Alimentary tract and pancreas

Randomised double blind trial of somatostatin in the treatment of massive upper gastrointestinal haemorrhage

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SUMMARY In order to evaluate the effect of somatostatin in the treatment of massive upper gastrointestinal bleeding a randomised double blind trial of 95 patients has been undertaken during a 28 months period. Patients with oesophageal varices have been excluded as well as patients with diabetes. All patients were endoscoped within eight hours of admission to the hospital, whereupon the source of bleeding and types of stigmata were assessed. Forty six patients, chosen at random, were given a 72 hour infusion of somatostatin, while the remaining 49 patients received infusion of placebo. The two groups were well matched for sex, age, and source of bleeding. On the day after admission, an additional endoscopy was performed at which eight patients in the somatostatin group and 16 in the placebo group were found to have a persistent bleeding. A total of five patients in the somatostatin group and 14 in the placebo group underwent surgery (Fisher’s exact test, 2-tail, p=0.04). Rebleeding occurred in six patients in the somatostatin group, of whom five experienced rebleeding after completion of the somatostatin treatment. In the placebo group, rebleeding occurred in five patients, of whom four rebled on the day after admission. The need for blood transfusions and the mortality rate did not differ significantly between the two groups. No toxic side effects were found as a result of the infusion of somatostatin. In this study, somatostatin reduced the number of patients needing surgery with massive upper gastrointestinal bleeding.

The mortality rate in massive upper gastrointestinal haemorrhage is still high especially in elderly patients. Neither the use of medication (cimetidine, tranexamic acid) nor endoscopic treatment (Nd-YAG or Argon laser, electrocoagulation) has proved sufficiently beneficial to be used routinely.

Somatostatin has been shown to be a potent inhibitor of gastric secretion of acid, pepsin, and intrinsic factor. The peptide inhibits both basal and hormone induced secretion when administered by intravenous route, and the basal gastric secretion when administered intragastrically. It also has a stimulative effect on gastric mucus production. Splanchnic blood flow decreases after intravenous infusion of somatostatin. In addition, somatostatin depresses pancreatic endocrine and exocrine function in man. Positive results from small scale trials where somatostatin has been used in the treatment of upper gastrointestinal bleedings have been reported.

Endoscopic assessment of bleeding stigmata has been shown to be of prognostic value in patients with upper gastrointestinal bleeding. The aim of the present randomised double blind study was to evaluate the effect of somatostatin in the treatment of massive upper gastrointestinal bleeding. The registration of endoscopic stigmata have been used to identify severe bleeders.

Methods

PATIENTS A total of 99 patients participated in the study, of whom four were excluded during the infusion period.
because the experimental protocol had not been followed. Thus a total of 95 patients admitted to the Department of Surgery, Södersjukhuset, Stockholm, between February 1981 and May 1983, with clinical signs of shock or preshock due to a bleeding lesion in the upper gastrointestinal tract were included in a randomised double blind trial. By definition, hypovolemic shock or preshock existed when at least two of the following criteria were fulfilled; systolic blood pressure \(\leq 100\) mmHg, pulse rate \(\geq 100\), a cold pale clammy skin, a history of fainting. All patients had been under observation in the intensive care unit for at least 12 hours. Patients with diabetes mellitus or bleeding oesophageal varices were not included in the study. Endoscopy was performed within eight hours of admission. The following day a control endoscopy was carried out to verify the preliminary diagnosis and to establish if there was current bleeding.

After the initial endoscopy the patients were selected at random for treatment with either somatostatin or placebo. The patients were numbered consecutively and each number corresponded to a box containing a set of coded vials for infusion. The somatostatin and placebo vials were blindly packed and were impossible to distinguish from each other.

