

Pain in Upper Abdominal Malignancy

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Üst Abdominal Tümörlerde Ağrı

Anahtar Sözcükler: Ağrı, analjezi, malignite, karın, solid tümör

Introduction

This review will cover selected aspects of pain in upper abdominal malignancy. Mechanisms of pain are poorly understood, although thought to be related to inflammation at least in some circumstances. Pain may be a marker of advanced disease. The clinical problem of how to treat pain can only be addressed by research studies that compare the effects of different treatments, using validated techniques to measure pain. Some of these measures are reviewed, and the significance of reported changes in pain scores in a number of clinical trials is discussed. In clinical practice, it is a desirable goal to render the patient pain-free, rather than simply to reduce pain scores. This objective, however, is much more difficult to achieve.

Pain Mechanisms in Upper Abdominal Cancer

Early cancers of the stomach, duodenum, pancreas and gallbladder rarely cause symptoms. However, as the tumor enlarges and involves other structures, the pain becomes a dominant feature (penetrating ulcerating tumor of the stomach in affecting the pancreas, retroperitoneal invasion of pancreatic cancers). It seems that the mechanism of pain is related to inflammation around the invading tumor, perhaps with injury of nerves directly by the secretion of tumor products (1-4). In pancreatic cancer, presentation with severe or persistent pain is associated with a high rate of local invasion, which makes the tumor irresectable (2-5), and which suggests that the invasion of nerves outside the pancreas is important in the generation of pain.

There is no doubt that effective treatment of the cancer is an effective means to control pain in patients with tumors that are amenable to surgery or chemotherapy. Surgical excision of the primary tumor removes the source of the pain and restores the patient to a normal condition. In pancreatic cancer, it has been shown that effective chemotherapy with gemcitabine produces a clinical benefit that is largely based on the reduction of pain (6).

Other mechanisms of pain that are recognized include inflammatory adhesions to the liver capsule over metastatic nodules and colicky pain arising from metastatic tumor deposits causing intestinal obstruction.

Pain Measurement

Pain measurement focuses on recording the patient's perception of pain. Although psychological and social factors also affect the patient's perception, there are at present

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no means to record these influences. All studies of pain in abdominal malignancy record pain severity as expressed either by the patient, or sometimes by proxy such as by caregiver or health professional.

There are three types of pain measurement tools: visual analogue scales (VAS), categorical verbal rating scales (VRS) [sometimes termed verbal descriptor scales (VDS)], and categorical numerical rating scales (NRS). These three scales produce data that correlate well with each other, although it has been reported that NRS has greater reliability in clinical trials (7).

It may be preferable to use multidimensional pain assessment tools, such as the Brief Pain Inventory (BPI), the McGill Pain Questionnaire (MPQ) or the Memorial Pain Assessment Card (8-10). The European Association of Palliative Care reviewed pain assessment tools (11) and recommended two multidimensional pain assessment tools for use in clinical research - the BPI and the MPQ. These instruments are well validated and available in many languages.

The BPI is easy to use. It has a two-factor structure recording the severity of pain and the impact of pain. The full BPI contains 20 items and there is a short form of the BPI for use in clinical trials. This has a diagram to identify the location of pain and four questions about pain intensity with one question about pain relief from treatment or medication. The BPI time frame for severity refers to the last week. The short form can be completed in 5 minutes and the full BPI in 10 minutes. The data can be assessed using either the worst pain or the arithmetic mean of severity of worst, least, average and current pain.

There are a number of difficulties in measurement that should be considered when using a pain assessment tool. The assessor should understand the sensitivity of the tool to detect effective treatment, and should estimate the clinical significance of recorded changes. It is important to be sure that the patient understands which pain is being assessed. For example, if a patient with abdominal cancer also has severe arthritis affecting knees and hips, it should be clear that the assessment is to focus on the cancer pain.

Ideally, the assessment of pain should be made by the patient. There is evidence that health professionals tend to underestimate pain; different professionals may also

have discrepant views on assessment of pain in the same patient (12,13).

It should be remembered that the patient may be a source of variability and reporting. Recall of pain is often inaccurate, as coping mechanisms such as denial and memory suppression as well as other interacting factors such as anxiety can affect the reporting of pain even over recall periods as short as 24 hrs.

Nevertheless, with an understanding of the limitations of pain measurement, it is possible to get valid and reproducible assessments using well-established instruments. The BPI seems particularly suited for use in routine clinical practice and in clinical trials designed to assess pain treatments. One drawback with this assessment system is the timeframe of one week; it may be more practical to ask patients to recall their pain over the previous 24 hrs.

