Managing malignant bowel obstruction

Professor David Currow

ImPACCT (Improving Palliative, Aged and Chronic Care through Clinical Trials and Translation)

Faculty of Health,

University of Technology Sydney

New South Wales, Australia

Managing malignant bowel obstruction

1. Clinical trials in palliative care

2. Surgical approaches to malignant bowel obstruction

3. Symptom control for inoperable malignant bowel obstruction

Managing malignant bowel obstruction

1. Clinical trials in palliative care

2. Surgical approaches to malignant bowel obstruction

3. Symptom control for inoperable malignant bowel obstruction

PaCCSC
Palliative Care Clinical Studies Collaborative

Improving the evidence base for clinical practice in palliative care

- Our clinical work demands that we continue to evaluate the net effect of our interventions on the people that we serve in the most rigorous ways available.
- This is the frailest clinical population and we must balance harms and benefits

PaCCSC
Palliative Care Clinical Studies Collaborative

Non-randomised versus randomised controlled clinical trial exploring the same question

Differences may range from a 90% underestimate of effect to a 150% overestimate mostly with wider confidence intervals .

Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. BMJ. 1998 Oct 31;317(7167):1185-90.

Improving the evidence base for clinical practice in palliative care

So today's fundamental questions are:

1. **What is the natural history of inoperable bowel obstruction due to cancer or its treatments (malignant bowel obstruction)?**
2. **Do any of our interventions cause harms?**

PaCCSC
Palliative Care Clinical Studies Collaborative

Improving the evidence base for clinical practice in palliative care

Given that there is no subjective component to the assessment of malignant bowel obstruction for vomiting or naso-gastric tube secretion volumes, there is no 'placebo effect'. *The placebo arm of any such study defines the natural history of the condition.*

Bowel obstruction

- Operable bowel obstruction – single point or adhesions, volvulus
- Inoperable bowel obstruction
  - multi-level disease
  - people who could not tolerate the catabolic insult of surgery even if minimally invasive
  - Both

  - Non-surgical options are limited
  - No registered standard pharmacological therapy

Bowel obstruction

- Identifiable groups at higher risk
- People with
  - documented intra-peritoneal disease
  - previous bowel obstruction

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Epidemiology of bowel obstruction

- Incidence and prevalence increase with more advanced disease

- Rates vary widely with differing diagnoses. Overall estimates are that 3%-15% of people with advanced cancer will have a bowel obstruction at some time in their clinical care.

- Median prognosis 1-9 months

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Epidemiology of bowel obstruction

	surgery (n=324)	non-surgical care (n=199)
Mean (days)	331	174
30 day mortality	26.7%	36.6%
Return to oral intake	80.1%	80.3%
Re-obstruction rate	17.9%	35.2%
Time to re-obstruct	36	223
Length of stay	8.4	15.6

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Prognosis with cancer-related bowel obstruction

Predictors of 30 day mortality (n=523)

Clinically: carcinomatosis

ascites

complete small bowel obstruction

Laboratory values:

hypoalbuminaemia

leucocytosis

Henry JC et al.
Surgery 2012

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Prognosis with cancer-related bowel obstruction

Predictors of 30 day mortality (n=523: 30% of presentations have ≥3/5 factors at presentation)

Scores	0 - 9.1% dead by 30 days
	1 - 14.9%
	2 - 21.9%
	3 - 38.8%
	4 - 42.9%
	5 - 69.2%

Henry JC et al.
Surgery 2012

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Predictors of return to oral intake by discharge

Radiographic evidence of large bowel obstruction (OR 4.97; 95%CI 1.3, 21.9)

Henry JC et al.
Surgery 2012

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

		Number of levels of obstruction	
		single	multiple
Functional Status	good	surgery	medical management
	poor	minimally invasive surgery / stenting	medical management

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Functional Status	Number of levels of obstruction: single	multiple
good	surgery	medical management
poor	minimally invasive surgery / stenting	medical management

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Functional Status	Number of levels of obstruction: single	multiple
good	surgery	medical management
poor	minimally invasive surgery / stenting	medical management

