

Review Article

Medical Treatment for Inoperable Malignant Bowel Obstruction: A Qualitative Systematic Review

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Abstract

The use of symptomatic agents has greatly improved the medical treatment of advanced cancer patients with inoperable bowel obstruction. A systematic review of studies of the most popular drugs used in the medical management of inoperable malignant bowel obstruction was performed to assess the effectiveness of these treatments and provide some lines of evidence. Randomized trials that involved patients with a clinical diagnosis of intestinal obstruction due to advanced cancer treated with these drugs were reviewed. Five reports fulfilled inclusion criteria. Three studies compared octreotide (OC) and hyoscine butylbromide (HB), and two studies compared corticosteroids (CSs) and placebo. Globally, 52 patients received OC, 51 patients received HB, 37 patients received CSs, 15 patients received placebo, and 37 patients received both placebo and CSs. On the basis of these few data, the superiority of OC over HB in relieving gastrointestinal symptoms was evidenced in a total of 103 patients. The latter studies had samples more defined in terms of stage and inoperability, and had a shorter survival in comparison with studies of CSs (less than 61 days, most of them less than 20 days). Data on CSs are less convincing, due to the methodological weakness of existing studies. This review confirms the difficulties in conducting randomized controlled trials in this population. J Pain Symptom Manage 2007;33:217–223. © 2007 U.S. Cancer Pain Relief Committee. Published by Elsevier Inc. All rights reserved.

Key Words

Cancer, bowel obstruction, corticosteroids, octreotide, hyoscine butylbromide

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Introduction

Bowel obstruction is a well-recognized complication in advanced cancer patients with abdominal or pelvic malignancy. Although it may develop at any time of the disease, it more frequently occurs in the advanced stage, with the highest incidence ranging from 5.5% to 42% in ovarian carcinoma, and from 4.4% to 24% in colorectal cancer.¹ These figures may underestimate the problem, as they derive

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from selected groups of patients. In several surveys, it was found that 3% of advanced cancer patients had intestinal obstruction, although bowel obstruction has been also reported to occur in up to 15% of patients.¹⁻³ These discrepancies may be attributable to the admission criteria of the palliative care units, which may admit only patients with severe physical and psychosocial distress, or patients in an advanced stage of disease.³

Most advanced cancer patients are inoperable. If surgery is not appropriate or possible, survival prognosis is generally poor. Although the onset of malignant obstruction means a short prognosis, the distressing gastrointestinal symptoms can be relieved.⁴

The introduction of new symptomatic agents has greatly improved the symptom management of such advanced cancer patients. Corticosteroids (CSs) have been advocated to reduce peritumoral inflammatory edema and improve intestinal transit, inducing both temporary symptom relief and reduction in obstruction. Moreover, they are able to reduce water and salt secretion in the lumen, and thereby act as antisecretive agents. As CSs are relatively inexpensive and well tolerated, this class of drugs has been largely used in the palliative care setting for relieving gastrointestinal symptoms or resolving obstruction.⁵

Anticholinergics also have been traditionally used as antisecretive drugs in combination with analgesics and antiemetics, due to the competitive inhibition of muscarinic receptors at the smooth muscle level, resulting in an impairment of ganglionic neural transmission in the bowel wall. Hyoscine butylbromide (HB), hyoscine hydrobromide, and glycopyrrolate have been commonly used.

Although HB has been the first drug used in the medical treatment of inoperable bowel obstruction as an antisecretive drug,⁶ in the last decade, somatostatin analogs, and particularly octreotide (OC), have been increasingly used to relieve gastrointestinal symptoms in advanced cancer patients with inoperable malignant bowel obstruction. OC affects gastrointestinal function by reducing gastric and intestinal secretion and bile flow by complex endocrine mechanisms.⁷

The aim of this study was to systematically review the studies of the most popular drugs used in the medical management of

inoperable malignant bowel obstruction in attempt to evaluate the effectiveness and provide some lines of evidence.

