

Original Article

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

David C. Currow, FRACP, Stephen Quinn, PhD, Meera Agar, FRACP, Belinda Fazekas, GradDipCommHealth, Janet Hardy, FRACP, Nikki McCaffrey, MSc, Simon Eckermann, PhD, Amy P. Abernethy, MD, and Katherine Clark, FRACP

Discipline, Palliative and Supportive Services (D.C.C., B.F., N.M., A.P.A.) and Flinders Clinical Effectiveness (S.Q., N.M.), Flinders University, Adelaide, South Australia; Sacred Heart Hospice (M.A.), Braeside Hospital, Sydney, New South Wales; Department of Palliative and Supportive Care (J.H.), Mater Health Services, South Brisbane, Queensland; Centre for Health Service Development (S.E.), Australian Health Services Research Institute, University of Wollongong, Wollongong, New South Wales, Australia; Duke University Medical Center (A.P.A.), Durham, North Carolina, USA; and Department of Palliative Care (K.C.), Calvary Mater Newcastle, Newcastle, New South Wales, Australia

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. © 2015 American Academy of Hospice and Palliative Medicine. Published by Elsevier Inc. Open access under [CC BY-NC-ND license](https://creativecommons.org/licenses/by-nc-nd/4.0/).

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

Address correspondence to: David C. Currow, FRACP, Discipline, Palliative and Supportive Services, Health Sciences Building, Repatriation General Hospital, Daws Road,

Daw Park, South Australia 5041, Australia. E-mail: david.currow@flinders.edu.au

Accepted for publication: September 22, 2014.

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 ($n = 15, 17, \text{ and } 68$) 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 ($n = 27, 22, \text{ and } 14$).^{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 anti-cancer 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 anti-cancer 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.

Table 1
Eligibility Criteria for the Phase III Study of Octreotide and Placebo for the Relief of Vomiting in Inoperable Malignant Bowel Obstruction

Inclusion criteria
<ul style="list-style-type: none"> • Age >18 years • Advanced cancer • Disease-modifying therapy (surgery, chemotherapy, radiotherapy, hormone therapy, biological/targeted therapies) is deemed by relevant practitioners unlikely to change the bowel obstruction • Presents with clinically confirmed bowel obstruction at any level with vomiting that precipitates a hospital admission or change in clinical care • Deemed by two consultant-level medical practitioners that this person has a bowel obstruction (partial or complete) for which immediate surgery is not indicated • Participant is capable of completing assessments and complying with the study procedures • Participant is able to give fully informed written consent • Not currently on octreotide
Exclusion criteria
<ul style="list-style-type: none"> • Previous adverse reaction to any of the study medications • Australia-modified Karnofsky Performance Score less than 30 at the beginning of the study • Participants who have participated in a clinical study of a new chemical entity within the month before study entry • Calculated creatinine clearance <10 mL/minute • Documented clinically significant cirrhosis • Venting or feeding gastrostomy or jejunostomy

Intervention: Treatments

This was a pragmatic, multisite, fixed-dose, parallel-arm, double-blind, block-randomized, placebo-controlled trial of the addition of a subcutaneous infusion of octreotide (600 µg/24 hours) compared with standardized therapies (regular parenteral dexamethasone [8 mg/day], ranitidine [200 mg/24 hours], and hydration [10–20 mL/kg/day unless overtly dehydrated at study entry]).^{19,20} Hydration practices differ greatly between participating centers and, in the absence of a gold standard, the study sought to standardize therapy. The “as-needed” therapies for expected symptoms also were standardized in this study: parenteral opioids for pain, hyoscine butylbromide for colicky pain, and haloperidol for nausea.²¹

Randomization and Blinding

Randomization schedules were developed for each site using random number tables, generated centrally. Participants were randomized in blocks of four by site in a 1:1 ratio. Site pharmacists who opened the treatment schedules to prepare the intervention were otherwise not involved in patient care. Syringes were identical in volume and color. No medications could be added to study syringes. Clinical staff, assessors, and participants were all blinded to treatment allocations.

Outcomes

Primary. The number of days free of vomiting as reported daily by patients²² was the primary outcome,

measured 72 hours after the first administration of all study medications.