Attempts to make pain recording more detailed, with a daily diary repeating the assessment every 24 hrs, have proved extremely difficult. Our experience with using a daily pain diary in a randomized trial of pain relief in patients with inoperable abdominal malignancy found extremely low rates of compliance with the pain diary. Fewer than one-third of the patients who had been selected as capable of completing pain diaries along with the other inclusion criteria were in fact able to complete diaries successfully for a shorter period of four weeks. There is an extensive literature that calls into question the validity of daily recording of pain. Many subjects in such studies complete the diaries retrospectively and the data cannot be relied on unless some mechanism is included to identify the precise timing of the pain record. In most cases this is impractical and is probably unnecessary for general use.

Treatment of Pain

As noted above, treatment of the tumor by surgery or chemotherapy is the best initial approach, and may produce useful pain relief. However, not all tumors are resectable or respond to chemotherapy, and after treatment, tumor recurrence or progression may be associated with severe unremitting pain. The majority of patients with severe abdominal pain will require treatment with regular opioid medication. Other approaches include addition of adjuvant analgesics to

supplement opioids, or the use of interventions to disrupt afferent nerve pathways, such a celiac plexus block (CPB) or thoracoscopic splanchnicectomy (TS).

Although most patients with inoperable upper GI tumors will experience severe pain during their illness, this is often not the case at diagnosis. For patients with less severe pain, simple analgesia with paracetamol or a non-steroidal analgesic may be sufficient. When severe pain develops, stronger analgesia is required. Most pain specialists use the three-step approach [WHO] (1: simple analgesics, 2: opioids for mild to moderate pain, such as codeine or dihydrocodeine, and 3: opioids for severe pain such as morphine or fentanyl), but there is currently interest in the development of two-step protocols, which move directly from simple analgesics to low-dose morphine. Drugs used in the treatment of pain have side effects themselves which may require additional treatment. In particular, there is no doubt that opioids in adequate doses for pain relief inevitably cause constipation. Patients receiving regular morphine or other opioids should also be treated from the outset with a stimulant laxative.

The different types of pain experienced by patients with upper gastrointestinal tumors (visceral, neuropathic, and inflammatory) may require a combination of drug types (opioid, neuro-active and anti-inflammatory, respectively) for adequate pain control. Morphine is the mainstay of treatment. It should be remembered that not all patients will respond adequately to morphine partly because of individual variations in opioid receptor expression, and also because some patients will have pain that is less opioid responsive, such as neuropathic pain that requires adjuvant treatment as described below. However, the majority of patients who have inadequate relief of pain with morphine are probably receiving an inadequate dose (14). When the need for opioid analgesia has been determined, the correct morphine dose can be achieved within 2-3 days. Normal release oral morphine (liquid or tablets) should be given every 4 hours and the dose is adjusted once or twice a day until the pain is controlled. Use of a double dose at bedtime has often been advocated to provide analgesia through the night. When pain has been controlled, the total daily dose of morphine should be calculated, and directly translated into two 12-hour doses of modified-release morphine tablets. Patients should be given a normal-release morphine preparation for breakthrough pain. The dose

should be one-sixth of the total daily morphine dose to ensure adequate control of breakthrough pain.

The side effects of morphine, such as constipation, nausea and vomiting, should be anticipated; prophylactic laxatives should be prescribed unless there is a strong reason not to do so. Constipation requires immediate and continuing treatment with a stimulant laxative such as a combination of magnesium hydroxide and senna. Nausea and vomiting are more common at higher doses of morphine, and usually resolve within a week, but antiemetics should always be prescribed "as required". If the patient had nausea on weak opioids, regular anti-emetic medication is indicated. Haloperidol is useful for opioid-induced nausea. Persistent nausea or vomiting should prompt investigation to exclude gastric outlet obstruction.

Patients with difficulty swallowing or who have unrelieved gastric outlet obstruction can have opioids by other routes: either by subcutaneous infusion from a syringe driver or by transdermal slow release patch. These options are more expensive, and when the mechanical obstruction has been relieved, an attempt should be made to convert to oral therapy.

Patients with persisting pain despite high-dose morphine treatment may have neuropathic pain. This may respond to low-dose amitriptyline (10 mg at night increasing to 25 mg at night after 3 days). If amitriptyline is contraindicated, alternatives include sodium valproate or gabapentin. Pain from hepatic metastases usually has an inflammatory component and may respond to a non-steroidal anti-inflammatory drug or dexamethasone.

