Octreotide in variceal bleeding

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Abstract

Bleeding from oesophageal varices has a high death rate. Injection sclerotherapy is the most appropriate treatment but facilities for this are not always available. Balloon tamponade and vasoactive therapy may be used as stop gap measures. Somatostatin and octreotide are therapeutic candidates for the treatment of variceal bleeding and there are several trials that have compared somatostatin and octreotide with other treatments for this condition. The results of these trials are summarised and discussed. A meta analysis of the group of trials of placebo or H₂ antagonists *v* somatostatin or octreotide showed a significant advantage of somatostatin or octreotide in terms of efficacy, but no difference in mortality. The trials discussed seem to show that somatostatin and octreotide are at least as effective as other treatments, with the benefit of fewer adverse effects, and thus represent the best vasoactive agents. Additionally, they may have a role as adjuvant treatment to emergency sclerotherapy for active bleeders and this must be further investigated.

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Bleeding from oesophageal varices is a medical emergency that still has a high mortality, about 20–25%, depending on the severity of the underlying liver disease.^{1,2} Bleeding is often massive. A particular feature of variceal bleeding is the frequency of very early rebleeding, which is a prognostic factor for death (as for peptic ulcer bleeding). Emergency treatment follows the same principles as for other types of gastrointestinal bleeding and consists of resuscitation, diagnosis, and control of bleeding. Most patients in the developed world have underlying cirrhosis, so that non-surgical options are favoured as first line treatments, because the operative mortality in cirrhotic patients is high.³ These options include vasoactive drugs, balloon tamponade, endoscopic injection sclerotherapy, banding ligation of oesophageal varices or a combination of these treatments. The aims of treating acute variceal bleeding are to control the haemorrhage, prevent early rebleeding, minimise the deterioration in liver function, and treat complications associated with blood loss.

In the last 15 years, endoscopic sclerotherapy has gained popularity as an emergency treatment for the control of acute variceal haemorrhage, achieving primary haemostasis in 70% with one injection session and up to 95% with two sessions.⁴ The facilities for injection sclerotherapy, however, are not always

available nor is the expertise required to inject a copiously bleeding varix. Consequently, in most centres, stop gap treatment such as balloon tamponade of the oesophagus or vasoactive therapy, or both, remain the first line treatment for acute variceal haemorrhage. Injection sclerotherapy or other definitive treatment is often delayed until the bleeding is controlled and the patient stable. Alternatively, the patient can be transferred to a referral centre when stable for definitive treatment.

Balloon tamponade of the oesophagus is effective in controlling acute variceal bleeding in about 70–80% of patients. Recurrent bleeding, however, occurs rapidly in roughly half of these patients and the complication rate of 15–20% is unacceptably high.⁵ An important consideration is that it is an uncomfortable and unpleasant experience for the patient. Consequently, if given the choice, most patients with bleeding oesophageal varices would prefer effective vasoactive treatment to balloon tamponade.

Additionally vasoactive drug therapy is the only treatment that does not require special skill and is immediately available. There is recent evidence that patients who continue to bleed or rebleed early are those with high variceal or portal pressures.^{6,7} This suggests that use of a vasoactive drug over several days is of potential therapeutic benefit.

VASOPRESSIN OR GLYPRESSIN WITH OR WITHOUT NITROGLYCERIN

Since its introduction in 1956 and until recently, vasopressin has remained the vasoactive treatment most widely used for the control of acute variceal bleeding. Of the 336 episodes of variceal bleeding treated with vasopressin in the 17 randomised clinical trials published to date, however, control of haemorrhage was only achieved in 145 instances, a success rate of less than 50%.^{8–24} In addition to doubts regarding its efficacy, vasopressin is associated with side effects in about 25% of the patients, several of which require withdrawal of treatment and some of which can be fatal. To minimise the side effects and enhance the vasoactive effects of the drug, two new therapeutic approaches using vasopressin have been proposed. The first entails the use of a vasopressin analogue, triglycyl-lysine vasopressin (terlipressin or glypressin), which has some biological activity in itself but is enzymatically cleaved in vivo to lysine vasopressin. Placebo controlled trials have shown glypressin to be effective.^{25,26} The second approach entails concomitant administration of nitroglycerin. The rationale for this treatment is that nitroglycerin does not change the effects of vasopressin on portal pressure, but

