Use of octreotide in the acute management of bleeding esophageal varices

Daniel C Sadowski MD FRCP

The call came at 3:00 am. I clumsily reached for the phone in the dark, trying to clear my fuzzy head. I groaned; night calls to a gastroenterologist usually mean one of two things: an upper gastrointestinal bleed or a foreign body in the esophagus, both of which often require urgent endoscopy.

“Good morning doctor,” said the unreasonably cheerful casualty officer. “We have a 45-year-old male who began vomiting blood 2 h ago.” I sighed and began fumbling for my slippers.

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“He has known liver cirrhosis and previous bleeding from esophageal varices one year ago. He was subsequently lost to follow-up.” I put down my keys.

“On examination he is alert with a stable blood pressure and no postural changes. He has spider nevi on his anterior chest, a palpable spleen and moderate ascites.” I took off my slippers.

“His hemoglobin is 110 and his PT INR is 1.3. What do you want me to do?”

“Right,” I said confidently, lying back down in my soft bed. “Let us start some octreotide. Give him a 50 mcg bolus IV now and then begin an infusion of 50 mcg/h. Admit him and plan for urgent endoscopy first thing this morning.” I promptly fell asleep, confident that my patient was receiving the best treatment for his bleeding esophageal varices.

Acute hemorrhage from esophageal varices is a medical emergency; despite early diagnosis and treatment the associated hospital mortality remains high. The clinical research summarized in this paper shows that octreotide has a beneficial effect on portal hemodynamics in cirrhotic patients. In randomized controlled trials octreotide has been effective in halting initial hemorrhage and in preventing reoccurrence of bleeding. Somatostatin and octreotide appear to be equivalent in terms of therapeutic efficacy but octreotide is the less expensive option. For suspected variceal bleeding an octreotide infusion should be initiated immediately. To prevent further bleeding the drug should be continued for two to five days after endoscopic variceal ligation.

Key Words: Bleeding esophageal varices, Octreotide

CLINICAL TIPS
pensation or sepsis. Available therapeutic modalities for acute variceal bleeding include vasoactive drugs, balloon tamponade, endoscopic variceal ligation, sclerotherapy and portocaval shunting procedures. Recently, attention has focused on octreotide as a treatment modality for those bleeding from esophageal varices. The purpose of this review is to present the relevant clinical research on octreotide and suggest a rational approach to the use of this drug.

**OCTREOTIDE, SOMATOSTATIN AND PORTAL HEMODYNAMICS**

Octreotide is a synthetic analogue of naturally occurring somatostatin-14. In pharmacological doses this octapeptide inhibits gastrointestinal exocrine secretions and stimulates intraluminal fluid absorption (2,3). While the biological effects of this peptide are essentially those of native somatostatin, octreotide appears to be more potent and to have a dramatically longer half-life (4,5). Unlike somatostatin, octreotide can be administered subcutaneously.

Because of the inaccessibility of the portal vein in humans, indirect methods such as hepatic vein catheterization or Doppler flowmetry have been employed in the study of portal hemodynamics. In cirrhotic patients, several investigators (6-10) have observed a significant decrease in estimated portal venous pressure after administration of somatostatin and octreotide. This effect persisted for up to 3 h after the octreotide infusion was stopped (11). The responsible mechanisms are unknown but may involve direct vasoconstriction of splanchnic vasculature, vasodilation of the portal system or inhibition of vasoactive hormones such as glucagon (12). However, not all investigators have confirmed these pressure-related findings (13,14). For example, Lin et al (15), in a study of 20 patients with hepatitis B cirrhosis, did not find any change in the hepatic venous pressure gradient after either low or high dose infusions of octreotide.

More consistent measurements have been observed using measurements of azygous vein flow, which reflects collateral and variceal bloodflow. Reproducible reductions in azygous bloodflow have resulted from both octreotide and somatostatin infusions (10,16). Intravascular pressure can be measured using either fine needle puncture or compression techniques. A close correlation appears to exist between variceal bleeding events and elevated intravascular pressure (17). The effects of somatostatin or octreotide infusions on intravascular pressure are under debate. Investigators have reported both increases and decreases in pressure during drug infusions (18-20). The heterogeneity of these responses may be due to differences in measurement techniques, disease severity and/or systemic vascular effects of the drugs.

