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COCHRANE'S CORNER

The drama of cancer pain: when the research abandons patients and reason

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Reading a systematic review is often an educational experience that makes you think about things in a different way. This review from The Cochrane Library highlights the disconcerting gap between what we would like to know and how much we actually know in a relevant clinical problem. Pain is a common dimension of cancer disease: at least two thirds of patients experience pain at some time during the course of their illness [1]. In at least 10% of these patients the pain is difficult to control. Their pain often falls into two categories: it responds poorly to opioids or it is episodic and breaks through despite background opioid analgesia. In both cases a possible solution is opioid switch. What do we know about its efficacy?

Facing the lack of research

Most patients with cancer develop pain requiring strong opioids. Morphine is the drug of choice, as recommended by the World Health Organization, for the management of moderate to severe cancer-related pain [1]. However, a significant minority do not achieve adequate analgesia with morphine. In this group of patients, intolerable side effects such as vomiting, delirium and myoclonus preclude dose escalation. It has been observed clinically that switching from one opioid, which has failed to control pain or caused intolerable side effects, to an alternative opioid can result in improved tolerability, pain control, or both. Some clinicians claim that some patients need to change the type of strong opioid at least once to achieve optimal pain control with acceptable side effects [2].

In 2004 Quigley published a Cochrane systematic review with the aim of investigating the usefulness of opioid rotation/switching/substitution for patients with cancer pain [3]. The reviewer started to search for randomised controlled trials. Surprisingly his search strategy retrieved no randomised trials. Indeed Quigley moved on considering the results of observational studies. He found 23 case reports and series, 15 retrospective patient records review and 14 prospective uncontrolled studies. The majority of the reports used morphine as a first-line opioid and the most frequently used second-line opioid was methadone. All reports, except for one, concluded that opioid switching is a useful clinical manoeuvre for improving pain control and/or reducing opioid-related side effects.

In the "implication for practice" section the authors concluded that a robust evidence base for the practice of opioid switching does not exist.

The poor designs

Observational studies share a similar purpose with randomised controlled trials: to test descriptive causal hypotheses about manipulable causes [4]. However, in observational studies, researchers have little control over confounding variables (i.e., worsening of the disease) and the delivery of the intervention (i.e., switch of route). Indeed observational designs are intrinsically weak evaluative designs, as secular trends and sudden changes make it difficult to attribute observed changes to the intervention.

While observational studies could contribute to the understanding of better pain management, the unaccounted biases that are inherent in the study design increase the uncertainty and significantly hamper the judgement of a direct causal relationship between the intervention and the outcome. Many authors of included studies claimed in their conclusions that the switched opioid can rapidly produce an improvement in patient pain. For example, Bruera et al. stated: "We conclude that custom made capsules and suppositories of high-dose methadone are an effective, safe and low-cost alternative in patients receiving high doses of parenteral opioids" [5]. This conclusion could be criticised for being overzealous in the inference of causality due to potential rival hypotheses that might have explained findings. These threats to internal validity are so plausible that Cook and Campbell describe the results of uncontrolled trials as "generally uninterpretable" [4]. They also argue that investigators using such quasi-experimental methods need to rule out all plausible rival hypotheses before any causal relationship can be inferred. We believe that there are many plausible rival hypotheses that could also explain the study results that have not been excluded by the investigators (e.g., route of administration, co-interventions such as anticonvulsants).

When can observational studies be helpful?

Case series are used to generate hypotheses about the causal relationship between two variables or to assess the feasibility and the safety of an emerging technology or treatment. Hundreds of case series have been published up to now to test, for instance, the safety and the feasibility of tomotherapy, a new radiation treatment modality, or the telemanipulator da Vinci, a robotic surgery. Randomised controlled trials comparing the new technology with the standard intervention are now necessary before implementing the technology as a routine treatment.

Observational prospective controlled studies can be used to assess the effectiveness of interventions on long-term outcomes or rare events that are not suitable for evaluation within experimental studies. An example could be the effect of methadone maintenance treatment for heroin-dependent subjects on all-cause mortality.

Observational cohort studies could also be used to assess the effectiveness of intervention in clinical settings where randomisation is not practically feasible nor ethically acceptable; for example randomised controlled trials are not ethically feasible to assess the effectiveness of bilateral prophylactic mastectomy or bilateral prophylactic salpingo-oophorectomy as a risk reduction strategy for women with BRCA germline mutation.

Feasible randomised controlled trials

Effectiveness of opioid therapy for pain relief in cancer patients could definitely be assessed by randomised controlled trials. For example, the Cochrane review that assesses the efficacy of oral morphine for cancer pain includes 45 randomised controlled trials with 2061 subjects [6], while the Cochrane review on opioids for the management of episodic pain in cancer patients includes 4 randomised double-blind controlled trials with 393 participants [7].

Is this evidence sufficient? Despite the importance of cancer pain control in patients' agendas, we have very little and often sub-optimal evidence. The median number of patients enrolled in randomised trials of primary analgesics (NSAIDs, opioids and adjuvants) was 70 or fewer. Furthermore, these trials constitute about 1% of the published literature on cancer pain, enrol 1 in 10 000 patients at risk for cancer pain in developed countries, are often heterogeneous and are often of poor methodological quality [8]. We do not know which route of administration is better, which drug to select first, which one as a second line or when to use combinations. Nothing about children. Methodologically sound trials with cancer pain relief as a primary outcome are required in patients with well defined disease and pain.

The clinicians and researchers engaged with cancer pain should weigh the words that Doug Altman wrote more than ten years ago in an editorial which is still dramatically current: "We need less research, better research, and research done for the right reasons" [9].

Clinician's point of view

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To avoid pain is a universal right.

According to the World Health Organization the consumption per capita of morphine is one of the more reliable pointers of the quality of the analgesic therapy for cancer pain and other strict physical suffering.

Patient studies have contributed largely to the decrease in cancer death rates in the world. Clinical studies have also led to better pain control methods, such as continuous pain-medication infusion pumps, first developed in the early 1980s, but the problem of cancer pain control represents one of the main problems in the management of cancer patients, particularly in minorities, women and the elderly.

Unfortunately, it shares with pain control in general the difficulties in precisely evaluating the efficacy and the appropriateness of treatment strategies. This stems from several reasons, including: difficulties in distinguishing the different causes and mechanisms of cancer pain; the need for a multidisciplinary approach including general practitioners, specialists who may be able to care for patients who have difficult pain problems including palliative care physicians, clinical nurse specialists (CNS), pain relief anaesthetists, pharmacists, psychologists and physiotherapists; and the difficulties in assessing the precise contribution of the individual drugs, most often administered simultaneously.

More high-quality experimental studies are urgently needed, with more complete descriptions of pain, improved statistical reporting, controls over adequacy of and compliance to the intervention, use of single interventions, and use of more complex measures of affective outcomes.

Only in this way will we be able to obtain good-quality evidence to translate into good-quality Evidence-Based Guidelines.

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