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

		Number of levels of obstruction	
		single	multiple
Functional Status	good	surgery	medical management
	poor	minimally invasive surgery / stenting	medical management

Managing malignant bowel obstruction

1. Clinical trials in palliative care

2. Surgical approaches to malignant bowel obstruction

3. Symptom control for inoperable malignant bowel obstruction

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Surgery – advanced gynaecological and gastroenterological cancers

Systematic review

poor data on key issues:

- patient characteristics especially for identifying any group more likely to respond

- outcome measures (including toxicities)

- duration of benefit

Feuer DDJ et al. CDSM 2000, 2009

Surgical management of malignant bowel obstruction

- There are marked variations in clinical practice concerning surgery in these patients between different countries, gynaecological oncology units and general clinical teams, as well as referral patterns from oncologists under whom these patients are often admitted.

- To assess the efficacy of surgery for intestinal obstruction due to advanced gynaecological and gastrointestinal cancer.

Feuer DDJ et al. CDSM 2000, 2009, 2016

.

Surgical management of malignant bowel obstruction

- **SEARCH METHODS:**
- Up to June 2015:
- **SELECTION CRITERIA:**
- Prospective and retrospective studies
- Advanced gynaecological and gastrointestinal cancers
- Published trials reporting on the effects of surgery for resolving symptoms in malignant bowel obstruction in adults

Feuer DDJ et al. CDSM 2000, 2009, 2016

Surgical management of malignant bowel obstruction

RESULTS:

- 43 studies examining 4265 participants (up from 938 patients from 25 studies in 2000).
- No firm conclusions can be drawn from the many retrospective case series so the role of surgery in malignant bowel obstruction remains controversial.

Feuer DDJ et al. CDSM 2000, 2009, 2016

Surgical management of malignant bowel obstruction

RESULTS:

- Clinical resolution varies from 26.7% to over 68%, though it is often unclear how this is defined.
- Success with ability to feed 30% - 100%.
- Rates of re-obstruction 0% - 63% although timeframes were often not cited
- Postoperative morbidity and mortality varied widely
- There were no data available for quality of life.
- Most included studies were at high risk of bias for most domains.

Feuer DDJ et al. CDSM 2000, 2009, 2016

Surgical management of malignant bowel obstruction

RESULTS:

- In order to compare outcomes in malignant bowel obstruction, there needs to be a greater degree of standardisation of management.

- *Since the last version of this review none of the newly included studies have provided additional information to change the conclusions.*

Feuer DDJ et al. CDSM 2000, 2009, 2016

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Surgery – advanced gynaecological cancers

- **Surgical versus medical management**

Systematic review

- **Only one study, and woman with poor function were excluded from surgery, and those with surgery survived longer (although 3/22 died in peri-operative period). No quality of life data were collected.**

Kucukmetin A et al.
CDSM 2010

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Surgery – advanced gynaecological cancers

Surgical versus medical management

Retrospective case note series

- 53 woman. No randomisation. Poorer function in woman who did not get surgery.

- 20 had surgery; one perioperative death; 11 colostomies and 7 ileostomies.

- Median survival 146 days in surgical group compared with 69 days in the women who had medical management.

Goto T et al. Oncol Letters 2012

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Single level, poor function

- new treatments in the last 25 years:
  - minimally invasive surgery
  - stenting
  - somatostatin analogues

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Stenting versus minimally invasive surgery

- Surgery remains the dominant treatment for malignant incurable large-bowel obstruction, with emerging data on self-expanding metallic stents.
- The aim of this study was to compare quality of life and survival when treated with a stent or surgical decompression.

Young CJ et al Dis Colon Rectum 2015;58(9):838-49

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Stenting versus minimally invasive surgery

- **P -** Patients with malignant incurable large-bowel obstruction were randomly assigned to surgical decompression or stent insertion.
- **O -** EuroQOL EQ-5D quality of life.
- Secondary end points: overall survival; 30-day mortality; stoma rates; postoperative recovery; complications; and readmissions.

