Original Paper

Pancreatology

Pancreatology 2009;9:755–763
DOI: 10.1159/000199441

Received: May 21, 2008
Accepted after revision: January 23, 2009
Published online: January 15, 2010

An Open Randomized Comparison of Clinical Effectiveness of Protocol-Driven Opioid Analgesia, Celiac Plexus Block or Thoracoscopic Splanchnicectomy for Pain Management in Patients with Pancreatic and Other Abdominal Malignancies

C.D. Johnson[a] D.P. Berry[b] S. Harris[c] R.M. Pickering[c] C. Davis[a] S. George[c] C.W. Imrie[d] J.P. Neoptolemos[e] R. Sutton[e]

[a]Southampton General Hospital, Southampton, [b]Leicester General Hospital, Leicester, [c]University of Southampton, Southampton, [d]Glasgow Royal Infirmary, Glasgow, and [e]Royal Liverpool University Hospital, Liverpool, UK

Key Words
Celiac plexus block · Medical management · Pain management · Protocol-driven opioid analgesia · Thoracoscopic splanchnicectomy

Abstract
In inoperable malignancy, pain relief with opioids is often inadequate. Nerve block procedures may improve symptom control. Our aim was to assess celiac plexus block (CPB) and thoracoscopic splanchnicectomy (TS) in patients receiving appropriate medical management (MM). ***Methods:*** Patients with confirmed irresectable malignancy of the pancreas or upper abdominal viscera who required opioid analgesia were randomized to MM alone, MM+CPB, or MM+TS. Randomization was stratified by treatment centre, tumour type and previous opioid medication. The primary endpoint was pain relief at 2 months. ***Results:*** 65 patients (58 pancreas cancer) were randomized, 18 withdrew or died within 2 months. Effective pain relief was achieved in only one third of subjects at 2 weeks, and just under half at 2 months (MM: 6/19 and 5/12 evaluable patients; CPB: 5/14 and 5/9; TS 4/14 and 4/11). There were no significant differences between the groups in pain scores or opioid consumption, and there was no correlation between continued use of opioids and effective pain relief. ***Discussion:*** Previous randomized studies have shown small differences in pain scores, but no difference in opioid consumption and quality of life. The absence of any benefit from interventions in the present study questions their value.

Pain is a common problem in upper abdominal malignancy, and may contribute to anorexia and weight loss. Different strategies are used to manage pain. Medical management (MM) is based on opioid analgesia, but many patients experience side effects, and pain relief may

Data Safety Monitoring Committee: D. Machin; A. Andren-Sandberg, Karolinska; N. Campkin, Queen Alexandra Hospital, Portsmouth.
Chair of Trial Steering Committee: M. Bennett, St Gemma's Hospice, Leeds.

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1424–3903/09/0096–0755$26.00/0

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Colin D. Johnson
University Surgical Unit (816), Southampton General Hospital
Tremona Road, SO16 6YD Southampton (UK)
Tel. +44 23 8079 6146, Fax +44 23 8079 4020
E-Mail c.d.johnson@soton.ac.uk

be incomplete. Opioid analgesia may be supplemented by a range of adjuvant analgesics; nerve ablation procedures offer an alternative to medical therapy.

The upper abdominal viscera are supplied by the splanchnic nerves, via the celiac plexus, which carry the sensations of pain to the central nervous system. Interruption of pain pathways by celiac plexus block (CPB) can reduce opioid requirements. A randomized placebo-controlled trial of intraoperative CPB in patients with pancreatic cancer showed lower pain scores in the treatment group throughout the follow-up [1]. Others confirmed lower pain scores after percutaneous CPB in patients not undergoing operation [2–6].

An alternative approach to achieve visceral denervation is to divide the splanchnic nerves within the chest [7–12]. Transhiatal splanchnicectomy performed at laparotomy was reported in 51 patients with over 80% good results [11]. Thoracoscopic splanchnicectomy (TS) avoids the morbidity associated with laparotomy or thoracotomy and has achieved good results. However, there is no published evidence comparing the effect of TS with either opioid analgesia or CPB.

