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REVIEW ARTICLE

The role of parenteral nutrition in patients with malignant bowel obstruction

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Abstract

Purpose The role of parenteral nutrition in the treatment of malignant bowel obstruction is underestimated since palliative literature mainly focuses on gastric aspiration, nothing per os and antisecretory therapy. The purpose of this review is the appraisal of the literature with a focus on the potential contribution of parenteral nutrition.

Methods Literature included in a recent meta-analysis and in a Cochrane review on parenteral nutrition in malignant bowel obstruction and updated through PUBMED until March 2019 has been reviewed.

Results Prompt withholding of food intake, nasogastric aspiration and then the use of antisecretory agents represent the milestones of treatment which are applied to all patients with malignant bowel obstruction. After this initial approach, excluding few surgical patients and those defined as imminently dying, there is a heterogeneous group of patients achieving a benefit in a few days but with a prompt recurrence of symptoms as they attempt to reassume some food intake. Parenteral nutrition in hospital or at home addresses to these patients provided their life expectancy is likely to depend on progressive nutritional deterioration due to the prolonged starvation more than on the tumour spread. These patients on home parenteral nutrition can survive a few months with some indefinite benefit on quality of life whereas untreated patients have a survival of few weeks.

Conclusion Parenteral nutrition should be considered in selected patients who benefit from standard palliative treatment of malignant obstruction and are obliged to maintain a total bowel rest for weeks or months.

Keywords Home parenteral nutrition · Malignant bowel obstruction · Intravenous nutrition · Palliative therapy in cancer

Introduction

Malignant bowel obstruction (MBO) has been recently defined by the Clinical Protocol Committee at the International Conference on MBO [1] as a syndrome characterized by the following: (a) clinical evidence of a bowel obstruction (via history/physical/radiographic examination), (b) bowel obstruction beyond the ligament of Treitz, (c) intra-abdominal primary cancer with incurable disease and (d) non-intra-abdominal primary cancer with clear intraperitoneal disease.

Retrospective and autopsy series have reported that intestinal obstruction occurs in different types of primaries with the following frequencies: colon-rectum, 10–28.4%; ovary, 20–50%; stomach, 6–19%; pancreas, 6–13%; bladder, 3–10%; and endometrium, 3–11% [2, 3].

MBO most commonly affects the small bowel in isolation (61%), but may also be confined to the large bowel (33%) or involve both small and large bowel simultaneously (20%) [4].

The role of parenteral nutrition (PN) in hospital or at home (HPN) is controversial in the literature: some authors [1, 5–8], who reported on different approaches to MBO, did not mention either PN or HPN; others [9] would limit PN for patients who are undergoing surgery to enable subsequent chemotherapy and have a post-operative survival likely to be more than 3 months. More recently two systematic reviews on HPN in patients with MBO have been published: the first [10] reported a mean survival of 116 days, median 83 days, with 45% and 24% still alive at 3 and 6 months and only 2% survival at 1 year, the second one [11] concluded that there was no proof whether HPN improves survival or quality of life (QoL) as the certainty of evidence was very low for both survival and QoL.

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Methods

The aim of this paper is an appraisal of the literature in order not to define which is the best treatment of the MBO, but rather which is a rational multi-step approach to it with a special emphasis on the role of PN in patients who are in hospital or at home. For this purpose, we mainly considered the literature quoted in the recent meta-analyses and Cochrane review [10, 11] as well as the one retrieved from a PUBMED research updated to March 2019. Furthermore, since literature on PN in MBO is quite heterogeneous, with no large randomized clinical trials and ranging from case reports to prospective studies, we mainly focused on large prospective series in order to have more reliable findings.

