Role of Octreotide and Somatostatin in the Treatment of Intestinal Fistulae

G. Dorta
Division of Gastroenterology CHUV/PMU, University Hospital, Lausanne, Switzerland

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Introduction
Intestinal fistulae are rare but serious diseases. They usually arise as a complication of abdominal surgery, abdominal trauma, Crohn’s disease, intra-abdominal abscesses, radiation therapy, chemotherapy and neoplasia. Most intestinal fistulae are due to abdominal surgery. Some 75–85% of small bowel fistulae are complications of abdominal surgery [1–3]. The complications strongly correlate with the anatomical site of the fistula, the volume and the composition of the fistula output, as well as the underlying pathology. Conservative treatment consists of correcting water and electrolyte imbalances and repleting ongoing losses, protecting the skin around the fistula, treatment and prevention of infection, and the restoration and maintenance of the nutritional status with intravenous hyperalimentation.

Under conservative medical treatment, the spontaneous closure rate of intestinal fistulae varies between 24 and 72% within 27–39 days, and the mortality lies between 5 and 29%, predominantly secondary to infections [1, 4–6]. Despite progress in medical management, the mortality rate has not changed during the past 30 years [6] and the time to closure under conservative medical treatment is long and often associated with all the inconveniences and complications of prolonged hospitalization. Therefore, new treatment modalities for intestinal fistulae are warranted. New hope was offered by treating intestinal fistulae with the agents octreotide and somatostatin. These two substances reduce gastrointestinal, biliary and pancreatic secretions, decrease gut motility, and increase water and electrolyte absorption in the small intestine [7–10]. The fistula output can thus be reduced...
by both agents, and one could speculate that the two agents might have a beneficial effect on fistula closure. The effects on gastrointestinal secretion and absorption evoked by octreotide and somatostatin do not clinically differ, but octreotide has a 30- to 100-fold longer elimination half-life time than somatostatin [11]. This fact simplifies the treatment modalities.

Intestinal fistulae of Crohn’s disease had occasionally been treated with octreotide. Within the perspective of the excellent results afforded by antitumor necrosis factor-\( \alpha \) treatment, octreotide treatment may no longer have a place in the treatment of fistulae associated with Crohn’s disease [12, 13].

**Literature Review: Octreotide and Somatostatin in the Treatment of Intestinal Fistulae**

The first clinical trial of octreotide in fistulae of the small intestine was published in 1987 [10]. In a blind crossover trial which lasted 4 days, the authors demonstrated that the fistula output could be dramatically reduced by the administration of octreotide. Within the past 11 years, a large number of papers covering the treatment of intestinal fistulae with octreotide or somatostatin have been published. Unfortunately, there were only a few prospective, controlled studies. Furthermore, there was no publication that compared the efficacy of somatostatin versus octreotide in the treatment of intestinal fistulae in a randomized study.

The multiple case reports concerning octreotide in the treatment of intestinal fistulae are not reviewed because they provide only stage IV evidence regarding the efficacy of octreotide treatment in intestinal fistulae.

Furthermore, several patient series and multiple case reports concerning octreotide in the treatment of intestinal fistulae have been published in the last years. The most important series shows fistula closure rates ranging from 43 to 75% within 6–37 days. These results are not different from the healing rates observed under conservative medical treatment. The patient number varies between 14 and 40 patients. In all these studies, octreotide had been administered in a dosage of 300 \( \mu \)g daily, until fistula closure [14–17].

Complications of octreotide treatment reported in these series were not frequent and mostly of a minor nature: pain at the injection sites occurred in 15–30% of the patients [14, 17]. One patient, who had previously received somatostatin treatment, developed a mild hypersensitivity reaction that could be controlled with oral antihistamines [17].

In a retrospective study, the treatment with octreotide significantly increased the fistula closure rate and decreased the mortality rate when compared to the control subjects. Unfortunately, in this study, as well, the data analysis did not separately treat patients with intestinal and pancreatic fistulae [18]. Another retrospective study compared four different treatment modalities: wound care only, conservative treatment including total parenteral nutrition, conservative treatment including total parenteral nutrition in association with an octreotide dosage ranging from 150 \( \mu \)g to 1,500 \( \mu \)g, and surgical treatment. The number of patients in each treatment group was very small and did not permit any statistical analysis. However, patients treated with octreotide or surgery had a better fistula closure rate when compared to the other two treatment modalities [19].