Pain relief in upper abdominal malignancy may also be achieved by destruction of the afferent neural pathways. Pain from the abdominal viscera is transmitted through the sympathetic nervous system via the celiac plexus and the splanchnic nerves. There are many uncontrolled reports supporting the use of CPB in these patients (15,16). The procedure is designed to destroy the afferent nerves from the pancreas and upper gastrointestinal tract as they pass through the neural plexus alongside the celiac trunk and aorta. Similar results are obtained whether the injection is placed by an anterior percutaneous, posterior percutaneous, endoscopic, or open surgical approach, and whether the aim is to destroy the nerves at the level of the celiac trunk, aorta, or

subdiaphragmatic splanchnic nerves. Eighty percent of patients achieve a good response with useful pain relief. The well-known tendency for effectiveness to decrease with time when CPB is used in benign disease appears irrelevant in patients with these malignancies who have a median survival of only a few months.

In pancreatic cancer, one-fourth of patients have severe pain at diagnosis, and over 70% of the remainder will develop such pain during follow-up (17). The likely contribution of pain to clinical features such as anorexia and weight loss, very common in these patients, and the link between pain and impaired quality of life (18) have led some clinicians to use additional interventions such as CPB early in the course of the disease, to prevent or delay the onset of severe pain. It seems especially appropriate to administer a CPB during surgery to palliate obstructive symptoms (17,19-21). A randomized placebo controlled trial suggested that CPB used in this situation not only delays onset of severe pain, but improves nutritional status and may prolong life (17).

Interruption of pain pathways by CPB or TS can reduce opioid resistant pain, and may be useful to reduce opioid dose, and thus limit side effects. Some patients suffer side effects such as nausea and drowsiness, and almost all patients become constipated, requiring treatment with laxatives. Some patients suffer dry mouth or itching. Adjustment of dose and dealing with opioid-induced side effects may require multiple visits to the specialist clinic, and nerve division by CPB or TS may offer better pain control and less need for medical supervision.

In an overview of published studies, chemical ablation of the celiac plexus or nerves (CPB) diminished the need for opioid analgesia in 87% of 418 patients (22). However, that review identified serious deficiencies. Very few studies stated the opioid requirement after treatment and information was lacking on long-term effectiveness. A randomized placebo controlled trial of intraoperative CPB showed lower pain scores in the treatment group throughout the follow-up (17). Subsequent studies have confirmed the value of percutaneous CPB in patients not undergoing operation: approximately 80% of patients experience reduction or abolition of pain. A recent randomized controlled trial showed that percutaneous CPB can reduce pain scores in patients with inoperable pancreatic cancer (23). During the first six weeks, pain

scores were lower after CPB than in medically treated controls. However, there was no difference in opioid use between the two groups.

CPB has side effects: transient hypotension, diarrhea, and (rarely) anterior spinal artery syndrome or aortic pseudo aneurysm. It is possible, although very unlikely, that the procedure may damage other nerves and may cause unforeseen bleeding or paralysis (in 1 person per 683 blocks performed) (24). An alternative approach to achieve visceral denervation is to divide the splanchnic nerves within the chest (21,25-29). Transhiatal splanchnicectomy performed at laparotomy was reported in 51 patients, with over 80% good results (21). TS avoids the morbidity associated with laparotomy or thoracotomy and in small series has achieved good results. Visual analogue pain scores (VAS) were reduced by 50% in 44 patients who had bilateral TS for pancreatic pain and over half no longer needed opioids (30). In another study, unilateral TS produced immediate abolition of pain (mean VAS before: 7.4; day 1: 1.0) and significant reduction in mean VAS for three months (31). Nearly all patients became opioid-independent. However, there is no published evidence comparing the effect of TS with either opioid analgesia or CPB. On theoretical grounds, it is likely that the complications of transient hypotension and diarrhea will be as frequent as with CPB. TS enables precise localization and division of the splanchnic nerves as they course beneath the pleura on the posterior mediastinum. Several reports indicate that bilateral TS is safe and it appears to be at least as effective as CPB in terms of early pain relief (26,30).

Because of a lack of controlled trial data, we have recently compared percutaneous CPB or TS with best medical management and with each other (*NaTTS trial, unpublished*). This trial is needed because it is not clear whether these techniques, especially TS, can reduce pain and morphine requirements in unselected patients who require pain relief for upper abdominal malignancy. In addition, reports of differences in pain scores are difficult to interpret in the clinical setting. More relevant is the number of patients who are rendered pain-free by different treatment strategies. Our data suggest that in patients with incurable malignancy, focus on the physical pain alone is not sufficient: many patients fail to achieve good pain relief. Attention must also be given to the psychological and social distress of the patients, and this may be more important for many than the addition of invasive nerve block procedures.

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