Young CJ et al Dis Colon Rectum 2015;58(9) :838-49

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Stenting versus minimally invasive surgery

- Fifty-two patients
- Stent insertion was successful in 19 of 26 (73%) patients. The remaining 7 patients required a stoma
- 24 of 26 (92%) surgery group required a stoma ($p < 0.001$).

Young CJ et al Dis Colon Rectum 2015;58(9):838-49

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Stenting versus minimally invasive surgery

- No stent-related perforations or deaths.
- Surgery group had significantly reduced quality of life compared with the stent group from baseline to 1 and 2 weeks ($p = 0.001$ and $p = 0.012$), and from baseline to 12 months ($p = 0.01$)
- Both groups reported reduced quality of life.

Young CJ et al Dis Colon Rectum 2015;58(9):838-49

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Stenting versus minimally invasive surgery

- 30-day mortality: stent 8%; surgery 15% (p = 0.668)
- Median survival: 5.2 and 5.5 months (p = 0.613)
- Stent group: significantly reduced:
  - procedure time (p = 0.014);
  - post-procedure stay (p = 0.027);
  - days nil by mouth (p = 0.002); and
  - days before solids (p = 0.022)

Young CJ et al Dis Colon Rectum 2015;58(9):838-49

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Stenting versus minimally invasive surgery

CONCLUSIONS:

- Stent use in patients with incurable large-bowel obstruction has a number of advantages:
  - faster return to diet;
  - decreased stoma rates;
  - reduced post-procedure stay; and
  - some quality-of-life benefits

Young CJ et al Dis Colon Rectum 2015;58(9):838-49

Managing malignant bowel obstruction

1. Clinical trials in palliative care

2. Surgical approaches to malignant bowel obstruction

3. Symptom control for inoperable malignant bowel obstruction

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Single level, good function

- Exclude non-cancer related causes: adhesions, volvulus

- Is cytoreductive surgery and local or systemic therapy indicated?

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Multi-level obstruction, good function

- A poor prognostic feature, even with relatively good function

- Are there indications for a radical approach to managing this person's disease?

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

- Corticosteroids for resolving malignant bowel obstruction (n=89 patients in RCTs)
- Dexamthasone 6 - 16mg per twenty four hours
- Trend that is not statistically significant towards resolution of bowel obstruction (NNT 6 (3 to infinity))
- No excess mortality at one month in those treated with corticosteroids

Feuer DDJ et al. CDSM 2000, 2008

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Medications to reduce gastrointestinal tract secretions

- 7 studies in a meta-analysis

- H_2 antagonists are more effective than proton pump inhibitors at reducing the volume of gastric secretions

Clark K et al. Anaesthesia 2009;64(6): 652-7

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Multi-level obstruction, poor function

- no head-to-head trials of surgery compared to medical management

- controlled trials to date of somatostatin analogues

PaCCSC
Palliative Care Clinical Studies Collaborative

Management of malignant bowel obstruction

Multi-level obstruction, poor function

Considerations

- hydration
- decompression / suction
- oral intake
- medications to:
  - commence
  - continue
  - cease

Octreotide / lanreotide

- Somatostatin analogues, with lanreotide being a monthly dose
- Different effects on small bowel (decreased transit time) compared to large bowel (markedly increased transit time)
- Theoretical benefit in bowel obstruction
  - reducing secretions
  - reducing the secretion of a number of hormones from the upper gut that may worsen the symptoms of bowel obstruction

Lanreotide and octreotide

- D - double-blind, randomised study for efficacy and safety, parallel group study
- P - peritoneal carcinomatosis and symptoms of inoperable malignant bowel obstruction
- I - lanreotide microparticles 30mg AND 600mcg / day octreotide (n=32 of 51 planned)
- C – placebo (n=32 of 51 planned)
- Both arms methylprednisonolone days 1-6
- O – absence of nasogastric tube, vomiting less than 2x / day, no anticholinergic use
- Intention to treat 38% versus 28%

Laval G et al.
Bull Cancer
2012;99(2):E1-9

Lanreotide

- D - double-blind, parallel group study
- P - two episodes of vomiting and inoperable bowel obstruction. No further anti-neoplastic therapy
- I - lanreotide microparticles 30mg (n=43)
- C - placebo (n=37)
- O - ≥ 3 consecutive days with one or less episodes of vomiting per day after naso-gastric tube removal at day 7 (of 10)
- Intention to treat 42% lanreotide versus 30% placebo (p=0.24)

