

Review

Pro/con debate: Octreotide has an important role in the treatment of gastrointestinal bleeding of unknown origin?

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Abstract

Whether it is the primary reason for admission or a complication of critical illness, upper gastrointestinal bleeding is commonly encountered in the intensive care unit. In this setting, in the absence of endoscopy, intensivists generally provide supportive care (transfusion of blood products) and acid suppression (such as proton pump inhibitors). More recently, octreotide (a somatostatin analogue) has been used in such patients. However, its precise role in patients with upper gastrointestinal bleeding is not necessarily clear and the drug is associated with significant costs. In this issue of *Critical Care*, two expert teams debate the merits of using octreotide in non-variceal upper gastrointestinal bleeding.

Clinical scenario

A 59 year old male has been admitted to the intensive care unit with febrile neutropenia and septic shock. The patient has been diagnosed with acute myelogenous leukemia and following induction is pancytopenic. He is mechanically ventilated and receiving H₂ antagonists. You are called because the patient is having large amounts of melena and a modest amount of blood returning from his nasogastric tube. He is hemodynamically unstable. You transfuse blood, platelets and plasma as appropriate, and start an intravenous proton pump inhibitor. Endoscopy cannot be performed until the following day. You have to decide whether to treat the patient empirically with intravenous octreotide. You know it has a role in certain types of gastrointestinal (GI) bleeding but you are uncertain if you should be using it when the cause of bleeding is unclear. Your administrator tells you the drug is relatively expensive.

Pro: Yes, octreotide does have an important role in the treatment of gastrointestinal bleeding of unknown origin

Yaseen Arabi and Bandar Al Knawy

There is evidence to support the use of octreotide in variceal and non-variceal upper GI bleeding (UGB). As a somatostatin analogue, octreotide binds with endothelial cell somatostatin receptors, inducing strong, rapid and prolonged vasoconstriction [1]. Octreotide reduces portal and variceal pressures as well as splanchnic and portal-systemic collateral blood flows [2]. It also prevents postprandial splanchnic hyperemia in patients with portal hypertension [3] and lowers gastric mucosal blood flow in normal and portal hypertensive stomachs [4]. Octreotide inhibits both acid and pepsin

secretion. As a result, it prevents the dissolution of freshly formed clots at the site of bleeding [5].

The use of octreotide as a first, single therapy versus emergency sclerotherapy in bleeding esophageal varices was examined in a Cochrane systematic review of 12 randomized controlled trials (RCTs), including 6 trials of octreotide [6]. Emergency sclerotherapy was not significantly superior to any of the pharmacological treatments with regard to the assessed efficacy outcomes. In fact, adverse events were

GI = gastrointestinal; NVUGB = non-variceal upper gastrointestinal bleeding; PPI = proton pump inhibitor; RCT = randomized controlled trial; UGB = upper gastrointestinal bleeding.

significantly more frequent with sclerotherapy [6]. Octreotide is also effective as an adjunct to endoscopic therapy of variceal bleeding [7]. In patients with bleeding from portal hypertensive gastropathy, octreotide was found to be more effective than vasopressin and omeprazole in achieving complete bleeding control with less time and fewer blood transfusions required to control bleeding [8].

Octreotide may also be effective in non-variceal UGB (NVUGB). In a meta-analysis, somatostatin or octreotide were compared to H₂ antagonists and placebo and found to reduce the risk for continued bleeding or rebleeding. The drugs were efficacious for peptic ulcer bleeding and showed a trend toward efficacy for non-peptic ulcer bleeding (mostly caused by gastritis). However, the quality of some of the included studies has been questioned [9]. In addition, the comparison with H₂ blockers or placebo is less relevant to current practice considering the proven superiority of proton-pump inhibitors [10]. The panel of the Nonvariceal Upper GI Bleeding Consensus did not support the routine use of somatostatin or octreotide in non-variceal UGB. However, because of the favorable safety profile, the panel suggested that somatostatin or octreotide might be useful for patients

with uncontrollable bleeding awaiting endoscopy or awaiting surgery or for whom surgery is contraindicated [11].

UGB in critically ill patients has major consequences. Studies have demonstrated that UGB is associated with a significant attributable mortality (relative risk 4.1, 95% confidence interval 2.6 to 6.5) and length of intensive care unit stay (7.9 days, 95% confidence interval 1.4 to 14.4 days). Each episode resulted in a mean of 11 blood product transfusions, and 24 days of treatment, leading to an attributable cost of \$12,000 [12]. Unfortunately, data about the efficacy and cost effectiveness of octreotide in critically ill patients are lacking. However, octreotide has several features that make its use favorable in this population; it can be started quickly without the need for someone with endoscopy training to initiate, it has a relatively rapid onset of action and is relatively free of significant adverse effects [13].