Secondary. Secondary outcomes included patient-rated Global Impression of Change (GIC) as a summary quality-of-life measure scored between –3 (much worse) and +3 (much better),²³ the number of patient-reported episodes of vomiting, episodes of vomiting per day, survival, nausea (National Cancer Institute Common Toxicity Criteria Adverse Events [NCI CTC AE]),²⁴ the Brief Pain Inventory (BPI),²⁵ functional status (Australia-modified Karnofsky Performance Status [AKPS]) scale,²⁶ and protocol-defined as-needed symptom control medications (hyoscine butylbromide for colicky pain, opioids for pain, haloperidol for nausea) (Table 2). *A priori*, a secondary analysis was done to see whether any clinico-demographic factors helped to predict response to octreotide.

Treatment failure included people with persistent vomiting, insertion of nasogastric tube or venting gastrostomy, or a surgical procedure. Toxicity was prospectively monitored for key symptoms using the NCI CTC AE.²⁴

Statistical Analysis

Power Calculation and Sample Size. There is no established gold standard for assessing the outcomes of treatment of malignant bowel obstruction.²⁷ The number of days free of vomiting is an objective, patient-centered measure. A minimally significant difference in days free of vomiting between arms was, *a priori*, set at 17% to power the study, reflecting consideration of what would be required to demonstrate net benefit of octreotide.²⁸ Sample size was based on the Mann-Whitney U test. A total of 92 participants (46 each arm) provided 80% power at a

Table 2
Symptom Control Measures During the Study

Pain
Hyoscine butylbromide (Buscopan®) 20 mg bolus subcutaneously each hour could be administered at the discretion of the treating clinician for colicky or uncontrolled pain up to maximum of 120 mg/24 hours.
If necessary, an opioid may be administered according to local protocol for pain unrelieved by hyoscine butylbromide
Nausea
Uncontrolled nausea should be treated with haloperidol as the medication of choice according to local protocols.
Metoclopramide and domperidone are to be avoided. 5HT ₃ antagonists may be considered.
Vomiting
Uncontrolled vomiting is treated with
1. Push doses of hyoscine butylbromide up to 120 mg/24 hours by infusion or repeated bolus subcutaneously.
2. Insertion of a nasogastric tube to decompress the upper gastrointestinal tract may be an option. This will be regarded as a treatment failure for study outcomes.
3. A trial of metoclopramide may be considered if it is part of a local protocol, with close supervision of the site investigator

two-tailed type 1 error of 0.05 to detect a deviation in δ of 0.17 from both groups having the same number of days free of vomiting.

Analysis. The primary analysis was undertaken on an intention-to-treat basis. Missing data were imputed using standard multiple imputation techniques with 20 resamples drawn.²⁹ Proportions were compared using Pearson chi-square, and means were compared using t-tests or Mann-Whitney U tests, as appropriate. The presence or absence and the number of episodes of vomiting for each patient over the study were analyzed using logistic and negative binomial regression, respectively, adjusting for baseline characteristics: oral intake, opioid dose, body mass index, age, gender, and level of bowel obstruction (gastric/gastric outlet, small bowel/multi-level, large bowel). Longitudinal analyses also were conducted using generalized estimating equations with robust standard errors and the appropriate link and distribution. All longitudinal models were adjusted for day, study arm, the product term *study arm by day*, gender, and age. Nausea was modeled as an exponential distribution in two stages. For those subjects experiencing nausea, intensity was modeled with errors following a gamma distribution with a log link. The presence or absence of nausea was then modeled using a log link and binomial errors. Both models included average pain as a covariate. The use of hyoscine butylbromide also was modeled using logistic regression, adjusting for

average pain and background opioid use. Pain was treated as a continuous variable, and change in pain over time was evaluated using a model with Gaussian errors and an identity link. GIC as the summary quality-of-life measure was treated as an ordinal variable and analyzed using ordinal logistic regression with robust standard errors and clustering over individuals. There was no evidence of violation of the proportional odds assumption (using Stata's *omodel* command). Survival between groups was assessed using Cox proportional hazards modeling, adjusting for age, gender, and AKPS scale. A check of the proportional hazards assumption revealed no model violation.

All results are reported as ratios (octreotide:placebo): odds ratio (OR), incidence rate ratio (IRR), or hazards ratio (HR) with 95% CIs. A *P*-value less than 0.05 (two-tailed) was accepted as statistically significant. All analyses were conducted using Stata 12.1 (StataCorp LP, College Station, TX).