**CLINICAL TRIALS WITH SOMATOSTATIN AND OCTREOTIDE**

Clinical trials involving patients with acute bleeding from esophageal varices have evaluated the effects of somatostatin compared with those of placebo, vasopressin and injection sclerotherapy. In a randomized double-blind trial, Burroughs and co-workers (21) demonstrated that intrave-

![Diagram](image-url)
nous somatostatin (250 μg/h) over five days was superior to placebo in controlling initial hemorrhaging, as well as in reducing early rebleeding and transfusion requirements. Valenzuela et al (22) were unable to reproduce a therapeutic effect in a similarly designed trial; however, the high response rate (83%) in the placebo group suggests significant patient selection bias. A recent meta-analysis of published clinical trials examined the relative therapeutic efficacies of somatostatin and vasopressin. Somatostatin was more efficacious than vasopressin in controlling acute variceal hemorrhage; somatostatin also had a lower rate of adverse events (23). Somatostatin compared favorably with balloon tamponade in the control of initial hemorrhage (24,25). In a study of 70 patients, Planas et al (26) demonstrated that somatostatin if infusion was as effective as injection sclerotherapy in both controlling initial bleeding episodes and preventing early rebleeding. Also, significantly fewer major complications were observed in the somatostatin group (26).

An overview of published clinical trials on octreotide is found in Table 1. In one study of 100 patients, Sung et al (27) demonstrated that octreotide was as effective as emergency sclerotherapy in controlling initial hemorrhage and preventing rebleeding episodes. In that trial the majority of rebleeding episodes occurred within 48 h of presentation. In a subsequent study, the same investigators demonstrated that octreotide in combination with endoscopic band ligation significantly reduced the incidence of early rebleeding over band ligation alone (28). Besson's group (29) found a significant reduction in early rebleeding in 199 patients when octreotide was combined with standard sclerotherapy (29). McKee et al (30) found octreotide to be as effective as balloon tamponade in controlling initial hemorrhage. In an attempt to reduce rebleeding, Primignani et al (31) used subcutaneous injections of octreotide (300 μg/day) for up to 29 days after the initial bleeding episode had been controlled with endoscopic sclerotherapy. No difference in rebleeding rates was found between treatment or placebo groups; however, this lack of difference may be a function of the low dose used (31). Octreotide has also been found to be more effective than vasopressin and its longer acting analogue terlipressin in controlling acute bleeding; as well, substantially fewer side effects were noted in the octreotide group (32-34).

In all of the studies cited above, no difference was seen in patient mortality between treatment groups. The exception was the study from McKee and colleagues (30), which found a substantially higher mortality in the esophageal tamponade group.

<table>
<thead>
<tr>
<th>AN APPROACH TO THE MANAGEMENT OF BLEEDING ESOPHAGEAL VARICES</th>
</tr>
</thead>
<tbody>
<tr>
<td>The goals of treatment in acute variceal bleeding are to control the initial hemorrhage, prevent early rebleeding, minimize deterioration in liver function and treat complications associated with blood loss (35). Priority is given to airway management, along with early establishment of good venous access. Resuscitation involves administration of intravenous...</td>
</tr>
</tbody>
</table>