Forty six patients were given an infusion of cyclic somatostatin-14 (Kabi, Stockholm, Sweden) at a dosage of 250 \(\mu g/h\), after a bolus injection of 250 \(\mu g\), and 49 patients were given placebo which was administered in the same manner as somatostatin. The infusions were given at a constant rate for a duration of 72 hours and no additional treatments except blood transfusions were administered. The patients were given parenteral nutrition during the infusion period. Patients with rebleeding, as indicated by shock symptoms – that is, blood pressure drop, increase in pulse rate or vomiting of fresh blood after the 72 hour infusion period were given an infusion of somatostatin for an additional 72 hour period.

The indications for surgical treatment were: (a) when the magnitude of bleeding necessitated more than 6 units of blood to keep stable circulation, or (b) when cases of rebleeding necessitated transfusion of more than 4 units of blood.

The two groups of patients were well matched regarding age, sex distribution, present drug treatment, smoking, and alcohol habits (Table 1). At the onset of the study, routine laboratory tests including B-Hb, P-simplastin-A, B-thrombocytes, S-ASAT, S-ALAT, B-glucose and P-gastrin as well as blood pressure and pulse rate were equivalent in the two groups. P-insulin was higher in the placebo than in the somatostatin group (Table 2). Gastrin and insulin were determined by radioimmunoassay. Blood-Hb and B-glucose were measured upon admission and then at least once every day for the five following days. The other laboratory tests were measured upon admission and on day 1, day 3 and day 5 after the admission. These days were chosen for laboratory tests as the infusion started after admission and a second endoscopy was performed on day 1 and the infusion stopped on day 3.

The trial was approved by the local ethical committee. The planning of the trial included an evaluation of the preliminary results after one year,\(^23\) and the final results after a total trial period of 28 months.

Statistical analyses were carried out using Fisher’s exact test (2-tail), \(\chi^2\), Student’s \(t\) test and Wilcoxon’s test.

### Results

The bleeding lesions found in the two groups are listed in Table 3. Peptic ulcer was the most common source of bleeding. Other diagnoses were gastric cancer, Mallory-Weiss, bleeding at the site of biopsy and exulceratio simplex. Four patients in each group had bleeding from erosions in the oesophagus, stomach, or duodenum. No source of bleeding could be found for two patients in each group. Only four patients had inconsistent diagnoses after the second endoscopic examination as compared with the initial evaluation.

In six patients diagnosis of the source of bleeding was not feasible at the time of the first endoscopy in most cases due to an overlying blood clot, but was identified when the second endoscopy was carried out.

Thirty eight patients in the somatostatin group and 41 in the placebo group has lesions with stigmata, which were classified according to Foster et al.\(^{20}\) and are listed in Table 4. There was no important difference in the distribution of stigmata

<table>
<thead>
<tr>
<th>Table 1 - Miscellaneous findings in the two groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Somatostatin group</strong></td>
</tr>
<tr>
<td><strong>Total (no 46)</strong></td>
</tr>
<tr>
<td>Age, mean (range)</td>
</tr>
<tr>
<td>Male:female</td>
</tr>
<tr>
<td>Alcoholics</td>
</tr>
<tr>
<td>Regular consumption of:</td>
</tr>
<tr>
<td>Antacids</td>
</tr>
<tr>
<td>Cimetidine</td>
</tr>
<tr>
<td>Salicylates</td>
</tr>
<tr>
<td>Cortisone</td>
</tr>
<tr>
<td>Antiphlogistic drugs</td>
</tr>
</tbody>
</table>
between the two groups. In the somatostatin group 36 patients had had clinical or endoscopic signs of active bleeding on the day of admission. On the following day (day 1), endoscopic examination revealed eight patients with continuous bleeding. A total of five patients were operated on in the somatostatin group, which is significantly less than in the placebo group (Fisher's exact test, 2-tail, p=0.04). Gastric ulcers were the source of bleeding in two cases, duodenal ulcers in two cases and a stomal ulcer in a single case. In four patients, an operation was indicated because of continuous bleeding and in one patient because of a rebleed. In one patient a gastric ulcer bleeding necessitated an acute operation after an infusion period of three hours while three patients were operated on within 24-48 hours after the infusion had started. The stigmata found in the operated patients are listed in Table 4.