Results

The CONSORT participant flow is outlined in Figure 1. The study recruited to its intended cohort (Table 3). No person required dose adjustment for renal failure. Sixty-four people provided advanced consent; of whom, 21 were randomized. No participant had his/her therapy unblinded. Six participants

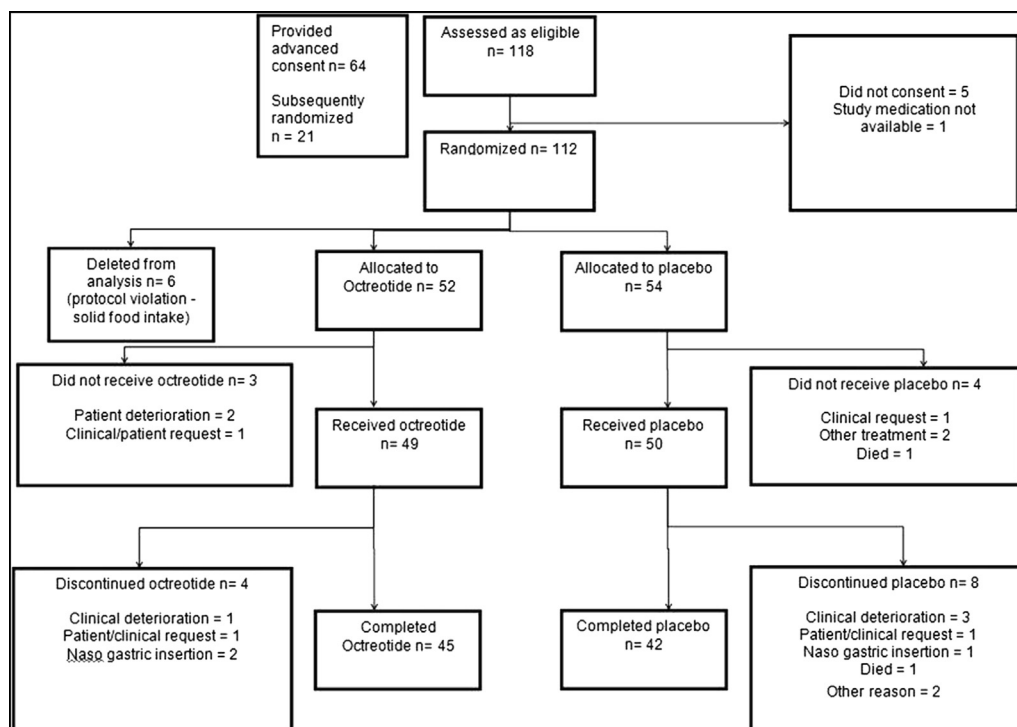


Fig. 1. CONSORT participant flow diagram.

Table 3
Baseline Characteristics of Study Participants

Baseline Characteristics	Octreotide	Placebo
Age (yrs), mean (SD)	62.9 (13.6)	66.3 (12.2)
Gender (female), n/N (%)	47/52 (90.4)	38/54 (70.4)
Body mass index, mean (SD)	24.0 (5.9)	24.8 (6.4)
Functional status, ^a median (interquartile range)	50 (40–60)	50 (40–60)
Pain score, ^b median (LQ–UQ)	3 (1–5)	4 (1.5–5)
Nausea, ^c median (LQ–UQ)	2 (1–2)	1 (1–2)
Level of bowel obstruction		
Gastric outlet/duodenal	9	5
Small bowel/multi-level	34	34
Large bowel	3	2
Indeterminate	8	11

LQ = lower quartile; UQ = upper quartile.

^aMeasured using the Australia-modified Karnofsky Performance Status Scale.

^bMeasured using the Brief Pain Inventory numerical rating scale (0–10) where 0 represents “no pain” and 10 indicates “pain as bad as you can imagine.”

^cMeasured using a numerical rating scale (0–10) where 0 represents no symptom and 10 represents worse possible symptom.

were removed from the analysis because of serious protocol violations (continued intake of solid food at randomization).