Mariani P et al. J Clin Oncol 2012;30(35):4337-43

Octreotide in hospice / palliative care

PaCCSC
Palliative Care Clinical Studies Collaborative

Three early randomised controlled trials:

- **Volume of nasogastric tube secretions on days 2,3 when compared to hyoscine butylbromide (n=17)**
- **Vomiting and nausea when compared to hyoscine butylbromide (n=15)**
- **Nausea and vomiting over baseline when compared to chlorpromazine / hyoscine butylbromide (n=68)**

- **Ripamonti C et al. JPSM 2000; Mercadante S et al. Supp Care Canc 2000; Mystakidou K et al. Anticanc Res 2002**

Octreotide vs placebo

- D - double-blind, block randomised, fixed dose, multi-site, parallel arm study

- P - vomiting and inoperable bowel obstruction (including surgical review). No further anti-neoplastic therapy indicated at that time

* Potential participants were able to provide advanced consent if they had experienced a previous bowel obstruction or were at high risk. 63 people gave advanced consent, of whom 21 went on to a bowel obstruction and were randomised.

Currow D et al. J Pain Symptom Manage. 2015;49(5):814-821

Octreotide vs placebo

- I - octreotide 600mcg / 24 hours by infusion (n=46)
- C - placebo (n=46)

- Both arms: ranitidine 200mg / 24 hours; dexamethasone 8 mg / 24 hours; 10-20mls/kg hydration / 24 hours

- Concomitant therapy – cease prokinetic agents
- Standardised breakthrough for:
  - Pain - morphine
  - Colicky pain – hyoscine butylbromide
  - Nausea – haloperidol

Currow D et al. J Pain Symptom Manage. 2015;49(5):814-821

Octreotide vs placebo

- O - days free of vomiting at 72 hours and no nasogastric tube
- Intention to treat 76 vomiting free days octreotide versus 81 placebo (p=0.724)