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prevents many of the systemic side effects particularly on the coronary circulation. Controlled clinical trials with glypressin¹⁴⁻²⁷ or combined vasopressin nitroglycerin^{18 19} treatment show that these treatments are associated with fewer side effects than vasopressin. An increased efficacy, however, of glypressin or combined vasopressin-nitroglycerin treatment over vasopressin alone has not been proved. The magnitude of splanchnic haemodynamic effects in terms of portal pressure reduction is variable, with little effect in some patients.²⁸

Somatostatin and octreotide

Somatostatin is a 14 amino acid peptide that was found to reduce splanchnic blood flow in normal humans.²⁹⁻³¹ In stable cirrhotic patients modest reductions in hepatic blood flow³² and wedged venous pressure³³⁻³⁶ have been reported by several groups, but others have found no effect on portal pressure^{32 37} or intravariceal pressure.³⁸ Azygos blood flow, a measure of collateral blood flow including variceal flow, has, however, always been shown to fall with somatostatin, and more noticeably than with vasopressin for a similar reduction in portal pressure.³⁶

Octreotide is a synthetic octapeptide of somatostatin (sharing four amino acids with somatostatin that are responsible for biological activity), which has similar pharmacological effects as the naturally occurring hormone but a considerably longer duration of action. Like somatostatin, octreotide significantly reduces portal pressure in experimental animals^{39 40} and in patients with portal hypertension^{41 42} after either an intravenous bolus administration or a continuous infusion. Subcutaneous administration produces a sustained reduction in portal pressure in rats with cirrhosis and portal hypertension.³⁹ Perhaps more importantly with respect to the control of the acute variceal bleed, the effects of octreotide on collateral blood flow⁴⁰ and azygos blood flow⁴³ are significantly greater than its effect on portal pressure in experimental animals and patients with cirrhosis and portal hypertension.

Octreotide has similar effects to somatostatin in stable cirrhotic patients (not bleeding), with little or no effect on wedged hepatic venous pressure,^{44 45} variable effects on intravariceal pressure,^{38 46} but a significant reduction in azygos blood flow.^{43 44 47} Bolus octreotide (25 µg) transiently but significantly reduces cardiac output in stable cirrhotic patients whereas a 50 µg/hour infusion had less noticeable effects. These effects are not clinically manifest during the studies.⁴⁸ It suggests that constant infusion rather than bolus injection is the optimal route of administration. A recent report on somatostatin and renal function in cirrhosis suggests it may adversely affect renal function.⁴⁹ The study was performed, however, under volume loading, which may have changed the balance of effects on endogenous vasodilators and the renin, angiotensin, and aldosterone system.⁵⁰ Another study in which no volume loading was given suggests a beneficial effect of octreotide

on renal function.⁵¹ In an animal model octreotide improves salt and water excretion.⁵² In all the clinical trials reported there are no reports of adverse effects on renal function of somatostatin or octreotide and no differences compared with the other treatment(s) evaluated in the trials.

