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Double-blind, placebo-controlled, randomised trial of octreotide in malignant bowel obstruction

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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 (600mcg/24hours by infusion). Both arms received standardized supportive therapy (infusion of ranitidine [200mg/24hours], dexamethasone [8mg/24hours] and parenteral hydration [10-20mls/kg/24hours]). 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 multivariable regression of the incidence of vomiting over the study showed a reduced number of episodes of vomiting in the octreotide group (IRR = 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 multivariable analysis suggests that further study of somatostatin analogues in this setting is warranted.

Keywords

double, blind, placebo, controlled, randomised, trial, octreotide, malignant, bowel, obstruction

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

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Conclusion. Although there was no reduction in the number of days free of vomiting, the multivariable analysis suggests that further study of somatostatin analogues in this setting is warranted.

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Key Words: malignant bowel obstruction, palliative care, octreotide, randomized controlled trial, net clinical benefit, vomiting

Running Title: Octreotide for Vomiting in Bowel Obstruction

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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 include: carcinomatosis; ascites; complete small bowel obstruction; hypoalbuminemia; and leukocytosis [3]. Therapies such as continuous nasogastric suction and intravenous 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 anti-spasmodics for colicky pain) [1].

There is no 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 AU: OF THE PRESENT STUDY? 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 300mcg/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 gynecological and urological 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 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 (DSMC) 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 prior to first recruitment (ACTRN12608000211369).

Study Setting

The study was conducted in twelve 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 <10mls / 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.

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 (600mcg / 24 hours) compared with standardized therapies (regular parenteral dexamethasone [8mg/day], ranitidine [200mg/24hours] and hydration [10-20mls/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.

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 by patients daily,[22] 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) to +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 scale (AKPS) [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 if 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]. *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 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(1) with 20 resamples drawn [28]. 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* evaluated using a model with Gaussian errors and an identity link. Global Impression of Change (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. A check of the proportional hazards assumption revealed no model violation.

All results are reported as ratios (octreotide: placebo): odds (OR); incidence rate (IRR); or hazards (HR) with 95% confidence intervals (CI). 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 Fig. 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 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, 42 and 49, 47, 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); 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.

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 multivariable regression analysis of the incidence of vomiting over the duration of the study showed 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 groups ($P>0.75$). Neither the presence of nausea ($P=0.37$) nor the intensity of nausea (numerical rating scale (NRS); $P>0.36$) were different between groups any day. Average baseline pain scores in both groups were 5.7 on the BPI, with no difference in pain between groups 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; $P=0·041$). 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.

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. (Figure 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. 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 the majority of people had small bowel involved in their obstruction [30], Hisanga et al. 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 [31]. Mystakidou also reported no change in pain at days three and six [14].

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 (AU$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 current study. Choosing a time 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 is also an important outcome of future controlled clinical trials.

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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

- 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

- 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 prior to study entry
- calculated creatinine clearance <10ml/min
- documented clinically significant cirrhosis
- venting or feeding gastrostomy or jejunostomy

Table 2. Symptom Control Measures During the Study

Pain

Hyoscine butylbromide (Buscopan®) 20mg bolus subcutaneously each hour could be administered at the discretion of the treating clinician for colicky or uncontrolled pain up to maximum of 120mg per 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 120mg per 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 metoclopromide may considered if it is part of a local protocol, with close supervision of the site investigator

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

[a] Measured using the Australia-modified Karnofsky Performance Status Scale.

[b] Measured 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."

[c] Measured using a numerical rating scale (0-10) where 0 represents no symptom and 10 represents worse possible symptom.

AU: PLS DEFINE LQ AND UQ

Figure Legends

Fig. 1. CONSORT participant flow diagram.

Fig. 2. Number of days free of vomiting between groups.

Fig. 3. Mean unadjusted number of vomiting episodes between baseline and day 1.