Within the past 6 years, there have been four placebo-controlled trials published that followed a conservative medical treatment using either octreotide or somatostatin (table 1). In a randomized, placebo-controlled trial using somatostatin (250 \( \mu \)g/h during 20 days), Torres et al. [20] treated 33 patients with intestinal fistulae and 7 patients with pancreatic fistulae. The interpretation of this study

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**Table 1. Effectiveness of octreotide/somatostatin in placebo-controlled trials**

<table>
<thead>
<tr>
<th>Group (first author)</th>
<th>Year</th>
<th>Patients with intestinal/other fistulae, n</th>
<th>Active drug</th>
<th>Effectiveness on:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Torres [20]</td>
<td>1992</td>
<td>33/7</td>
<td>Somatostatin</td>
<td>NS</td>
</tr>
<tr>
<td>Hernandez-Aranda [21]</td>
<td>1996</td>
<td>56/43</td>
<td>Octreotide</td>
<td>NS</td>
</tr>
<tr>
<td>Scott [22]</td>
<td>1993</td>
<td>19</td>
<td>Octreotide</td>
<td>NS</td>
</tr>
<tr>
<td>Sancho [23]</td>
<td>1995</td>
<td>26/5</td>
<td>Octreotide</td>
<td>NS</td>
</tr>
</tbody>
</table>

- = Not evaluated; NS = no statistical difference between placebo and active drug; Pos = positive effect of active drug.
is difficult because the cases of intestinal fistulae and pancreatic fistulae were not analyzed separately. Closure rate, healing time and mortality were similar in the placebo and in the somatostatin group. However, more complications occurred in the group treated with placebo than in the somatostatin group (68 vs. 35%, p < 0.05). Two patients undergoing somatostatin treatment developed hyperglycemia, which was controlled with insulin.

In the study by Hernandez-Aranda et al. [21], octreotide was given in a dosage of 100 μg t.i.d. in patients with enterocutaneous fistulae. Fifty-six of the 99 patients had small bowel fistulae, but unfortunately, these cases had not been evaluated separately. Overall, fistula closure rate, hospital stay and mortality rates were similar in the placebo and octreotide groups. Healing time in case of spontaneous closure of the fistula (18 vs. 27 days, p = 0.002) and the time patients required total parenteral nutrition (22 vs. 29 days, p = 0.04) were shorter in the octreotide group than in the placebo group.

Two other placebo-controlled trials including 19 and 26 patients with intestinal fistulas, respectively, showed no significant differences with respect to closure rate, healing time, complications and mortality [22, 23]. In these studies, octreotide 100 μg t.i.d. was administered during 12 and 20 days, respectively. In the trial by Sancho et al. [23], 4 of the 14 patients in the octreotide group had local pain at the injection sites, but no major adverse effects were reported.

**Discussion and Conclusions**

The evaluation of the efficacy of octreotide or somatostatin in the treatment of intestinal fistulae is difficult. There are many published patient series and case reports but only a few published controlled studies comparing octreotide or somatostatin versus placebo in the treatment of intestinal fistulae. Furthermore, these controlled studies have had very heterogeneous and small patient collectives, and often included patients with pancreatic fistulae. Unfortunately, analysis of the outcomes has not been carried out separately for the patients with intestinal fistulae. In all these studies, the fistula closure rate, mortality rate and hospitalization time were not decreased by octreotide or somatostatin treatment when compared to placebo. However, two controlled studies reported beneficial effects of octreotide and somatostatin. The study by Torres et al. [20] showed a lower complication rate in the group treated with somatostatin when compared with placebo, and the study by Hernandez-Aranda et al. [21] showed a faster healing time and patients in the octreotide group needed total parenteral nutrition for a shorter time than did those with placebo. Further prospective, controlled studies of octreotide treatment in patients with intestinal fistulae are needed to confirm the positive results obtained in the two cited studies. Ideally, these studies would include only patients having intestinal fistulae as well as a larger number of patients than those included in the published studies.

The multiple case reports, patients series and the two retrospective studies [18, 19] give only ‘stage III and IV’ evidence of the effectiveness of octreotide and somatostatin. In all the reviewed publications, side effects of octreotide and somatostatin were not frequent and always of a minor nature.

In conclusion, based on the published controlled trials and its endpoints, octreotide and somatostatin actually cannot be recommended for the treatment of intestinal fistulae and further prospective studies might confirm the positive preliminary results obtained in two controlled studies. However, there is ‘stage III and IV’ evidence regarding the effectiveness of octreotide and somatostatin. Patients with intestinal fistulae can be treated with octreotide or somatostatin, but treatment should be stopped if the fistula output does not decrease in the first 48 h of the treatment. The treatment of patients with high output fistulae may be simplified by octreotide or somatostatin treatment reducing depletion of fluid, electrolytes and protein.

**References**