The variability in splanchnic haemodynamic effects, particularly for portal pressure reduction, have led most clinicians to consider somatostatin or octreotide as unlikely therapeutic candidates to treat variceal bleeding. Although the reduction in azygos blood flow may be the important haemodynamic effect for the control of variceal bleeding, there is no proof that this is so. The effects on splanchnic haemodynamics, however, should be tempered by several considerations when considering the results of therapeutic efficacy in various trials of vasoactive drugs in portal hypertension. Firstly, in cirrhotic patients the variability in splanchnic haemodynamic effects in response to any vasoactive drug probably reflects normal biological variability or possibly variability because of as yet unknown pathophysiological differences among patients. This variability has been shown with vasopressin and propranolol, drugs used for the acute control and prevention of variceal bleeding respectively. It is now accepted that both these drugs have some therapeutic effect despite the variability in haemodynamic responses. As mentioned above, the therapeutic effect with vasopressin is modest and accompanied by many side effects. With propranolol, the therapeutic effect on rebleeding is also modest but with no serious side effects. In a primary prophylactic study, patients taking propranolol (or placebo) who did not reduce their hepatic venous pressure gradient to less than 12 mm Hg were shown to have more chance of bleeding.⁵³ The second consideration is that the dosage schedules of somatostatin in both research protocols and clinical studies have been largely empirical, usually giving a single bolus followed by an infusion. The third consideration is that the effects of somatostatin or octreotide and other vasoactive drugs during variceal bleeding may be quantitatively different from those seen in stable cirrhotic patients reported in haemodynamic studies, as patients present a different haemodynamic profile when bleeding, both in the splanchnic and systemic circulation, in comparison with stable patients. Thus, evidence for therapeutic efficacy must be sought in the results of clinical trials.

There are several trials that have compared somatostatin and octreotide with other treatment for acute variceal bleeding^{15 16 21-24 54-66} (Table). Apart from the trial by Walker *et al.*,⁶³ in which the side effects attributed to octreotide do not seem directly related, all studies show significantly fewer side effects with somatostatin and octreotide compared with the other therapies.^{15 16 21-24 54-66} Moreover, no patient required withdrawal of somatostatin or octreotide because of side effects, unlike the case with vasopressin.

The two double blind placebo controlled trials of somatostatin unfortunately give

Randomised clinical trials of somatostatin or octreotide* for the emergency treatment of variceal bleeding

Author (reference)	Date of publication	Patients or patient admissions	Duration of treatment	Efficacy of somatostatin or octreotide (%)	Other treatment (%)
Valenzuela ⁵⁹	1989	84	30 hours	65	83 (placebo)
Burroughs ⁶⁰	1990	120	5 days	64	41 (placebo)
Kravetz ¹⁵	1984	61	48 hours	53	58 (vasopressin)
Jenkins ¹⁶	1985	22	24 hours	100	33 (vasopressin)
Bagarani ²³	1987	50	48 hours	67	32 (vasopressin)
Saari ²⁴	1990	54	72 hours	66	52 (vasopressin)
Hsia ²¹	1990	46	24 hours	55	38 (vasopressin)
Walker ⁶³	1992	50	24 hours	68	80 (glypressin)
Hwang ^{*22}	1992	48	24 hours	63	46 (vasopressin)
Cardona ⁵⁵	1989	38	24 hours	45	55 (vasopressin/nitroglycerin)
Silvain ^{*62}	1991	50	24 hours	86	62 (glypressin/nitroglycerin)
McKee ^{*456}	1990	40	48 hours	50	70 (tamponade)
Avgerinos ^{*54}	1991	92	24 hours	71	80 (tamponade)
Jaramillo ⁵⁷	1991	39	<24 hours	58	50 (tamponade)
Di Febo ⁶⁶	1990	47	48 hours	78	92 (sclerotherapy)
Jenkins ^{*61}	1992	40	48 hours	90	90 (sclerotherapy)
Shields ⁵⁸	1992	80	5 days	77	80 (sclerotherapy)
Planas ⁶⁵	In press	45	48 hours	82	87 (sclerotherapy)
Sung ^{*64}	1993	65	48 hours	72	58 (sclerotherapy)

†Efficacy was also assessed in a third group given combined somatostatin and balloon tamponade.

contrasting results (Table).^{59 60} The trial by Valenzuela *et al*⁵⁹ suggests somatostatin is no more effective than placebo. The fact, however, that only 84 evaluable patients were recruited over 14 months in 11 centres shows a severe selection of patients. It is not clear from the paper how this occurred. The 83% placebo response rate is the highest reported in published works irrespective of the definition used to describe response. In the Royal Free study⁶⁰ particular attention was taken to guard against biases of differing intervals to trial entry and severity of bleeding. A statistically significant benefit of somatostatin in controlling variceal bleeding compared with placebo was shown when given over a five day period. Failure to control bleeding over this interval occurred in 59% of the placebo group and 35% of the somatostatin group and transfusion requirements were halved ($p=0.025$).