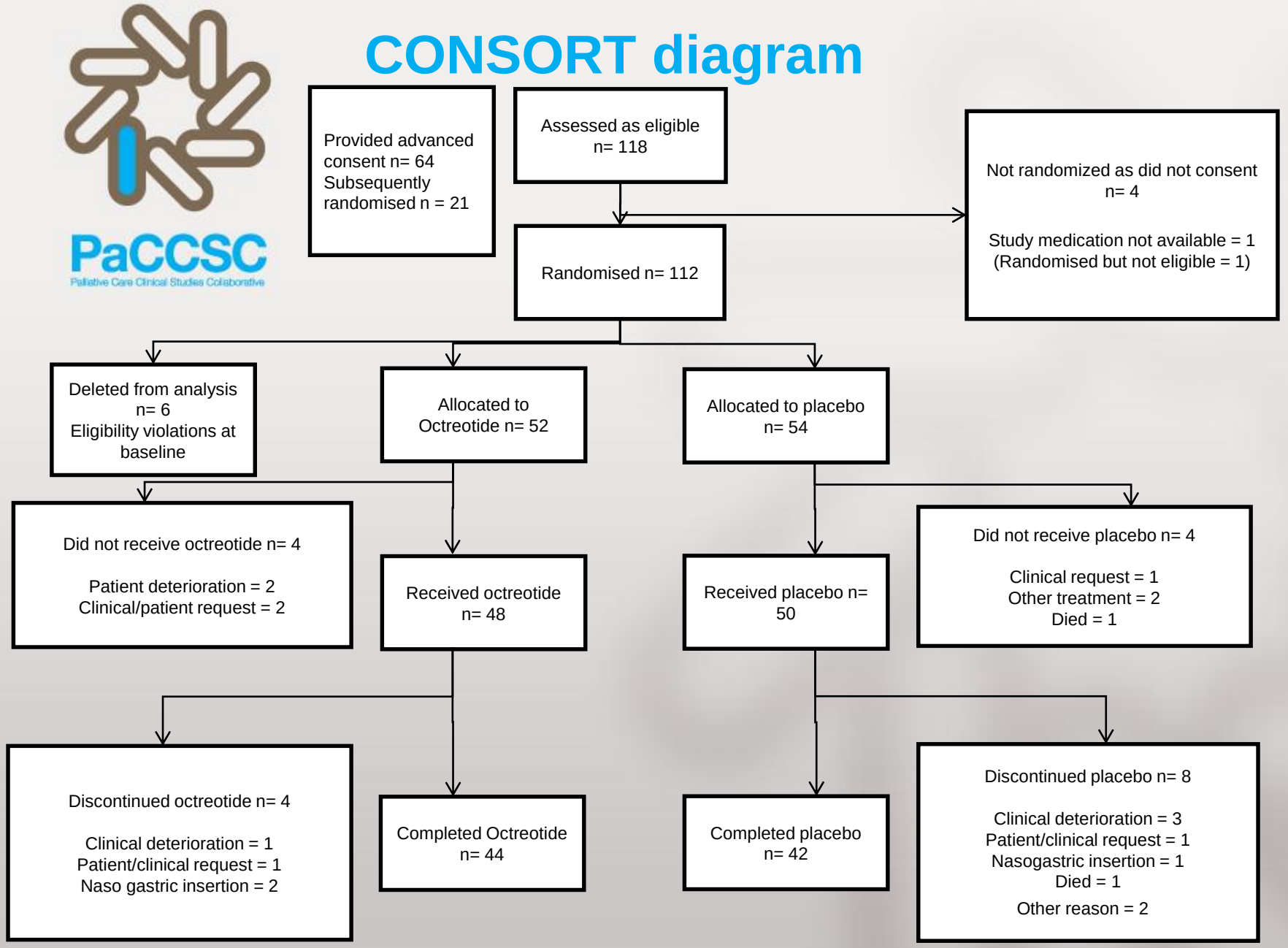
Currow D et al. J Pain Symptom Manage. 2015;49(5):814-821

Octreotide vs placebo

- Significantly greater chance of getting hyoscine butylbromide in the octreotide arm (5.7x by day 3)
- All but four participants had small bowel involvement
- Octreotide's effect on motility
  - Decreased transit time from stomach to caecum
  - Increased time from caecum to rectum

Currow D et al. J Pain Symptom Manage. 2015;49(5):814-821

CONSORT diagram



Octreotide vs placebo – magnitude and direction of differences

- Global impression of change – daily measures – no difference (p=0.96)
- Survival – no difference (p=0.28)
- Number of episodes of vomiting no difference
- Number of episodes of vomiting when controlling for age, gender, body mass index and oral intake, people on octreotide had a 50% reduction in the incidence of vomiting
- Nausea – no difference (tended to decrease in both arms; p=0.63)
- Pain – no difference (p=0.81)

Currow D et al. J Pain Symptom Manage. 2015;49(5):814-821

Octreotide vs placebo

- Unable to differentiate clinically between arms
- Well tolerated interventions
- Increased use of hyoscine butylbromide unexplained
- supports again the feasibility and importance of RCTs in testing clinical therapies
- Ultimately, an adequately powered, negative study
- Sufficient signal to consider further research

Currow D et al. J Pain Symptom Manage. 2015;49(5):814-821

PaCCSC
Palliative Care Clinical Studies Collaborative

Octreotide vs placebo

- D – consecutive case series
- P – 25 patients with MBO, 2 vomiting episodes / day for 2 consecutive days or an NGT
- I – 0.3mg / day octreotide / 6 days
- O -. 11/25 responded (resolution or improvement in nausea or vomiting)
- Colicky pain was one symptom that did not improve during treatment.

Shima Y et al. Jpn J Clin Oncol. 2008;38(5):354-359.

Octreotide vs butylbromide

- Octreotide compared to scopolamine butylbromide (SB) as an anti-secretory medication
- Inoperable malignant bowel obstruction (MBO), advanced ovarian cancer.
- Participants
- 3 day infusion of
  - Octreotide 0.3 mg/day (n=48)
  - Butylbromide 60 mg/day (n=49)
- Outcomes: Likert scales for episodes of vomiting; nausea; dry mouth; drowsiness; and continuous and colicky pain.