Pathophysiology and correlates with clinical presentation

The clinical debut of MBO is often different from the first appearance of symptoms in patients with other causes of intestinal obstruction. The acute excruciating pain characteristic of an obstruction due to a strangulated hernia or to a twisted small bowel loop over a peritoneal adhesions or bands or to the classic sigmoid volvulus, does not suggest a MBO and, in fact, should question a diagnosis of MBO, which usually exhibits a more discrete and subacute presentation. Also, the clinical picture of a mechanical intestinal obstruction caused by an intraluminal or more rarely an extraluminal mass is different from the MBO because of its progressive and unrelenting evolution, while the initial symptomatology of MBO follows a more capricious pattern characterized by ups and downs which occur spontaneously or driven by the simple reduction of the oral intake of solid food. Presentation of MBO is often subacute, with cardinal symptoms such as nausea, vomiting, pain, abdominal distention and absence of stools or passage of gas. In established MBO, nausea is present in 100%, vomiting in 87%–100%, colicky abdominal pain in 72%–80%, pain due to intestinal distension in 56%–90% and the absence of stools or emission of flatus in the previous 72 h in 85%–93% [12].

These episodes may be intermittent in cases of partial MBO, and patients may also describe passage of liquid stools due to bacterial liquefaction of the digestive content and intestinal hypersecretion. However, it has to be recognized that despite these discrepancies of the clinical presentation between MBO and other causes of bowel obstruction, both symptoms and clinical history sometimes overlap making a differential diagnosis impossible. It is also worthwhile to consider that benign causes of bowel obstruction are reported to be present in 3–48% of patients who present with obstruction after previous abdominal surgery for cancer [13–15].

MBO is often a mixed picture with mechanical- and ileus-related elements. Frequently, there is a diffuse neoplastic nodular or lymphangitic infiltration of both the seromuscular layer of the bowel wall and of the mesenterium which compromises the intestinal motility. Alongside the primary mechanical process of MBO, the presence of multiple levels of subacute obstruction is associated with an upregulation of serotonin and subsequent release of substance P, nitric oxide, acetylcholine, somatostatin and vasoactive intestinal peptide (VIP), which have a further inhibitory effect on gut motility and worsen the mucosal oedema. This finally translates into a further retention of secretions and consequent increase of the intraluminal pressure. The obstructive picture is frequently complicated by the confounding effects of opioids, immobility, poor dietary intake and intestinal neural dysfunction (either as a result of the tumour infiltration of the celiac and myenteric plexus or the electrolyte imbalances due to vomiting and dehydration or as part of a paraneoplastic process) and may be furtherly confounded by the administration of chemotherapy [16]. Such double obstructive mechanism explains the intermittent course of symptoms of MBO which in milder cases can spontaneously subside with a simple approach of fluid alimentation or *nihil* per os.

Priority of treatments

The approach to MBO has to be considered within a palliative perspective since this condition is usually a late event in the trajectory of the disease and patients have median survival ranging from 1 to 9 months after diagnosis [17–22]. Most of these patients have already received multiple lines of chemotherapy and thus are unlikely to mount a clinically meaningful response resulting in the resolution of MBO [23–25]. The main end point of MBO management is to achieve an optimal relief of debilitating symptoms and optimizing patient QoL.

It is natural that, even if the first evaluation of the patient has also to take a potential surgical approach into consideration, however, in presence of symptoms consistent with a bowel obstruction, the prompt measures include an intravenous hydration, a regimen of *nihil* per os and placement of nasogastric tube decompression. Some patients may improve to the point of allowing resumption of oral fluid or semifluid intake with these standard interventions, while others need antiemetics (metoclopramide or levosulpride) which are effective in relieving nausea and vomiting in 23–36% and 18–52% of cases respectively [26]. In case of persistent symptomatology, there is an indication for using scopolamine butylbromide or octreotide which is effective at suppressing VIP, along with several other stimulatory gut hormones. Randomized clinical studies [27–30] have shown that both treatments, but especially octreotide, are successful in diminishing pain and allowing nasogastric tube removal that is usually done when secretions do not exceed 1 L/24 h. The medical management of MBO often takes some days before there is a significant resolution of symptoms. The spontaneous resolution of MBO occurs in

about one-thirds of patients with inoperable MBO and 92% of those who settle spontaneously, do it by day 7. It is noteworthy that 72% of those who settle spontaneously, subsequently will develop another episode of obstruction [31].

Indication for surgery

A surgical approach should not be *en principle* denied, but only after a careful evaluation of both the general status of the patient and the abdominal picture.