A total of six patients rebled in the somatostatin group. Gastric ulcers were the source of bleeding in two cases, duodenal ulcers in three cases and oesophagitis in one case. All of the ulcer patients had stigmata, these were not present in the patient with oesophagitis. One patient experienced a limited rebleeding on day 2 during the infusion period, while the other five patients rebled on day 3 after the period of infusion of somatostatin. The patient with oesophagitis rebled on day 3 but no treatment was necessary as the bleeding stopped spontaneously. The remaining four patients were treated with somatostatin, three on day 3, and one on day 5. The latter had to be operated on whereas the others stopped bleeding. The patient operated on should have been given somatostatin on day 3 as he had obvious signs of rebleeding. This was, however, not carried out until day 5.

In the placebo group 40 patients had had clinical or endoscopic signs of active bleeding on the day of admission. On the following day, 16 patients showed continuous bleeding. A total of 14 patients were operated on and the stigmata of their bleeding lesions are listed in Table 4. In seven cases, gastric ulcers were the source of bleeding, in six duodenal ulcers and in one multiple Mallory-Weiss tears. All operations except one were performed within 48 hours after the infusion of placebo was started. The indications for acute surgery were continuous bleeding in 10 cases and rebleeding in four cases.

Five patients in the placebo group rebled and four of them on the day after admission. Four of them had duodenal ulcers and one a gastric ulcer, and all bleeding lesions had stigmata. One of these patients had a continuous minor bleeding and was treated with somatostatin on day 3, he stopped bleeding on day 5. A total of four patients in the placebo group with rebleeding were operated on as compared with one patient in the somatostatin group.

In the somatostatin group, two of the five patients operated on had a present treatment with cortisone or an antiphlogistic drug and in the placebo group

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**Table 2  Findings of laboratory tests, blood pressure and pulse rate upon admission**

<table>
<thead>
<tr>
<th>Laboratory tests</th>
<th>Reference values</th>
<th>Somatostatin group</th>
<th>Placebo group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td>B-haemoglobin</td>
<td>120-150 g/l</td>
<td>95</td>
<td>60-140</td>
</tr>
<tr>
<td>P-simplastin-A</td>
<td>70-130%</td>
<td>70</td>
<td>26-107</td>
</tr>
<tr>
<td>B-thrombocytes</td>
<td>&lt;0-70 µkat/l*</td>
<td>0-57</td>
<td>0-03-2-40</td>
</tr>
<tr>
<td>S-SAT</td>
<td>150-400×10⁹</td>
<td>234×10⁹</td>
<td>2-830×10⁹</td>
</tr>
<tr>
<td>Blood pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic</td>
<td>112</td>
<td>60-170</td>
<td>107</td>
</tr>
<tr>
<td>Diastolic</td>
<td>69</td>
<td>40-95</td>
<td>67</td>
</tr>
<tr>
<td>Pulse rate (per minute)</td>
<td>98</td>
<td>72-140</td>
<td>103</td>
</tr>
</tbody>
</table>

* Corresponds to <42 U/l. † Corresponds to 60-110 mg/100 ml.

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**Table 3  Sources of bleeding**

<table>
<thead>
<tr>
<th>Source of bleeding</th>
<th>Somatostatin group (no 46)</th>
<th>Placebo group (no 49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric ulcer</td>
<td>16</td>
<td>25</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>17</td>
<td>15</td>
</tr>
<tr>
<td>Stomal ulcer</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Erosive bleeding</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>
Table 4  Distribution of stigmata in both groups