Methods

Both published and unpublished reports were sought from an extensive search of electronic databases, including MEDLINE, PubMed, CancerLit, and Embase. A free-text search method was used, including the following words and their combinations: "intestinal or bowel obstruction" and/or "corticosteroids" or "steroids" and/or "octreotide," and/or "hyoscine butylbromide." Hand searching of relevant journals, and European conference proceedings were also considered. The references of all relevant reports and review articles were searched for additional trials. Any randomized trial that involved patients with a clinical diagnosis of intestinal obstruction due to advanced cancer treated with these drugs was considered. The quality of all the research found was graded using criteria previously reported.⁸

Results

Five reports fulfilled inclusion criteria in this systematic review (Table 1). A total of 102 patients were identified: 52 received OC, 51 patients received HB, 37 received CSs (methylprednisolone at low and high doses), 15 patients received placebo, and 37 patients received both placebo and CSs (dexamethasone). Two studies were not blinded;^{9,10} three were double-blind,¹¹⁻¹³ one of which had a crossover design with 5-day phases.¹³ Scarcity of retrieved data precluded any formal meta-analysis.

Study Duration and Survival

Study duration differed among studies, ranging from 3 to 10 days. One study, comparing OC and HB, was extended up to the day before death.¹¹ In OC and HB studies, patients receiving the study drugs mainly had a short survival, ranging from 4 to 61 days.^{9,10} Study medication did not influence survival, which varied from a few days to more than 300 days.¹² In studies of CSs, a longer survival was recorded. In one study, about 25% of patients survived for more than 90 days.¹² In another

Table 1
Randomized Studies Focusing on the Medical Management of Malignant Bowel Obstruction

Author, year	Population, study design, duration of study, survival	Outcome measures	Notes	Quality scale
Hardy et al., 1998	39 patients (2 withdrawals) RC DB CO a) Dexamethasone 16 mg—5 days b) Placebo—5 days 10 days 75 days (median)	Resolution of bowel obstruction	13 patients responded to CSs; 8 patients responded to placebo; unpleasant perianal sensation	3
Laval et al., 2000	58 patients (6 withdrawals) RC DB a) Placebo b) Methylprednisolone 40 mg c) Methylprednisolone 240 mg 3 days 41 days (median)	Resolution of bowel obstruction	68% on CSs; 33% on placebo	3
Ripamonti et al., 2000	17 patients RC a) OC 0.3 mg b) HB 60 mg 3 days 11 days (mean)	Gastric content, tube removal, nausea, pain, dry mouth, thirst, dyspnea, abdominal distension, drowsiness	OC better than HB; hydrated patients had less drowsiness and nausea	2
Mercadante et al., 2000	18 patients (3 withdrawals) RC a) OC 0.3 mg b) HB 60 mg 3 days 2–37 days	Vomiting, nausea, drowsiness, pain, fluids	OC better than HB for vomiting and nausea	2
Mystakidou et al., 2002	68 patients (15 withdrawals at day 6) RC DB a) OC 0.6–0.8 mg CHL 15–25 mg b) HB 60 mg CHL 15–25 mg 3–6 days, before death 7–61 days	Vomiting, nausea, pain, anorexia, fatigue	OC better than HB for vomiting and nausea; no differences after 6 days	2

RC = randomized-controlled; CO = crossover; DB = double-blind; OC = octreotide; HB = hyoscine butylbromide; CHL = chlorpromazine.

study, the median time from obstruction to death was 2.5 months.¹³ Of interest, these studies focused on the resolution of bowel obstruction rather than on symptom control.

Population and Setting

All studies were conducted with adults aged from 38 to 80 years. The population was defined as patients with “inoperable malignant bowel obstruction.” In one study, this definition was not clearly stated.¹³ Two studies of OC and HB were performed in both oncological ward and palliative home care settings, and one was conducted in a palliative care unit. Studies of CSs were performed in palliative care units.^{12,13}

Bowel Obstruction Diagnosis

Different primary tumors were causing bowel obstruction. Diagnosis was mainly based on clinical and radiological examinations, and

inoperability was decided after surgical consultation. Onset of symptoms was described in three studies only.^{9,10,13} Possible levels of bowel obstruction were also described in one study.¹⁰

Description and Methodological Quality of Studies

Five studies had similar entry criteria in terms of population, although different outcome measures were used; outcome measures sometimes were not well described. OC was compared with HB in three studies. Two of these were multicenter, open-label, and randomized studies, performed by two groups in two different settings, and included patients having a nasogastric tube or not, respectively. The follow-up was 3 days. The quality score of both studies was 2.^{9,10} The third study was randomized and double-blind, and patients concurrently received chlorpromazine.

The follow-up was 6 days, extended up to the day before death. The quality score was 3.¹¹ These studies were published in the last 5 years and were published in English. The former studies were undertaken in Italy, the latter in Greece.

