Original Article

Double-Blind, Placebo-Controlled, Randomized Trial of Octreotide in Malignant Bowel Obstruction

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Abstract

Context. Does octreotide reduce vomiting in cancer-associated bowel obstruction?

Objectives. To evaluate the net effect of adding octreotide or placebo to standardized therapies on the number of days free of vomiting for populations presenting with vomiting and inoperable bowel obstruction secondary to cancer or its treatment.

Methods. Twelve services enrolled people with advanced cancer presenting with vomiting secondary to bowel obstruction where surgery or anti-cancer therapies were not indicated immediately. In a double-blind study, participants were randomized to placebo or octreotide (600 μg/24 hours by infusion). Both arms received standardized supportive therapy (infusion of ranitidine [200 mg/24 hours], dexamethasone [8 mg/24 hours], and parenteral hydration [10–20 mL/kg/24 hours]). The primary outcome was patient-reported days free of vomiting at 72 hours.

Results. In a study that recruited to the numbers identified in its power calculation, 87 participants provided data at 72 hours (45, octreotide arm). Seventeen people (octreotide) and 14 (placebo) were free of vomiting for 72 hours ($P = 0.67$). Mean days free of vomiting were 1.87 (SD 1.10; octreotide) and 1.69 (SD 1.15; placebo; $P = 0.47$). An adjusted multivariate regression of the incidence of vomiting over the study showed a reduced number of episodes of vomiting in the octreotide group (incidence rate ratio = 0.40; 95% CI: 0.19–0.86; $P = 0.019$); however, people in the octreotide arm were 2.02 times more likely to be administered hyoscine butylbromide ($P = 0.004$), potentially reflecting increased colicky pain.

Conclusion. Although there was no reduction in the number of days free of vomiting, the multivariate analysis suggests that further study of somatostatin analogues in this setting is warranted. J Pain Symptom Manage 2015;49:814–821.

Key Words

Malignant bowel obstruction, palliative care, octreotide, randomized controlled trial, net clinical benefit, vomiting

Introduction

Between 3% and 15% of people with cancer will experience a bowel obstruction at some time.[1,2] In late-stage disease, when surgical and anti-cancer therapies are exhausted, mean survival after the diagnosis of a malignant bowel obstruction is four to five weeks.[1] When a patient has poor performance status and anti-cancer therapies are not an option, even minimally invasive surgery is unlikely to improve outcomes for someone with a malignant bowel obstruction.[3] Poor prognostic factors for 30 day survival after surgery

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include carcinomatosis, ascites, complete small bowel obstruction, hypoalbuminemia, and leukocytosis.[3] Therapies such as continuous nasogastric suction and IV fluids used in the acute care setting may, on occasion, be appropriate while an initial assessment is taking place but are rarely a long-term option.

Malignant bowel obstructions may cause vomiting, abdominal distension, and colicky or constant abdominal pain depending, in part, on the level(s) of the obstruction. Therapy for inoperable malignant bowel obstruction aims to lessen symptoms: vomiting (reducing frequency and volume by reducing gut secretions) and pain (opioids for constant pain and antispasmodics for colicky pain).[1]

There is neither standard clinical approach nor registered medication to treat people with inoperable malignant bowel obstructions. Two Cochrane reviews were unable to find quality studies to help inform surgical practice.[4,5] A Cochrane review showed a trend favoring dexamethasone over placebo in resolving obstructions.[6] More recent data suggest that steroids independently may improve the outcome for people treated with octreotide.[7] A meta-analysis demonstrated superiority of ranitidine over other agents, including proton pump inhibitors, in decreasing the volume of upper gut secretions.[8] These two therapies, therefore, were included in both arms as standard therapies.

Somatostatin has a complex action, with roles as hormone, paracrine factor, and neurotransmitter in the upper gut.[9] Octreotide, as a somatostatin analogue, has the theoretical potential to reduce symptoms in malignant bowel obstruction.

In the setting of malignant bowel obstruction, with no local or systemic disease-modifying treatments as immediate options, five controlled trials have now been reported, with the larger two studies using lanreotide ($n = 80$)[10] or lanreotide with octreotide cover for the first six days (which only recruited 64 of its intended 102 participants).[11] Findings from these studies did not support the use of somatostatin analogues, whereas three studies of octreotide 300 μg/day (n = 15, 17, and 68) appeared to show benefit.[12–14] More recent open-label, single-arm, uncontrolled studies appear to show overwhelming benefits for octreotide in symptomatic bowel obstructions in gynecologic and urologic cancers ($n = 27$, 22, and 14).[7,15,16] There has been no unified approach to the standard therapies that should be used in such studies, the dose of octreotide, or the primary end points; however, previous studies have helped to inform the design and analyses of this current pragmatic study.[17]

The aim of this study was to evaluate the net effect of adding octreotide or placebo to standardized therapies administered to all participants on the number of days free of vomiting for populations presenting with vomiting and an inoperable bowel obstruction secondary to cancer or its treatment, where anticancer therapies including surgery were not immediately indicated. The null hypothesis was that there was no difference in the number of days free of vomiting between arms.

Methods

Development, Ethics, Consent, and Monitoring

The study was reviewed by an internal peer-review scientific committee with input from the Australian Therapeutic Goods Administration and the Pharmaceutical Benefits Branch of the Department of Health. The study was overseen by an independent Data Safety Monitoring Committee and approved by each site's human research ethics committee. Participants provided written informed consent. People with a previous bowel obstruction that had resolved or who had known widespread peritoneal carcinomatosis were eligible to provide advanced consent so that, if in the future they experienced bowel obstruction because of cancer or its treatments, after assessment they could immediately commence the study protocol. Participants were identified by a range of clinicians including those in emergency, surgical, general medicine, and oncology departments and palliative care services in participating institutions and their associated community teams. Once identified, consent was obtained and follow-up provided by trained palliative care research nurses. The trial was registered before the first recruitment (ACTRN12608000211369).

Study Setting

The study was conducted in 12 palliative care service networks across Australia, as part of the Australian Government-funded national Palliative Care Clinical Studies Collaborative. The study recruited from August 2008 to May 2012.

Eligibility Criteria

People with vomiting secondary to a malignant bowel obstruction where surgery or further anticancer therapies were not immediately appropriate were eligible (Table 1). Bowel obstruction was diagnosed on clinical grounds by two independent medical practitioners. Consultations with the treating oncologists ensured specific anti-cancer therapies were not immediately indicated.

People with calculated creatinine clearance <10 mL/minute,[18] severe cirrhosis, or a venting gastrostomy or jejunostomy were excluded. Patients with nasogastric tubes *in situ* were eligible only if they continued to vomit.