Very rarely, if there is only one crucial point of obstruction within a context of diffuse bowel involvement, a gastroduodenal or colorectal stent may be indicated. However, it is easier to define the factors which argue against the option of laparotomy rather than those supporting a surgical approach, and these rely more on the common experience and a good surgical sense, than on scientific studies. Such factors which were already identified by the Working Group of the European Association for Palliative Care about 20 years ago [4] include the following:

a) Presence at the clinical abdominal examination or at the CT scan of multiple masses which announce an extreme difficulty of entering the peritoneal cavity, mobilizing the loops enough to determine the major sites of obstruction and to perform a surgical decompression and, in addition, would suggest a high risk of iatrogenic complications;
b) Presence of a woody abdomen or of fixed, non-dilated loops at the CT scan which means that we are facing with a frozen peritoneal cavity and the obstruction is caused by a widespread infiltration of the bowel walls alongside of the mesenterium. In such cases, there is no dilation because the loops are rigid, peristalsis simply does not exist and there is nothing to decompress;
c) Presence of multiple abdominal scars suggesting a recent futile laparotomy and warning against the risk of an overestimation of the potential benefit of a new surgical exploration;
d) Finally, the presence of massive ascites. However, this factor, alone has a relative importance, especially when the primary tumour is in the ovary.

Effect of parenteral nutrition on survival

Although symptoms of MBO recur after an initial medical control in about 4/5 of patients [31] and in 32–71% of surgically treated patients [32–38], the role of PN in contrasting the consequences of progressive starvation is scotomized in the oncologic literature.

Since the milestone of the medical therapy of MBO is a bowel rest achieved through the gastric aspiration, the antisecretory therapy and obviously *nihil* per os, this approach, despite being effective in relieving symptoms, appears destined to a total failure in the medium term since, provided MBO is not complicated by perforation and tumour progression is not tumultuous, the patient will later succumb from progressive starvation. Hence, the role of PN is not to cure the MBO, but it has only a permissive role since it allows to prolong the span of the bowel rest while maintaining the patient alive.

A vast literature has shown that mean survival of cancer patients undergoing a total or almost total macronutrients deprivation (usually for MBO) is 62 days in patients after a surgical exploration only [27, 31, 39–41] and 52 days in hospitalized patients without any nutritional support [4, 31–38, 42]. If we consider cancer patients discharged at home without HPN, mean survival is still shorter with reports of 19, 27 and 15 days [42–44], respectively. Two recent reviews reported different survival data of patients on HPN for MBO: Naghibi et al. [10] reviewed 9 studies [25, 45–52] on 311 patients and observed a mean survival of 101 days (median about 83 days), the recent Cochrane review by Sowerbutts et al. [11] included 11 studies on an overall number of 696 patients [46–49, 51–56] and reported a survival ranging from 40 to 400 days [49–56] with a mean/median value of 202/210 days.

Regardless of the discrepancy of the findings of these reviews, it appears that administration of PN is always associated with a longer survival than that of patients without nutritional support. Although any comparison between results of treatments reported in different publications is exposed to several bias, this is the only evidence of the potential role of PN because in this area it is not ethically possible to perform a randomized clinical trial. In fact, this would mean to accept that a control arm of aphagic patients does not receive an adequate nutritional support. For this purpose it appears meaningful to mention the only randomized clinical trial comparing PN versus no-PN in patients with MBO which was performed in Seoul, Korea, in 2014. Oh et al. [57] enrolled 31 consecutive patients with a life expectancy of 12 weeks (or less) and 16 patients were randomized to the PN group and 15 to simple hydration (about 370 Kcal/day). Median survival was 8 days in the fluid group and 13 days in the PN group, and this difference was not statistically significant. The study, which should originally include 116 patients, ended early because many patients and families were extremely concerned about starvation. There are several major flaws which make this study blameable for scientific and ethical reasons:

1. If patients on PN survived only 13 days, this means that they were dying because of the too advanced stage of the tumour and not because of starvation. Only if the patients are expected to die prior from progressive