In summary, in the absence of RCTs, the existing evidence of efficacy along with the favorable benefit-risk profile support the decision to use octreotide as an initial empirical therapy in critically ill patients with active UGB awaiting more definitive endoscopic diagnostic and therapeutic interventions.

Con: Octreotide prior to upper endoscopy for bleeding

Alan N Barkun and Marc Bardou

The following discussion focuses on NVUGB as the current patient is much less likely to have portal hypertension.

Current guidelines do not recommend routine octreotide in NVUGB [11]. In contrast, high dose proton pump inhibitors (PPIs) improve outcomes of patients at high risk of peptic ulcer rebleeding, including mortality [10,11,14,15]. The resultant profound acid suppression probably stabilizes clot [11] and, possibly, accelerates healing of bleeding lesions over the 72 hours following endoscopic hemostasis [16,17]. Somatostatin and octreotide inhibit acid, and decrease both pepsin secretion and gastroduodenal mucosal blood flow [5,18]; but the impact on patient outcomes may differ between both agents [5,18]. A meta-analysis has suggested that somatostatin (12 studies) and octreotide (2 studies) improved outcomes versus placebo or H₂-receptor antagonists (thought to be equivalent to placebo [19,20]) in patients with NVUGB [21]. Yet 13 of the 14 included RCTs were carried out before 1989. Standards of care have significantly evolved since then. More contemporary RCTs, totaling 242 patients, have shown no benefits attributable to somatostatin or octreotide, either alone or with ranitidine, compared to the control group administration (placebo or ranitidine) [22-24], except for a subgroup of 15 patients with oozing ulcers [24]. In one of few head-to-head comparisons with PPIs, human gastric pH data showed enhanced acid suppression for octreotide compared to pantoprazole. However, the acid

suppressing effect of pantoprazole was less than previously reported [25], and differences disappeared after the initial 6 to 12 hours of the 24 hour intravenous infusions [26]. An older, underpowered RCT showed no difference in outcomes between omeprazole and a combination of somatostatin and ranitidine in severe GI bleeding [27].

It is thus unlikely that somatostatin or octreotide can improve on results of high dose PPIs in patients with NVUGB, particularly bleeding ulcers, following endoscopic hemostasis. But what about administration to patients while awaiting endoscopy?

PPI infusion prior to endoscopy decreases the proportion of patients subsequently found to have high risk ulcer stigmata [16,17], but does not improve outcomes. It is unlikely, therefore, that somatostatin or octreotide would help in a patient population bleeding principally from NVUGB - the usual setting as this group comprises 80% to 90% of all bleeders seen [28]. Because of their effect on decreasing portal pressure, somatostatin and analogues have been used in acute variceal bleeding. In this patient population, meta-analyses [29] have shown no benefit of somatostatin over placebo in improving outcomes, while octreotide was no better than immediate sclerotherapy [30]; none, including vapreotide [31], decreased mortality at follow-up, although the latter two agents improved control of bleeding.

In conclusion, there exists no reason to initiate intravenous octreotide in the current setting, based on published efficacy data, let alone cost considerations. Somatostatin or octreotide can be considered in patients with NVUGB on a case-by-case basis, as additional pharmacotherapy, while awaiting endoscopy in very actively bleeding patients [11].

However, the definitive treatment of all patients with NVUGB remains early endoscopy as it has been shown to yield accurate diagnosis and prognostication, while improving outcomes and the cost-effective management of patients at high and low risk of rebleeding [11].

Pro's response: Defining the indication

Yaseen Arabi and Bandar Al Knawy

Octreotide use as an adjunct to endoscopic therapy [21,24,32] should be distinguished from its use as an initial therapy awaiting endoscopy [6]. The latter application in NVUGB is not well studied. However, octreotide as a first therapy for variceal bleeding was found to be as effective as emergency sclerotherapy with less adverse events [6].

Octreotide is not a substitute for PPIs or endoscopy. However, the latter is not always available or medically possible; only 19% of endoscopies were performed after working hours in one study [33]. Therefore, in our patient with active bleeding awaiting endoscopy, we will follow the consensus statement and initiate octreotide infusion [11].

Con's response: Octreotide prior to upper endoscopy for bleeding

Alan N Barkun and Marc Bardou

Octreotide is useful in patients with UGB, but its routine administration prior to endoscopy is supported neither by existing efficacy data nor cost benefit studies. Published evidence has guided a Consensus panel to recommend its use, on a case-by-case basis, in patients with very active bleeding while waiting for endoscopy hemostasis or surgery

[11]. It is probably also reasonable to consider administration in patients with a high probability of an esophageal variceal bleeding prior to endoscopy with possible banding. The mainstay of diagnosis and mortality-improving treatment for patients with peptic ulcers at high risk of rebleeding remains early endoscopy.

Competing interests

AB is a consultant for AstraZeneca and Atlana Pharma.

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