Primary Outcome

We recorded data at the end of Days 1, 2, and 3 on 50, 46, and 42 and 49, 47, and 45 subjects in the placebo and octreotide arms, respectively (Fig. 1). For the primary outcome, there was no statistically significant difference in the 1) number of days free of vomiting between groups ($P = 0.71$; Fig. 2) and 2) total number of people free of vomiting for all 72 hours (octreotide, $n = 17$ and placebo, $n = 14$; $P = 0.67$) and mean (SD) number of days free of vomiting in each group (1.87 [1.10], octreotide and 1.69 [1.15], placebo; $P = 0.47$). No Grade 3 or 4 toxicities occurred.

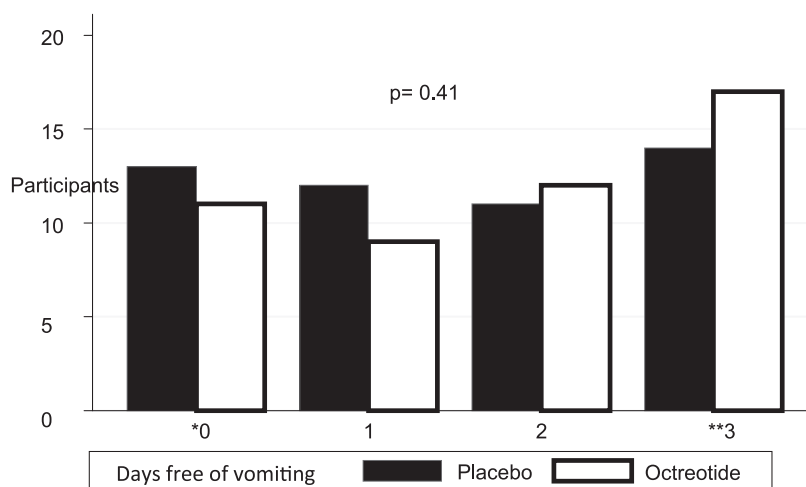


Fig. 2. Number of days free of vomiting between groups. P -value for difference in medians from the Mann-Whitney U test. *Any people in these columns had vomiting on each of the three days of the study. **Any people in these columns had no vomiting during the study.

Secondary Outcomes

Both groups demonstrated a significant drop in the mean unadjusted number of vomiting episodes between baseline and Day 1 (Fig. 3). An adjusted multivariate regression analysis of the incidence of vomiting over the duration of the study showed that the octreotide group experienced a reduction in the number of episodes of vomiting compared with the placebo group (IRR = 0.40; 95% CI: 0.19–0.86; $P = 0.019$).

At 72 hours, 31 of 42 (74%, octreotide) and 31 of 37 (84%, placebo) rated their GIC >0. Both groups were likely to report a positive daily change in outlook (OR = 1.8; 95% CI: 1.39–2.36; $P < 0.001$), but there was no difference between the groups ($P > 0.75$). Neither the presence of nausea ($P = 0.37$) nor the intensity of nausea (numerical rating scale; $P > 0.36$) was different between groups on any day. Average baseline pain scores in both groups were 5.7 on the BPI, with no difference in pain between groups on any day. Both groups experienced slight reductions in daily pain scores (approximately 0.25 points). There was no difference in survival between groups at last census date (HR = 1.24; 95% CI: 0.81–1.92; $P = 0.33$).

Compared with placebo, people in the octreotide arm were 2.02 times more likely to be administered hyoscine butylbromide each day ($P = 0.004$). By study end, the OR between groups rose to 3.24 (95% CI: 1.06–9.96; $P = 0.041$). The average number of doses/participant/group at study end was 0.51 (octreotide) and 0.17 (placebo).

No clinico-demographic factors identified characteristics of people more likely to have a clinical response to octreotide in the symptomatic treatment of vomiting secondary to bowel obstruction from cancer or its treatments.