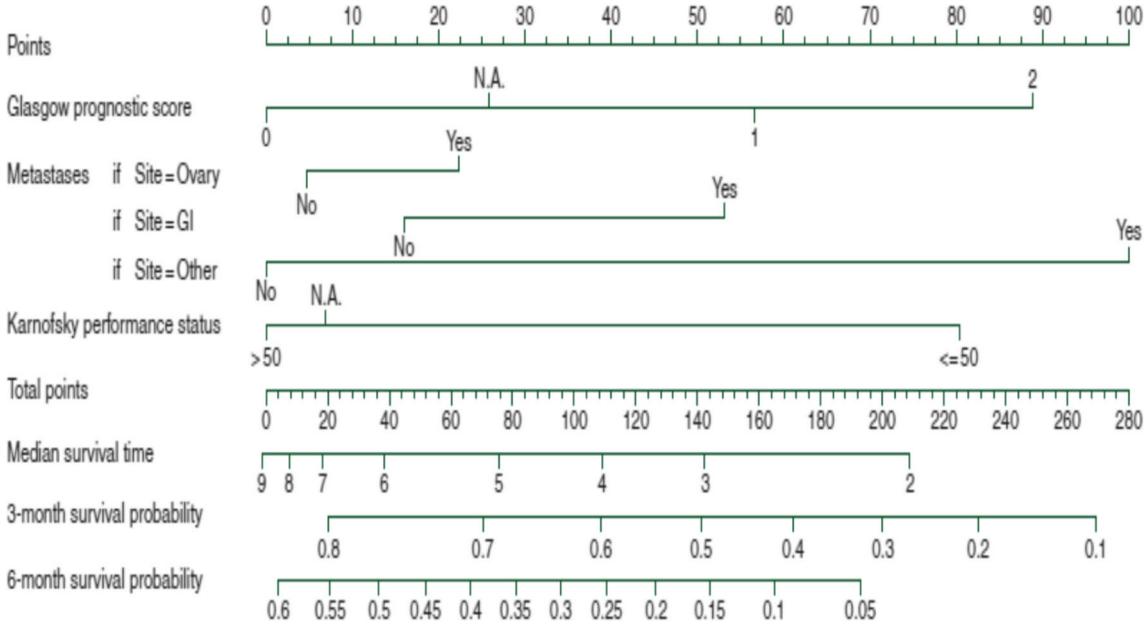

Fig. 1 Cox modelling based nomogram for predicting 3 and 6-month and median overall survival. With this nomogram, the category of each prognostic factor is assigned a score using the topmost 'Points' scale, then a sum is calculated across all patient characteristics so as to obtain the 'Total points' that are eventually converted into the desired statistics (adapted from ref [60])

starvation (which usually takes some weeks or 2–3 months) and not from uncontrolled tumour growth, there is a rationale for attempting to use PN. The authors grossly overestimated the life expectancy of their patients' population and the enrolment of metastatic patients with a low performance status (ECOG 3 or 4), anaemia, lymphopenia and low serum albumin, finally resulted in selecting a series of almost imminently dying patients with no indication for PN.

2. The study was closed early because many patients and families were repulsed by the idea of the study due to their concerns about starving to death if the patient was allocated to the control arm. It is clear that there was, on one side, a very poor comprehension of the study by the patients (or their relatives) when they signed the consent and, on the other side, ethical problems were grossly underestimated by the researchers.
3. Finally, the major risk of this paper is that a hasty reader reaches the conclusion that there is no role for PN in patients with MBO, without being aware of the serious flaws of the study.

Since the recent ESPEN guidelines [58] recommend that "artificial nutrition is indicated if patients are unable to eat adequately (e.g. no food for more than one week or less than 60% of requirement for more than 1–2 weeks)", almost all patients with MBO should be candidate for a short-term PN program if an effective palliation through *nihil* per os lasts for a few weeks. The potential indication for a PN in home care program mainly relies on the answer to two questions: is this

Table 1 Change of quality of life in patients on HPN for Malignant Bowel Obstruction

