Use of Strong Opioids in Advanced Cancer Pain: A Randomized Trial

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Background

- The World Health Organization (WHO) therapeutic ladder for the treatment of cancer pain has recommended using nonsteroidal anti-inflammatory drugs (NSAIDS) or acetaminophen as first-line treatment for cancer pain.
- This recommendation has come under intense scrutiny, as these treatments may be inadequate for cancer pain, particularly given the well-established efficacy of opioids for cancer pain treatment.
- Physicians often underutilize opioids in cancer pain treatment due to the fear that opioid use will lead to dependence.
- This study evaluated the use of strong opioids as first-line treatment in patients with terminal cancer, compared to the WHO guidelines for opioid use as third-line treatment.

Methods

- 100 patients with a diagnosis of cancer and under palliative home care were included.
- Patients receiving disease-oriented treatment were included, although such treatment was not required.
- Patients were age 15 years or older, had somatic or visceral pain with untreated pain intensity no greater than 6/10 on a visual analogue scale over the past week.
- Patients who were unable to perform follow-up, who had impaired sensory or cognitive function, and who had previously used strong opioids were excluded.
- Patients were randomly assigned to two groups:
  - Group A: Treated according to WHO therapeutic ladder with non-opioids as Step I, "weak" analgesics combined with non-opioids as Step II, and "strong" opioids combined with non-opioids as Step III.
  - Group B: Treated immediately with strong opioids, with dosages determined on a per case basis.
- In both groups, opioids could be combined with non-opioid analgesics.
- If immediate-release drugs were used, the evening dose was doubled to reduce the risk of breakthrough nighttime pain.
- Rescue medication in the form of higher dose or additional drugs was used to treat breakthrough pain.
- Co-analgesic drugs with additional, non-pain indications were permitted in some cases because of demonstrated efficacy in certain pain syndromes (e.g. anti-convulsants, anti-depressants, etc.)
- The least invasive route of drug administration was preferred.
- If necessary, anesthetic and neurolytic blocks, psychotherapy, and physiotherapy were also provided.
- If a patient underwent a neuroablative procedure due to pain refractory to pharmacologic intervention, the patient was excluded from the study.
- All patients were evaluated by the same pain clinician once weekly. Evaluation included multidimensional quality of life (QOL) measures, treatment side effects, drug tolerability, satisfaction with analgesic treatment, and Karnofsky Performance Status (KPS).
- Patients were also asked to keep a pain diary and to rate their daily pain as well as the side effects from therapy.
- A responsible relative was also delegated to provide daily evaluation of pain.
- Endpoints included pain intensity, general condition, KPS, QOL, patient satisfaction with the therapy, number of weeks described as satisfactory, and incidence of therapeutic change.
Results

- 8 patients were excluded (2 in Group A, 6 in Group B) for the following reasons: refusal to continue in study, receiving neuroablative therapy, lost to follow-up, or duration of treatment less than 15 days.
- There were no differences between the two groups with respect to age, gender, primary site of disease, primary site of pain, duration of treatment, baseline QOL, baseline KPS, or mean pain score.
- Both groups experienced decline in KPS and disease-related QOL during the trial.
- Patients treated with first-line strong opioids (Group B) experienced greater decrease in pain intensity scores compared to patients treated according to the WHO guidelines (Group A) (-2.61 vs. -1.92, p=0.04).
- Group B also had a higher percentage of cumulative weeks during which treatment was defined as "satisfactory" (85.6% vs. 80.5%, p=0.04), and a higher percentage of cumulative weeks without a therapeutic change (48.9% vs. 59.3%, p=0.001).
- The patients' general condition, as scored by the patients themselves, was better in Group B than in Group A (4.98 vs. 4.23, p=0.007).
- There was no difference in general condition between the two groups as scored by a responsible relative.
- When a therapeutic change was initiated, both the pain intensity reported by the patient and the patient's general condition scored by a relative was better in Group B compared to Group A.
- Nausea was more frequent in Group B (437 episodes vs. 315 episodes, p=0.0001).
- There was no difference between the two groups in the rate of vomiting, constipation, gastro-enteric bleeding, and periods of mental confusion.
- 48% of patients in Group A progressed to strong opioids.

Authors' Conclusions

- The problem in treating cancer pain is not necessarily finding effective therapy, but rather appropriately choosing available therapies.
- The current study shows that NSAIDs, alone or in combination with weak opioids, are potentially effective in the treatment of mild or moderate pain; however, they are less effective than first-line strong opioids.
- Even in these patients with less intense pain (baseline pain score ≤6), strong opioids appear to be at least as effective and better tolerated.
- The reduction in both KPS and QOL in these patients is expected in patients with terminal cancer; however, the declines in these measures were the same in both groups.
- The greater reduction in pain intensity with the use of first-line strong opioids supports their use at an appropriate dosing schedule.
- The prescription of non-opioids or weak opioids may lead to side effects that actually present a greater risk to the patient than first-line strong opioids.
- The short period of survival together with the combination of effective adjuvant drugs may eliminate the fear of long-term tolerance and dependence.
- Strong opioids should be considered an important instrument in the care of patients with intractable pain.

Discussion

The current article compares two strategies for pain management in patients with terminal cancer. Given that cancer pain has such a profound effect on the QOL in these patients, optimizing pain control should be a priority in their treatment. This study shows that treatment with first-line "strong" opioid results in decreased pain intensity and may have been better tolerated, as evidenced by the lower frequency of therapeutic changes seen in the first-line strong opioid group. Although the WHO ladder for pain management has been shown to be effective, a stepwise approach to pain management may not be the optimal approach to management in this particular group of patients who often have limited life expectancies. In this study, careful titration of strong opioids resulted in improved pain control without significantly worsened toxicity. First-line strong opioids
should be considered in all patients with disease-related pain in patients with terminal cancer.

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