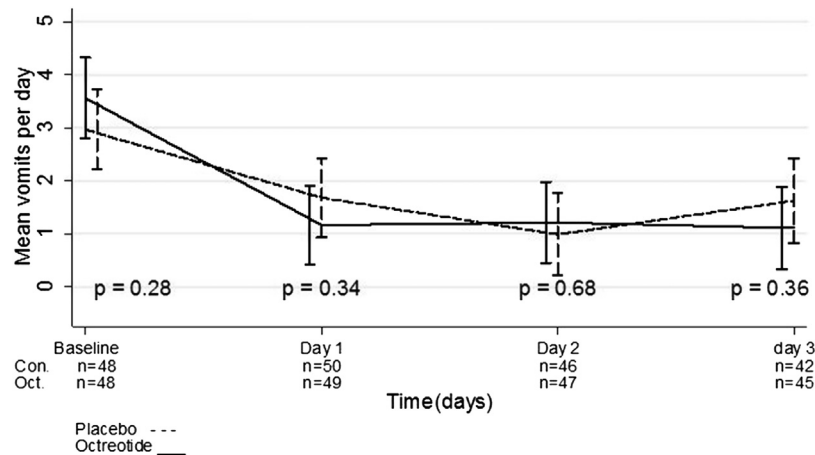


Fig. 3. Mean unadjusted number of vomiting episodes between baseline and Day 1. *P*-value for difference between groups and error bars are 95% CI.

Treatment Failure

After randomization, 19 participants did not complete the study: seven before medications were administered (octreotide $n = 3$; placebo $n = 4$) and 12 after (octreotide $n = 4$; placebo $n = 8$). No withdrawal was the result of toxicity (Fig. 1). None of the participants had surgery or a venting gastrostomy inserted. Three people required a nasogastric tube (octreotide $n = 2$; placebo $n = 1$).

Discussion

This rigorously designed and adequately powered study is the largest trial of somatostatin analogues completed internationally to date for this indication, having recruited to its planned cohort. The study standardized all therapies for both arms (with the exception of octreotide or normal saline) from currently available evidence and was conducted across a range of clinical settings (inpatient, consultative, and community), reflecting hospice/palliative care/oncology practices. The number of days free of vomiting is an objective, patient-centered primary outcome.

For a population presenting with vomiting, with no further anti-cancer treatment immediately indicated and an inoperable bowel obstruction, there was no statistically significant benefit in adding octreotide to standardized therapies on days free of vomiting, nausea, or pain. Other secondary outcomes (presence/absence and incidence of vomiting daily; number of episodes of vomiting) were not significantly different between groups and confirmed the magnitude and direction of the primary findings, but the study was not powered for secondary end points. Planned analyses found no obvious subgroup of participants who predictably responded to octreotide on which to focus future research. These findings are in

keeping with two of the three largest studies of somatostatin analogues to date.^{10,11,14}

Octreotide was well tolerated. There may have been more colicky pain, greater severity, or both in the octreotide group, given greater use of hyoscine butylbromide for colicky pain. This may be a result of reduced transit times from the stomach to cecum with octreotide, given that most people had small bowel involved in their obstruction.³⁰ Hisanaga et al.³¹ noted in a prospective study of 46 similar patients that only two symptoms did not improve on octreotide: the number of vomiting episodes and abdominal pain in the first four days of treatment. Mystakidou et al.¹⁴ also reported no change in pain at Days 3 and 6.

The use of a placebo arm is important as it reflects the effects of the standardized therapies received in both arms and isolates the specific additional benefits of octreotide in this clinical setting, given that in some people, bowel obstruction resolves spontaneously with conservative measures.^{1,32} Studies without a control arm using symptom control as the primary outcome are unreliable in defining the net benefit of an intervention.³³

Octreotide is relatively expensive (A\$82 daily) at this dose. This cost needs to be considered against the net clinical benefit from its use.³⁴ Treatment cost differentials were considered when choosing the minimum clinically meaningful difference in this study. The findings suggest no incremental value from octreotide.

Strengths

This study standardized supportive care in both arms using the best available evidence and then randomized to the intervention or placebo. The study was conducted across a range of clinical practices reflecting the patients seen in hospice/palliative care/oncology settings, enhancing external validity. The

primary outcome, days free of vomiting, is an objective, patient-centered measure reflecting the needs of people at the end of life. The chosen dose of octreotide was consistent with that of the other controlled trials.^{10–14,31} Secondary measures also reflect patient-centered outcomes—vomiting, nausea, and pain. Symptom scores were collected by actively seeking participant responses using standardized instruments validated in this patient population. Missing data and attrition rates were relatively low for a study in such a frail population.