Author	*N* pts	Type of study	QoL measure	Outcome
August 1991 [45]	17	Pro/retrospective	Effect of therapy	Benefit in 65% of pts
King 1993 [56]	61	Retrospective	Miscellanea	↓GI discomfort, nausea, vomiting, fatigue, ↑morale, social interaction
Mercadante 1995 [43]	25	Prospective	Symptoms	Good control in most pts
Pironi 1997 [51]	29	Retrospective	Effect of therapy	Good acceptance of PN in 66% of pts
Finocchiaro 1992 [62]	70	Prospective	TIQ	At 2 mos (27 pts): ↑31.5%, = 48%, ↓20.5%
Bozzetti 2002 [46]	69	Prospective	RSCL	Well-being assessment at baseline: very well 3, well 55, not well 38, missing 4. After 1 m (64 pts): ↑15, = 32, ↓17
Cotogni 2017 [53]	111	Prospective	EORTC QLQ-C30	Global QoL at baseline, 1,2,3 mos in 111,97,76,54 pts.: 52, 58, 60, 71 score

↓, decrease; ↑, increase; =, unchanged; *GI*, gastrointestinal; *PN*, parenteral nutrition; *TIQ*, Therapy Impact Questionnaire; *RSCL*, Rotterdam Symptom Checklist Questionnaire; *EORTC QLQ-C30*, EORTC Quality of Life questionnaire C-30

patient candidate to an early demise because of the nutritional deterioration or because to the rapid progression of the tumour? and is the quality of life acceptable for the patient?

The estimation of the life expectancy is notoriously difficult and imprecise and some help may be provided by a nomogram (Fig. 1) elaborated in some hundreds of cancer patients receiving HPN, most of them for MBO [59, 60].

Effect of parenteral nutrition on quality of life

Data on QoL in patients with MBO are particularly scanty. One study [61] reported a few patients receiving medical therapy for MBO and showed that they were quite severely symptomatic at presentation, but with therapy they clearly improve in terms of physical symptoms, psychological distress and overall QoL. Seven studies described quality of life of participants receiving HPN [43, 45, 46, 51, 53, 56, 62]. Three studies [46, 53, 62] used a validated instrument to measure quality of life: Bozzetti et al. [46] used the Rotterdam Symptom Checklist Questionnaire and reported that 96% of patients had some symptoms 80% of the time and there was a transient benefit in physical symptoms, followed by decline 2–4 months before death. Interestingly, over half of patients said they were "well" or "very well" (referring to overall health), despite requiring some help with activities of daily living. Cotogni et al. [53] used participant-completed European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 Version 3.0 (EORTC QLQ-C30) and reported that some domains as Global QoL, physical functioning, role functioning, emotional functioning, appetite loss, and fatigue scores had a statistically significant trend over time. Finocchiaro et al. [62] used the Therapy Impact Questionnaire (TIQ) and the Patient Generated Subjective Global Assessment (PG-SGA) and reported an improvement at 2 months in 31.5% and 37%, respectively (Table 1).

Altogether, it would appear from these papers that around half of the participants showed no change, a quarter to a fifth deteriorated and a quarter to a third improved.

Conclusion

There is no doubt that the initial approach to MBO relies on a palliative bundle including *nihil* per os, nasogastric aspiration and, in non-respondent patients, therapy with antisecretory agents. The further clinical evolution opens three different scenarios: a quite limited percentage of patients may benefit from a surgical approach, a relatively high percentage includes very advanced patients in which MBO coexists with a widespread diffusion of tumour to vital organs and extreme cachexia and treatment of MBO represents just a part of a more comprehensive palliative treatment of patients with a very short life expectancy. Such patients, obviously, are not fit for a program of PN. There is finally a third very heterogeneous group of patients whose MBO symptoms only subside if they are maintained at *nihil* per os (or very little oral fluid intake) and/or periodically need gastric aspiration and/or antisecretory therapy. This approach cannot last for more than a couple of weeks without parenteral nutritional support and these patients should undergo a comprehensive evaluation of those parameters predictors of the length of survival, to consider the potential option of a HPN program. This treatment has become so common and practical nowadays for a variety of patients with both benign and malignant intestinal failure that its use should not be viewed as an experimental approach requiring a validation through randomized clinical trials. Certainly, there still is a grey area as regards the indication in these patients but a trial and error approach [63] should not be discarded in conditions where no further alternative exists.

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