There is now some evidence that active bleeding at endoscopy (irrespective of when this is performed in relation to admission) may be predictive of poorer control of bleeding.⁶⁷ Thus, placebo treatment for active bleeders would not be acceptable in a present day trial. A meta analysis of previously published trials presented at the World Congress of Gastroenterology in September 1992 (Burroughs, Athens 1992, unpublished results) showed, however, that in a group of trials of placebo^{59 60} or H₁ antagonists *v* somatostatin there was a statistically significant advantage of somatostatin in terms of efficacy but no difference in mortality. There was no statistical heterogeneity in these results despite the trial by Valenzuela *et al*,⁵⁹ which reported no difference between somatostatin and placebo.

In the group of trials of somatostatin or octreotide *v* vasopressin or glypressin with or without the addition of nitroglycerin^{15 16 21–24 55 62 63} (Table) there were no statistical differences in either efficacy or mortality and the results were virtually identical. As already mentioned, however, every trial apart from that by Walker *et al*⁶³ had a statistically significant reduction in complication rate in the groups treated with somatostatin or octreotide. In the three trials *v*

balloon tamponade (one with octreotide)^{54 56 57} there was no statistically significant difference in efficacy or mortality. In the group of four trials *v* sclerotherapy,^{58 61 65 66} there was no statistical difference in efficacy or mortality between somatostatin or octreotide and injection sclerotherapy. Moreover, a recent trial of octreotide *v* sclerotherapy by Sung *et al*,⁶⁴ performed in a skilled endoscopic unit, showed no differences in control of bleeding, early rebleeding, blood product use, or mortality between the two treatments.

Given that emergency sclerotherapy is now commonly used to control variceal bleeding irrespective of concomitant vasoactive treatment, it is reasonable to use it for active bleeding at endoscopy, as it permits a therapeutic measure to be given at initial diagnostic endoscopy. Indeed the Athens 1992 meta analysis (Burroughs, unpublished results) examined all trials of vasoactive drugs with or without use of balloon tamponade *v* injection sclerotherapy and showed the second to have a statistically significant advantage in terms of efficacy and mortality. There is always an interval before endoscopy, however, so that sclerotherapy cannot be given immediately. Occasionally bleeding is so severe that visibility is obscured. Sometimes the patient cannot safely have endoscopy without an endotracheal tube because of the dangers of aspiration. Thus, an active drug that might ‘hold’ the bleeding in the interval before endoscopy or facilitate sclerotherapy, or both, by stopping active bleeding would be of great clinical use.

Recent studies of portal pressure⁷ in the first 48 hours after admission for variceal bleeding have shown that ‘difficult’ bleeders – that is, those who seem to continue to bleed or have early variceal rebleeding – have a higher portal pressure. The studies were small so that it was difficult to establish a threshold pressure for an increased risk of ‘uncontrolled’ bleeding, but when the hepatic venous pressure gradient fell to below 16 mm Hg, there was a much smaller risk of rebleeding. Studies of intravariceal pressure show that it closely varies with central venous pressure and a lower pressure results in less early rebleeding.⁶ Thus, there is a good rationale for using vasoactive drugs for the initial treatment of variceal bleeding but also to keep a portal hypotensive effect for several days, when the risk of rebleeding is most common.

The clinical trials performed to date suggest that both octreotide and somatostatin are at least as effective as the conventional vasoactive drugs, balloon tamponade, and injection sclerotherapy in the treatment of variceal haemorrhage with the advantage of fewer side effects. Thus, they represent the best vasoactive agents pending further trials. Most importantly, however, these drugs need to be assessed as adjuvant treatment to emergency sclerotherapy for active bleeders.

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