Limitations

Other studies have followed people longer than the 72 hour primary census point in this present study. Choosing a period long enough to be meaningful and short enough to optimize participant retention is a key balance in hospice/palliative care studies.¹⁷ Benefit from a medication to reduce vomiting should be seen within three days, even if maximal benefit takes longer. Whether higher doses of octreotide have greater benefit could be explored in future work, but the chosen dose was double the dose used in two of the three studies available at the time of design and the same as the dose in the third study.^{12–14}

The conservative intention-to-treat analysis is supported by the secondary analyses exploring the presence/absence and incidence of vomiting daily and the number of episodes of vomiting during the study, which confirmed the primary findings in direction and magnitude.

Implications for Clinical Practice

This study does not support the routine use of octreotide in addition to ranitidine and dexamethasone for the symptomatic treatment of inoperable malignant bowel obstruction. There may be benefit in subpopulations, but their characteristics were not evident from attempts to identify such populations across the patients recruited in this study. Octreotide was well tolerated, but the higher likelihood of hyoscine butylbromide administration for colicky pain suggests that there may be a symptomatic burden from octreotide in some patients.

Future Research Directions

A key question is the relative contribution of dexamethasone and ranitidine to any change seen in vomiting. This needs to be elucidated in future studies.

This study also opens the way to future work including formal evaluation of ranitidine or dexamethasone or both or neither in this clinical setting and recruitment of an enriched cohort where a combination of ranitidine and dexamethasone has failed to control vomiting at 72 hours. The choice between

octreotide or a newer somatostatin analogue such as pasireotide needs to be carefully considered in future studies, given that the effect on the volume of upper gastrointestinal secretions or gut motility may differ between both compounds. A better understanding of the characteristics of people most likely to respond symptomatically to a somatostatin analogue also is an important outcome of future controlled clinical trials.

Disclosures and Acknowledgments

This study was funded by the Australian Government's Department of Health under the National Palliative Care Strategy. The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. All authors declare no conflicts of interest.

The authors thank all the patients who willingly participated in this study at a very difficult time in their lives and to the research officers and coordinators for their invaluable work. The nursing, pharmacy, and medical teams at each site provided invaluable support.

References

1. Tuca A, Guell E, Martinez-Losada E, Codorniu N. Malignant bowel obstruction in advanced cancer patients: epidemiology, management, and factors influencing spontaneous resolution. *Cancer Manag Res* 2012;4:159–169.
2. Mercadante S, Spoldi E, Caraceni A, Maddaloni S, Simonetti MT. Octreotide in relieving gastrointestinal symptoms due to bowel obstruction. *Palliat Med* 1993;7:295–299.
3. Henry JC, Pouly S, Sullivan R, Sharif S, Klemanski D. A scoring system for the prognosis and treatment of malignant bowel obstruction. *Surgery* 2012;152:747–756; discussion 756–757.
4. Kucukmetin A, Naik R, Galaal K, Bryant A, Dickinson HO. Palliative surgery versus medical management for bowel obstruction in ovarian cancer. *Cochrane Database Syst Rev* 2010;CD007792.
5. Feuer DJ, Broadley KE, Shepherd JH, Barton DP. Surgery for the resolution of symptoms in malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. *Cochrane Database Syst Rev* 2000;CD002764.
6. Feuer DJ, Broadley KE. Corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. *Cochrane Database Syst Rev* 2000;CD001219.
7. Murakami H, Matsumoto H, Nakamusa M, Hirai T, Yamauchi Y. Octreotide acetate-steroid combination therapy for malignant gastrointestinal obstruction. *Anticancer Res* 2013;33:5557–5560.
8. Clark K, Lam L, Currow D. Reducing gastric secretions—a role for histamine 2 antagonists or proton pump inhibitors in malignant bowel obstruction? *Support Care Cancer* 2009;17:1463–1468.