<table>
<thead>
<tr>
<th></th>
<th>At first endoscopy</th>
<th>Placebo group</th>
<th>In operated patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Somatostatin group</td>
<td>Placebo group</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ulcer patients</td>
<td>Total</td>
<td>Ulcer patients</td>
</tr>
<tr>
<td></td>
<td>(no 36)</td>
<td>(no 46)</td>
<td>(no 42)</td>
</tr>
<tr>
<td>Stigmata*</td>
<td>29</td>
<td>38</td>
<td>36</td>
</tr>
<tr>
<td>Active bleeding</td>
<td>13</td>
<td>20</td>
<td>19</td>
</tr>
<tr>
<td>Blood clot</td>
<td>18</td>
<td>19</td>
<td>25</td>
</tr>
<tr>
<td>Protruding vessel</td>
<td>8</td>
<td>10</td>
<td>9</td>
</tr>
</tbody>
</table>

* Some patients had more than one stigma.

three of the 14 patients operated on had such a treatment (Table 1).

The mean±SD number of blood units given was 5·8±5·3 units in the somatostatin group and 7·2±6·5 units in the placebo group (NS, Wilcoxon's test). The operated patients in the somatostatin group were given a mean number of 17·0±8·0 units of blood and in the placebo group 14·2±4·9 units (NS, Wilcoxon's test). The non-operated patients in the somatostatin group were given a mean number of 4·4±2·7 units of blood and in the placebo group 4·4±4·7 units (NS, Wilcoxon's test).

The mortality rate in the study was 5·3% which included four patients in the somatostatin group and one in the placebo group. The causes of death were heart failure, myocardial infarction, gastric cancer, disseminated pulmonary cancer and a complicated postoperative course in a patient with pituitary insufficiency. Two of the patients who died had been operated on.

No side effects of the somatostatin infusions were found. One patient in the somatostatin group and two in the placebo group needed insulin administration. There were no important differences between the two groups upon admission and during the five following days regarding blood pressure and routine laboratory tests. P-gastrin, P-insulin, B-glucose, B-thrombocytes and pulse rate did not differ between the two groups.

Upon admission the P-gastrin, the P-insulin and the B-glucose levels were significantly raised in both groups when compared with the normal range (Table 2). On the next day the gastrin concentrations decreased significantly in both the somatostatin group (46±67 pg/ml, mean±SD) and in the placebo group (116±165 pg/ml) as compared with the concentrations upon admission. Comparing the gastrin concentrations during day 1 in the two groups, the decrease was more pronounced in the somatostatin group (t test, p=0·04). The insulin concentrations remained raised in both groups for the five days after admission. As a result of the infusions of somatostatin, the B-glucose concentrations increased to 12·8±5·6 mmol/l during day 1 and to 11·7±4·5 mmol/l during day 2.

At the time of admission values of the B-thrombocytes as well as the pulse rates were similar in the two groups. On the following day, however, the thrombocyte concentration was significantly less in the somatostatin group. The same was found for the pulse rates which were lower in the somatostatin group than in the placebo group during the following three days.

Discussion

In the present trial only patients with massive upper gastrointestinal bleeding have been included. Massive bleeding has been defined as a state where clinical signs of shock or preshock with an effect upon the circulation are observed. These strict criteria have presumably tended to exclude patients with erosive gastritis, duodenitis, and oesophagitis as only eight patients with erosive bleedings were included. Patients with oesophageal varices were excluded as well as patients with diabetes: the former, as we are at present running a randomised trial on the effect of sclerotherapy, and the latter, to avoid the effect of somatostatin on the pancreatic islets in patients with diabetes mellitus.

Endoscopy was performed within eight hours of admission and on the following day. This latter control endoscopy served two purposes, to verify the initial diagnosis and to establish if bleeding was present on the day after admission. An assessment of the stigmata as described by Foster et al20 was used in our series. The distribution of stigmata corresponded to that found by other workers.6 20-22 Kayasseh et al18 reported a sequential analysis comparing somatostatin and cimetidine in which eight of 10 patients given somatostatin stopped bleeding and the other two were operated on. Limberg and Kommerell19 have presented the results from a study of 18 patients who were given
Trial of somatostatin in treatment of gastrointestinal haemorrhage

This for six to eight hours with no effect on the bleeding. This was followed by infusion of somatostatin for at least 20 hours. The 18 patients had 23 episodes of bleeding and somatostatin failed to stop the bleeding in five patients.