Figure 1

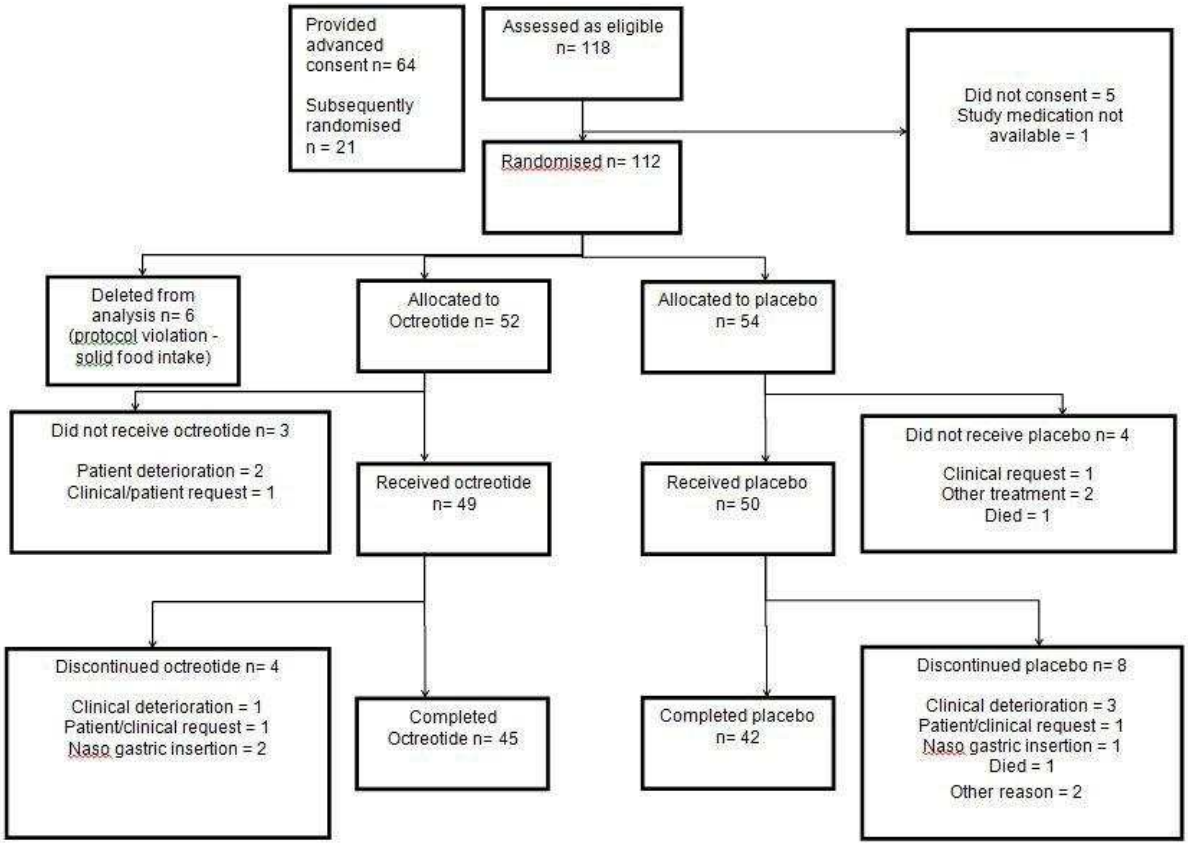
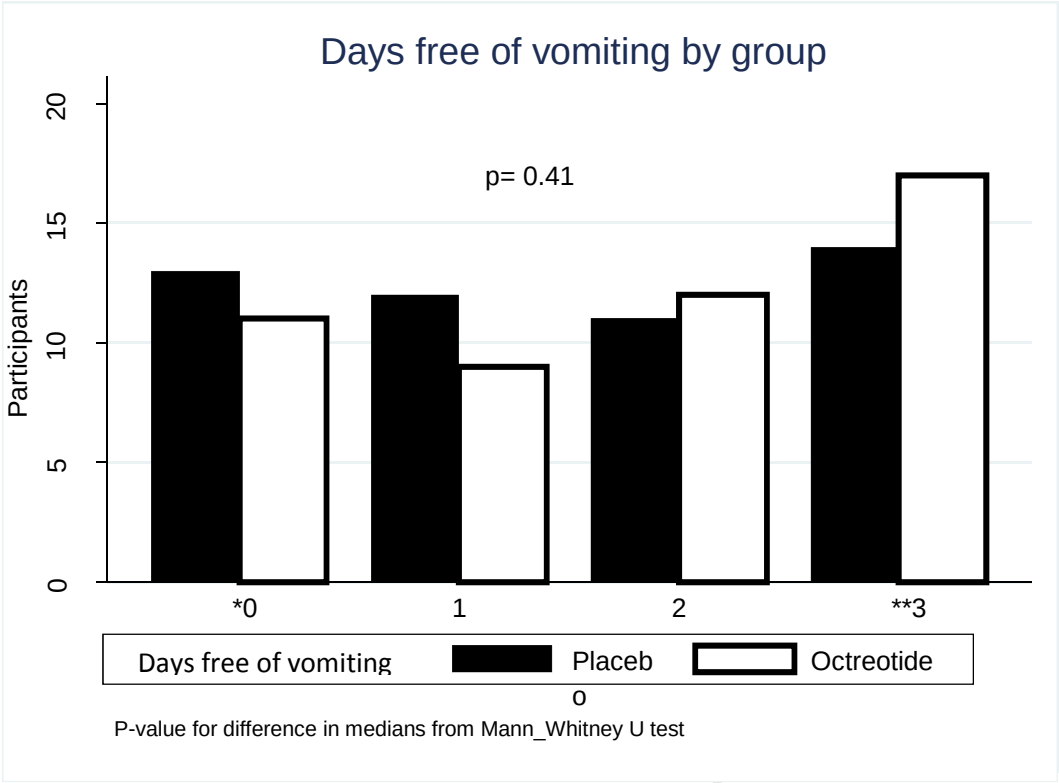


Figure 2



* 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

Figure 3