Two studies examined the effects of CSs in the management of inoperable intestinal obstruction. These studies were flawed by several methodological limitations. In a multicenter national French study, methylprednisolone in low and high doses was compared with placebo using a randomized, controlled, double-blind design. Fifty-eight patients were recruited from 12 palliative care units, out of the initial 31 centers. Fifty-two patients were analyzed. Six patients left the study (three died). Patients were allowed to take several drugs, including antiemetics, antisecretive drugs (excluding somatostatin analogs), analgesics, and parenteral fluids, which were well balanced in the groups.¹² Although the Oxford quality score was 3, statistical methods were not reported. The relation between dosage and efficacy could not be determined because of the small number of patients recruited.

In another study, two trials in different periods were performed to improve accrual. Most patients were on chemotherapy. Given that the second trial was started 6 years after, it is likely that chemotherapy regimens significantly changed, introducing a bias that may have been reinforced by some minor modifications of the protocol in an attempt to improve the recruitment. The crossover design, when the primary outcome is the resolution of bowel obstruction at Day 5, makes the evaluation poorly appropriate.¹³ The Oxford quality score was 3, but statistical methods were not attempted and only descriptive analysis was shown. The study samples in the CS studies had longer survival in comparison with the samples selected for studies of OC and HB.

Outcomes

In the first study, performed in 17 patients already having a nasogastric tube for a mean of 4.3 days (range 1–12), the gastric content was the principal outcome measure, after which removal of the gastric tube was allowed in the presence of minimal gastric content.¹⁰ Patients with upper bowel obstruction were excluded and no other drugs were allowed,

except for analgesics. Description was available on an individual basis for each patient. OC and HB doses were 0.3 mg/day and 60 mg/day, respectively. Mean gastric secretions halved within 24 hours in OC patients and were less than 400 ml/day in the following 2 days. Patients were stratified by groups of hospitalized patients receiving parenteral fluids (as parenteral nutrition) and oral fluids, and home care patients receiving minimal amounts of fluids orally. When considering this latter group of 10 patients, OC was more effective in decreasing gastric secretions, and tube removal was possible more often and earlier than in patients receiving HB. There was a trend suggesting that hydration may decrease drowsiness and nausea, but possibly limiting the effects of antisecretive agents on gastric secretions.

In the second study of 18 patients,⁹ the principal outcome was symptom intensity: vomiting episodes, nausea, drowsiness, dry mouth, and pain. OC and HB doses were 0.3 mg/day and 60 mg/day, respectively. Analgesics and haloperidol 5 mg/day were allowed. OC was more effective than HB in reducing vomiting episodes and nausea. Patients were stratified according to the level of hydration provided in the two settings of home care and oncological ward. Lower levels of hydration were associated with nausea regardless of the treatment.

In the third study, which recruited a higher number of patients ($n=68$),¹¹ OC and HB were given in doses of 0.6–0.8 mg/day and 80 mg/day, respectively, which are higher than those used in previous studies.^{9,10} Patients with high level of bowel obstruction were also included. Chlorpromazine 5–25 mg/day and analgesics were allowed in both groups, and no hydration or parenteral nutrition was provided. Vomiting, nausea, pain, fatigue, and anorexia were monitored. Nausea and vomiting significantly improved in the OC group in comparison with the HB group 3 days after starting the protocol (vomiting control: 91% with OC vs. 64% with HB). However, at Day 6 and at the day before death (reported in the abstract, from 7 to 61 days, no mean is provided) differences were not significant. This finding was attributed to patient dropout (15 patients withdrew before Day 6). Mean doses of opioids were lower with OC than with HB.

Two double-blind studies compared CSs with placebo. The first study was a crossover study, using 4 mg of dexamethasone every 6 hours for 5 days or saline intravenously. If the obstruction resolved within 5 days, the treatment was discontinued; otherwise, the patient was crossed over to the other arm for a further 5-day period. Response was defined as the resolution of the bowel obstruction. The trial terminated and subsequently was reopened for further accrual. The overall response rate was 60%, differing in patients who concomitantly received chemotherapy or not (70% and 47%, respectively). Response was 62% with dexamethasone and 57% with placebo. The median time from obstruction to death was 2.5 months (range >1–18 months). The authors were unable to make any conclusions as to the effectiveness of dexamethasone.¹³