In the above mentioned studies, somatostatin was administered in the same manner as in the present trial, that is, as a bolus injection of 250 µg followed by an infusion of 250 µg/h. Our results show the effect of this dose on plasma gastrin and blood glucose. At approximately one third of this dose, however, the gastric mucous output is significantly increased and the gall bladder and the pancreatic enzyme secretion significantly inhibited. Thus, a lower dose might have the same effect on the plasma gastrin concentrations.

The duration of the somatostatin infusion has varied in the trials between 20–120 hours. As no toxic side effects of a 250 µg/h dose of somatostatin infused for a duration of 72 hours were found, we used this to insure that we could elicit an effect as well as compare our results with previous studies.

In other studies with somatostatin, the stigmata of the bleeding lesions have not been reported. As most ulcers stop bleeding spontaneously and evidently patients with stigmata run a greater risk of continuous bleeding or rebleeding we have focused our interest on this. A total of 79 patients (83%) in the trial had lesions with stigmata. One patient was operated on because of clinical signs of continuous bleeding and one patient with rebleeding from oesophagitis had no stigmata at the time of endoscopy. Otherwise all patients who were operated on or showed rebleeding had lesions with stigmata.

Foster et al. found 41.7% of patients with peptic ulcers with stigmata had further haemorrhage and 53.3% needed emergency surgery. In the present study 29 ulcer patients in the somatostatin group had lesions with stigmata and five (17%) were operated on. In the placebo group of 36 ulcer patients, 14 (39%) were operated on.

Five patients rebled in the placebo group and four of them were operated on while only one of the six patients with rebleeding in the somatostatin group was operated on.

The reduction of the number of acute operations for bleeding peptic ulcers in the somatostatin group might be because of the inhibitory effect on the gastric acid and pepsin secretion. This might then facilitate platelet aggregation and make the clotting more effective as the pH is raised owing to the absence of acid and pepsin. The reduction in thrombocyte counts in the somatostatin group as compared with the placebo group may be a confirmation of such a hypothesis.

As shown in Table 1, three times as many patients in the placebo group were under medication with cortisone or antiphlogistics as compared with the somatostatin group. This medication has not affected the number of operations in the placebo group (2/5 vs 3/14).

Upon admission the patients in the two groups had raised concentrations by B-glucose, P-gastrin, and P-insulin. Raised plasma gastrin was found both in gastric and duodenal ulcer patients. During the infusion of somatostatin the gastrin concentrations decreased and the glucose concentrations increased. It was surprising that somatostatin did not decrease insulin concentrations because somatostatin is known to inhibit the release of both gastrin and insulin.

Hypergastrinaemia has been reported in a severely burnt patient who developed massive bleeding from a stress ulcer but otherwise, to our knowledge, no reports exist in which the gastrin concentrations in upper gastrointestinal bleeding have been measured. It is possible that gastrin and gastric acid hypersecretion might play a role in the genesis of bleeding ulcers.

The small numerical difference in mortality between the two groups is not statistically significant (p=0.19). The limited number of patients included in the trial, however, prevents an accurate judgement of the side effects of the somatostatin treatment. Only two of the five deaths were caused by the upper gastrointestinal bleeding.

In conclusion, somatostatin significantly reduced the number of emergency operations necessary in cases of massive upper gastrointestinal bleeding.

The most probable explanation for the positive effect of somatostatin is suggested to be its inhibitory effect on gastric secretion of acid and pepsin thereby enhancing the possibility for platelet aggregation and plasma clotting. The circulatory effects of somatostatin are probably of lesser importance. Our evidence supports the recommendation that patients with massive bleeding from lesions bearing stigmata should be treated with somatostatin.

References


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