Despite these apparent advantages, nerve block procedures have not been widely used in patients with inoperable malignancy. This may reflect availability of service provision, or concerns about possible complications of these interventions. The side effects of CPB include transient hypotension, diarrhoea, and (rarely) anterior spinal artery syndrome or aortic pseudo-aneurysm. The risk of permanent paralysis has been estimated to occur in 1 person per 683 blocks performed (0.15%) [13]. TS has not been studied as extensively as CPB, but on theoretical grounds it is likely that the complications of transient hypotension and diarrhoea would be as frequent as with CPB. Other side effects reported from thoracoscopy include arterial bleeding requiring thoracotomy [14], chylothorax [15] and lung injury causing pneumothorax-requiring drainage.

The aim of this trial was to compare MM alone, MM+CPB and MM+TS for the relief of pain in patients with inoperable upper abdominal malignancy, in a prospective open randomized design. The primary endpoint was pain relief at 2 months after randomization.

Methods

This was a multicentre trial in the United Kingdom. Four teaching hospitals recruited patients. Patients were eligible if they had clinical, radiological or histological evidence of irresectable primary or secondary malignancy in the upper abdominal viscera (pancreas, stomach, oesophagus, duodenum, bile duct or gallbladder, or hepatic metastases of any origin), including recurrence after resection of a primary tumour, and if they had pain requiring any opioid medication at least once per day. Patients with irresectable pancreatic and gastric cancer were also eligible before the onset of abdominal pain (which usually develops in this group). Patients were excluded if they had any previous thoracic surgery or history of pulmonary tuberculosis or other intrathoracic inflammatory conditions likely to cause extensive adhesions, if they were unfit for general anaesthesia or if they had advanced disease with anticipated life expectancy less than 1 month. Patients were informed of the study by the responsible clinician, given written information, and allowed at least 24 h to consider their decision before randomization.

Randomization

After each participant had consented to the trial, a random treatment allocation was obtained by telephone from the Liverpool CR-UK Clinical Trial Centre. Randomization to the three treatment groups (MM alone, MM+CPB, MM+TS) was in blocks of 3 and was stratified by treatment centre, tumour type (primary pancreatic or other) and by current opioid status (opioid naïve: not taking strong opioids or started strong opioids within 3 days before recruitment, or opioid non-naïve: taking strong opioids for more than 3 days before recruitment).

Trial Procedures

MM was provided to all patients according to an agreed protocol for opioid dose escalation and reduction (Appendix 1; see online suppl. data at www.karger.com/doi/10.1159/000199441). Briefly, oral morphine (or other opioid) was prescribed according to standard practice at each centre. Opioid rotation was not used. To achieve pain control, morphine dose was increased by 30–50% increments until pain was controlled or side effects prevented further increment. If the patient was taking regular immediate release morphine, this was then converted to a 12-hourly modified release preparation with appropriate dose of immediate release morphine for breakthrough pain. If pain decreased after an intervention, dose reduction was advised by reduction to half the dose of strong opioid after the procedure and continued dose reduction by 50% daily until pain occurred, or the patient was taking 30–60 mg immediate or modified release morphine per day. Then, according to clinical judgment, opioids were stopped or replaced by regular weak opioid. Opioid rotation (planned rotation through a series of opioid drugs not triggered by side effects on the previous drug), was not advocated. Opioid switching (changing from one strong opioid to another) was used for side effects, or impaired oral intake from nausea, vomiting or dysphagia. Continuous infusion of diamorphine or conversion to transdermal fentanyl were advised in these circumstances.

Adjuvant analgesia was also described in this protocol, if pain could not be relieved by opioids. For neuropathic pain, amitriptyline, sodium valproate or gabapentin were used. For liver capsule pain, either a non-steroidal analgesic or dexamethasone was prescribed.

CPB was performed under local anaesthesia (with sedation if required) with 24 h observation in hospital after the procedure. In each centre the local protocol was followed for imaging guidance (image intensifier, computed tomography or endoscopic ultrasound). Each operator placed the injection of a neurolytic agent