In a multicenter study of 58 patients randomly treated with a low or high dose of CS and placebo, 52 were available for analysis. Twelve patients having a nasogastric tube were not taken into consideration for analysis, despite being included in the initial protocol. In the remaining 40 patients, resolution of bowel obstruction was obtained twice as often as in the medicated group (including both dose groups, low and high CS doses, respectively) when compared to the control group. Improvement of symptoms was not detailed, as no definition or specific measures were included. Moreover, timing of assessment and duration of benefit were not described. The definition of bowel obstruction was broad and generic. Vomiting was present only in 62% of patients, including subjects with a nasogastric tube (23%). This means that fewer than half of patients had vomiting. Survival was quite extended, 25% of patients being alive 90 days after starting the treatment.⁹

Adverse Effects

Several patients receiving dexamethasone complained of an unpleasant perianal sensation, and one patient was withdrawn because of gastrointestinal toxicity.¹⁰ No other effects could definitively be attributed to CSs.¹² Minor skin reactions were equally reported in patients received OC and HB plus chlorpromazine subcutaneously.¹¹ No differences in dry

mouth were found between OC and HB groups.^{9,10}

Discussion

Conducting scientifically sound trials in this population is a considerable challenge. The small number of randomized published trials reflects the difficulty of recruiting an adequate number of patients from among terminally ill cancer patients. We recognize that large amounts of information are needed to overcome random effects in estimating direction and magnitude of treatment effects. To prove or disapprove any effect from a treatment, some hundreds of patients would have to be randomized, but in the setting of advanced cancer, subjects are often unwell, attrition rate is high, and it is not unusual to fail to complete studies because of clinical deterioration. Moreover, staff members are often reluctant to recruit dying patients to any more experimentation.

This systematic review examined the effect of the most common drugs used for the medical management of gastrointestinal symptoms due to malignant bowel obstruction. Only five papers were relevant for a review of controlled clinical trials.

The importance of study design needs to be emphasized. The use of a placebo control may potentially expose patients to unnecessary unrelieved gastrointestinal symptoms, as most drugs commonly used are considered to produce a benefit, despite lack of clear evidence. A crossover design could amplify the effect, but this approach is unlikely in an unstable population with short survival, and the use of a washout period would possibly be considered unethical.

In a previous meta-analysis including any kind of study regarding CSs, a trend in the evidence that dexamethasone may bring about the resolution of bowel obstruction was reported.¹⁴ Some of these studies, previously labeled as gray literature, were finally published and reviewed in the present analysis. CSs were compared with placebo in two studies, which showed a weak effect in relieving gastrointestinal symptoms. These studies were flawed by several methodological problems, regardless of the number of patients. In one study,

inclusion criteria were unclear, as some patients were included and then excluded (patients with nasogastric tubes) from analysis, many drugs able to relieve gastrointestinal symptoms were allowed, timing of assessment and outcome were uncertain, and data on different doses of methylprednisolone were summed to be compared with placebo.¹² In the second one, the chances of resolution of bowel obstruction were largely determined by whether the patients were receiving chemotherapy; the regimen was likely to be changed during the long period that elapsed between the two phases of study, the disease stage was relatively early, and there was a lack of definition of inoperability. The use of a crossover design in such unstable patients, who may have a spontaneous resolution, is confounding.¹³ Survival was quite extended when compared with other controlled trials of OC and HB, 25% of patients being alive 90 days after starting the treatment,¹² or having a mean survival of 75 days.¹³

Other studies have compared the effects of antisecretory drugs, acting with different mechanisms.^{10–12} All these studies confirmed the superiority of OC over HB in a total of 103 patients, a sample relatively large in this context. Nausea and vomiting improved more with OC than with HB, in studies with similar designs and outcomes, at least on a short-term basis. The study populations were more defined in terms of stage and inoperability, and had a shorter survival in comparison with CSs studied (less than 61 days, most of them less than 20 days). These groups seem to be more representative of advanced cancer patients who are often considered inoperable. No comparison has been done between CSs and OC or HB.

Conclusion

Despite decades of experience since the first proposal of medical management of gastrointestinal symptoms in inoperable advanced cancer patients, few data are available from randomized clinical trials. These data are compromised by several methodological flaws and a low level of recruitment capacity, due to the characteristics of such patients. Moreover, the modern approach seems to be more directed

toward a multimodal treatment, including different agents, particularly drugs with relatively low toxicities and different mechanisms of action, which may synergistically or additively improve gastrointestinal symptoms or partially resolve bowel obstruction.¹⁴ On the basis of data published in randomized trials, OC can be reasonably considered more effective than HB in relieving symptoms due to inoperable bowel obstruction, while the role of CSs still remains debatable and requires further studies in a more selected population. More efforts are needed in research, possibly promoting multicenter studies, to establish the most cost-effective treatment in this kind of population.

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