Peng X et al. World J Surg Oncol 2015 ;13:50

Octreotide vs butylbromide

- Octreotide significantly reduced the amount of GI secretions at T1, T2, and T3 ($P < 0.05$) compared with SB.
- Nasogastric tube secretions
  - significantly reduced in the octreotide arm at D1, D2, and D3 compared with baseline ($p<0.05$)
  - significantly in butylbromide group only D3 compared with baseline
- Octreotide significantly reduced the number of daily episodes of vomiting and intensity of nausea compared with butylbromide

Peng X et al. World J Surg Oncol 2015 ;13:50

Octreotide vs butylbromide

- Continuous pain values were significantly lower with octreotide than butylbromide D2 and D3 ($p<0.05$)
- No significant changes in colicky pain

Peng X et al. World J Surg Oncol 2015 ;13:50

Somatostatin analogues in malignant bowel obstruction

- Systematic review – December 2016
- Relieving vomiting in malignant bowel obstruction with somatostatin analogues compared to:
  - placebo and/or
  - other pharmacologic agents

- MEDLINE, EMBASE, CINAHL, and The Cochrane Controlled Trials Register databases were systematically searched; reference lists of relevant articles were hand searched. Cochrane risk of bias tool was used.

Obita G et al. J Pain Symptom Manage 2016; 52(6):901-919

Somatostatin analogues in malignant bowel obstruction

- Systematic review – December 2016

RESULTS:

- Seven randomised controlled trials (RCTs) met the inclusion criteria (six octreotide studies and one lanreotide);
- 220 people administered somatostatin analogues and 207 placebo or hyoscine butylbromide.
- A somatostatin analogue was compared with
  - placebo (3 studies); and
  - hyoscine butylbromide (4 studies).

Obita G et al. J Pain Symptom Manage 2016; 52(6):901-919

Somatostatin analogues in malignant bowel obstruction

- Systematic review – December 2016

RESULTS:

- Two adequately powered multi-centre RCTs with a low Cochrane risk of bias reported no significant difference between somatostatin analogues and placebo in their primary end points.
- Four RCTs with a high/unclear Cochrane risk of bias reported that somatostatin analogues were more effective than hyoscine butylbromide in reducing vomiting.

Obita G et al. J Pain Symptom Manage 2016; 52(6):901-919

Somatostatin analogues in malignant bowel obstruction

- Systematic review – December 2016

CONCLUSION:

- High-level evidence from trials with low risk of bias found no benefit of somatostatin analogues for their primary outcome.
- There is low-level evidence of benefit with somatostatin analogues in the symptomatic treatment of MBO.

Obita G et al. J Pain Symptom Manage 2016; 52(6):901-919

Somatostatin analogues in malignant bowel obstruction

- Systematic review – December 2016

CONCLUSION:

- There is debate regarding:
  - the clinically relevant study end point for symptom control in MBO; and
  - when it should be measured.
- The role of somatostatin analogues in this clinical situation requires further adequately powered, well-designed trials with agreed, clinically important end points and measures

Obita G et al. J Pain Symptom Manage 2016; 52(6):901-919

PaCCSC
Palliative Care Clinical Studies Collaborative

Somatostatin analogues

- Unable to differentiate clinically between arms
- Well tolerated interventions
- Increased use of hyoscine butylbromide unexplained
- supports again the feasibility and importance of RCTs in testing clinical therapies
- Ultimately, an adequately powered, negative study
- Sufficient signal to consider further research

Conservative management of malignant bowel obstruction

Limited evidence to date from individual studies or meta-analyses

No definitions of standard therapies

Further key work needs to be done, but finally answering the role of corticosteroids and of H_2 antagonists seems crucial

Managing malignant bowel obstruction

1. Clinical trials in palliative care

2. Surgical approaches to malignant bowel obstruction

3. Symptom control for inoperable malignant bowel obstruction