9. Gyr KE, Meier R. Pharmacodynamic effects of Sandostatin in the gastrointestinal tract. *Metabolism* 1992;41(Suppl 2):17–21.
10. Mariani P, Blumberg J, Landau A, et al. Symptomatic treatment with lanreotide microparticles in inoperable bowel obstruction resulting from peritoneal carcinomatosis: a randomized, double-blind, placebo-controlled phase III study. *J Clin Oncol* 2012;30:4337–4343.
11. Laval G, Rousselot H, Toussaint-Martel S, et al. SALTO: a randomized, multicenter study assessing octreotide LAR in inoperable bowel obstruction. *Bull Cancer* 2012;99:E1–E9.
12. Mercadante S, Ripamonti C, Casuccio A, Zecca E, Groff L. Comparison of octreotide and hyoscine butylbromide in controlling gastrointestinal symptoms due to malignant inoperable bowel obstruction. *Support Care Cancer* 2000;8:188–191.
13. Ripamonti C, Mercadante S, Groff L, et al. Role of octreotide, scopolamine butylbromide, and hydration in symptom control of patients with inoperable bowel obstruction and nasogastric tubes: a prospective randomized trial. *J Pain Symptom Manage* 2000;19:23–34.
14. Mystakidou K, Tsilika E, Kalaidopoulou O, et al. Comparison of octreotide administration vs conservative treatment in the management of inoperable bowel obstruction in patients with far advanced cancer: a randomized, double-blind, controlled clinical trial. *Anticancer Res* 2002;22:1187–1192.
15. Kubota H, Taguchi K, Kobayashi D, et al. Clinical impact of palliative treatment using octreotide for inoperable malignant bowel obstruction caused by advanced urological cancer. *Asian Pac J Cancer Prev* 2013;14:7107–7110.
16. Watari H, Hosaka M, Wakui Y, et al. A prospective study on the efficacy of octreotide in the management of malignant bowel obstruction in gynecologic cancer. *Int J Gynecol Cancer* 2012;22:692–696.
17. Bellavance EC, Alexander HR Jr. Palliative interventions in patients with peritoneal metastases and malignant bowel obstruction. *J Clin Oncol* 2012;30:4290–4291.
18. Vervoort G, Willems HL, Wetzels JF. Assessment of glomerular filtration rate in healthy subjects and normoalbuminuric diabetic patients: validity of a new (MDRD) prediction equation. *Nephrol Dial Transplant* 2002;17:1909–1913.
19. Ripamonti CI, Easson AM, Gerdes H. Management of malignant bowel obstruction. *Eur J Cancer* 2008;44:1105–1115.
20. Steiner N, Bruera E. Methods of hydration in palliative care patients. *J Palliat Care* 1998;14:6–13.
21. Nakajima N, Hata Y, Kusumoto K. A clinical study on the influence of hydration volume on the signs of terminally ill cancer patients with abdominal malignancies. *J Palliat Med* 2013;16:185–189.
22. Olver IN, Matthews JP, Bishop JF, Smith RA. The roles of patient and observer assessments in anti-emetic trials. *Eur J Cancer* 1994;30:1223–1227.
23. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain* 2001;94:149–158.
24. National Cancer Institute. Cancer therapy evaluation program. Common terminology for adverse events V3.0. Available at: http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm. Accessed April 10, 2013.
25. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore* 1994;23:129–138.
26. Abernethy AP, Shelby-James T, Fazekas BS, Woods D, Currow DC. The Australia-modified Karnofsky Performance Status (AKPS) scale: a revised scale for contemporary palliative care clinical practice [ISRCTN81117481]. *BMC Palliat Care* 2005;4:7.
27. Saxby C, Ackroyd R, Callin S, Mayland C, Kite S. How should we measure emesis in palliative care? *Palliat Med* 2007;21:369–383.
28. Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR, Clinical Significance Meeting Group. Methods to explain the clinical significance of health status measures. *Mayo Clin Proc* 2002;77:371–383.
29. Schafer JL. Multiple imputation: a primer. *Stat Methods Med Res* 1999;8:3–15.
30. Londong W, Angerer M, Kutz K, Landgraf R, Londong V. Diminishing efficacy of octreotide (SMS 201-995) on gastric functions of healthy subjects during one-week administration. *Gastroenterology* 1989;96:713–722.
31. Hisanaga T, Shinjo T, Morita T, et al. Multicenter prospective study on efficacy and safety of octreotide for inoperable malignant bowel obstruction. *Jpn J Clin Oncol* 2010;40:739–745.
32. Sanderson C, Hardy J, Spruyt O, Currow DC. Placebo and nocebo effects in randomized controlled trials: the implications for research and practice. *J Pain Symptom Manage* 2013;46:722–730.
33. Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ* 1998;17:1185–1190.
34. Stinnett AA, Mullahy J. Net health benefits: a new framework for the analysis of uncertainty in cost-effectiveness analysis. *Med Decis Making* 1998;18:S68–S80.