospital stay was €6944. A small variation was observed between the three subgroups and median cost was €6636, €7111 and €7812 for the somatostatin, the octreotide and the standard medical treatment group, respectively. These differences were not statistically significant (Kruskal Wallis test, p = 0.459).

DISCUSSION

Gastrointestinal and pancreatic fistula formation is a major complication of abdominal surgery associated with significant morbidity and mortality. The use of total parenteral nutrition was a major advancement in the field, since it improved spontaneous fistula closure rates from 10-20% to 60-70% and reduce mortality from 16-62% to 10-20%[2,16]. Nevertheless, the prolonged hospital stay along with the improved, but still significant mortality of fistulae, renders them a challenge in modern therapeutics. The reduction of gastrointestinal and pancreatic secretions has been a major goal in the pursuit of the optimal treatment and SMS, as well as octreotide, have been used on this basis with variable results. In several centres, the administration of octreotide or somatostatin has been proposed as the treatment of choice for gastrointestinal and pancreatic fistulae, since they have been reported to reduce time of closure, despite the non-significant influence on mortality and complication rates[9,12]. In the present clinical trial, 51 patients with gastrointestinal and pancreatic fistula were recruited in order to evaluate and compare the potential clinical benefit from the administration of SMS and octreotide.

The overall death rate of less than 4% (2 out of 51 patients), the fistula closure rate of approximately 60% (31 out of 51 patients) and the median time to fistula closure of 16 days observed in our study are within international standards[17]. Even though we were unable to detect statistically significant differences in terms of mortality and complication rate, the differences in closure rate were statistically significant (p = 0.003). In fact, spontaneous fistula closure rate was 27% in the group receiving standard medical therapy only, much less than the SMS and the octreotide groups (84% and 65%, respectively). This difference in closure rate has not been reported in certain

comparative studies[9,12,18]. This could be attributed to the standard medical group's relatively low closure rate in our study (27%). Nevertheless, the aforementioned studies reported that SMS led to strongest inhibition of fistulae output and to significantly lower healing periods. On the other hand, in accordance with our results, one prospective study comparing standard medical treatment with SMS for postoperative enterocutaneous fistulae, demonstrated the significant superiority of SMS in rates and time to closure [11]. In addition, a multicenter, prospective, double-blinded, placebo-controlled trial with octreotide showed statistical significance in the difference of spontaneous closure rates of 57% and 35% in the octreotide and in the standard medical treatment group, respectively[8]. The latter, though, could not be confirmed by another european study[19].

The differences in complication rate between the control group and the two groups receiving SMS and octreotide were noticeable, despite not being statistically significant. While in the control group the complication rate was 67%, in the somatostatin and the octreotide group it was 42% and 41%, respectively. These results, along with the fact that no adverse effects were observed for either drug, are consistent with the idea that there is a clinical benefit from the administration of these two agents. However, the number of patients included in this study is not sufficient to enable satisfactory statistical power and thus this clinical benefit could not be shown in terms of mortality and complication rate.

An important parameter in the treatment of fistulae is the cost--effectiveness of the therapeutic modality [20,21]. For SMS and octreotide, the issue of their significant cost has always been a major drawback for their clinical use. We could not find differences in the cost of therapy based on economic data provided by the administrative authority of our hospital. It appears that therapy with either somatostatin or octreotide at a similar cost to standard medical treatment achieve higher closure rates at a shorter length of hospital stay.

International literature lacks data on direct comparison between SMS and octreotide as far as it concerns fistulae management. In the current study the comparison between SMS and octreotide yielded insignificant results for all the recorded parameters, which could also be attributed to the fact that only a small cohort was included. SMS achieved a better spontaneous closure rate (84% vs 65%) than octreotide and provided equivalent results in terms of complication rate (42% vs 41%). Let us point out that SMS is a useful and effective therapy for severe acute pancreatitis and in preventing complications following ercp, whereas octreotide has no beneficial effect and may be deleterious in both these indications [17]. Altough SMS and octreotide are both effective in promoting the closure of pancreatic fistulae, the time to closure after commencement of therapy is much more variable and longer in patients treated with subcutaneous octreotide than those receiving intravenous SMS, possibly as a result of fluctuations in pancreatic enzyme secretion between consecutive administration of the hormone [17]. It has also been shown that subcutaneous administration of octreotide produces a sustained decrease in the volume of pancreatic juice secreted, but enzyme secretion rises progressively between consecutive administration of the analogue, which may delay the healing of fistula tract [20].

CONCLUSION

In conclusion, 51 patients with gastrointestinal and pancreatic fistulae were enrolled and received SMS, octreotide or nothing in combination with standard medical treatment. The spontaneous fistula closure rate was significantly higher in the subgroup of patients receiving either SMS or octreotide compared to the controls at a similar cost. SMS might also have a superior effect over octreotide and could be regarded as the pharmaceutical agent of choice in the conservative management of gastrointestinal fistulae.

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