**TABLE 1: Randomized controlled trials of octreotide in the treatment of bleeding esophageal varices**

<table>
<thead>
<tr>
<th>Study (reference)</th>
<th>Year</th>
<th>n</th>
<th>Octreotide dose</th>
<th>Initial hemostasis (%)</th>
<th>Early rebleeding (%)</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bascone et al (29)</td>
<td>1996</td>
<td>19</td>
<td>Sclerotherapy alone</td>
<td>100</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Sung et al (29)</td>
<td>1995</td>
<td>100</td>
<td>Sclerotherapy for 48 h</td>
<td>50</td>
<td>100</td>
<td>25</td>
</tr>
<tr>
<td>Poletti et al (31)</td>
<td>1994</td>
<td>87</td>
<td>Terlipressin + transdermal nitroglycerin</td>
<td>92</td>
<td>87</td>
<td>14</td>
</tr>
<tr>
<td>Shenol et al (33)</td>
<td>1993</td>
<td>64</td>
<td>24 h then 100 μg intravenously</td>
<td>90</td>
<td>80</td>
<td>12</td>
</tr>
<tr>
<td>Silvain et al (33)</td>
<td>1993</td>
<td>78</td>
<td>Subcutaneously at 12 and 18 h</td>
<td>90</td>
<td>50</td>
<td>27</td>
</tr>
<tr>
<td>Hwang et al (32)</td>
<td>1992</td>
<td>90</td>
<td>100 μg bolus IV, 25 μg IV for 24 h</td>
<td>90</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>Sung et al (28)</td>
<td>1992</td>
<td>84</td>
<td>50 μg bolus + 50 μg subcutaneously</td>
<td>90</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>Pedretti et al (34)</td>
<td>1992</td>
<td>90</td>
<td>25 μg bolus every 12 hours</td>
<td>90</td>
<td>50</td>
<td>10</td>
</tr>
<tr>
<td>Sung et al (27)</td>
<td>1991</td>
<td>96</td>
<td>Sclerotherapy alone</td>
<td>24</td>
<td>80</td>
<td>15</td>
</tr>
<tr>
<td>Besson et al (29)</td>
<td>1991</td>
<td>94</td>
<td>Sclerotherapy at presentation</td>
<td>24</td>
<td>60</td>
<td>14</td>
</tr>
<tr>
<td>Sung et al (26)</td>
<td>1990</td>
<td>95</td>
<td>Endoscopic band ligation alone</td>
<td>24</td>
<td>60</td>
<td>10</td>
</tr>
<tr>
<td>Sung et al (27)</td>
<td>1989</td>
<td>95</td>
<td>Endoscopic sclerotherapy at presentation</td>
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<td>Sung et al (26)</td>
<td>1989</td>
<td>95</td>
<td>Octreotide control</td>
<td>100</td>
<td>50</td>
<td>25</td>
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P values are given where significant differences were found between groups.
crystallloid solutions and transfusion of packed red blood cells and clotting factors where appropriate.

Many centres favour endoscopic sclerotherapy or band ligation once the patient has been stabilized. The advantage to this approach is that the site of bleeding can be identified and the hemorrhage controlled in most instances. While endoscopic banding appears to be safer than injection sclerotherapy, banding is not always possible if the patient is bleeding briskly or visibility is poor (36,37). The main difficulty in banding or sclerotherapy is that endoscopy facilities are not available in many centres on an emergency basis. In addition, even in experienced hands rebleeding rates after sclerotherapy or banding are as high as 40% (36,37). Therefore, a therapeutic agent that can be easily administered while the patient is being stabilized and transferred to an endoscopy facility is necessary. Vasopressin has traditionally been used in this capacity. However, because of vasopressin's side effect profile and the need for concomitant nitroglycerin administration, investigators have continued to search for better vasoactive agents. Unfortunately, while synthetic analogues of vasopressin such as terlipressin have proven efficacious, they have also similar adverse effects (33,38).

As discussed earlier, somatostatin and octreotide have proven efficacy in controlling the initial hemorrhage and in preventing rebleeding events. Moreover, in clinical trials the side effect profiles of both somatostatin and octreotide are minimal. While no head-to-head trials have been performed on these two agents, available evidence suggests a proven equivalence to esophageal banding in controlling initial hemorrhaging, and it is superior to banding alone in preventing rebleeding. It should be part of the therapeutic armamentarium of every Canadian hospital.

REFERENCES


CONCLUSIONS

Octreotide is a new peptide analogue effective in the treatment of bleeding esophageal varices. In clinical trials it has proven equivalence to esophageal banding in controlling initial hemorrhaging, and it is superior to banding alone in preventing rebleeding. It should be part of the therapeutic armamentarium of every Canadian hospital.


