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Original Article

Low-Dose Morphine versus High-Dose Tramadol for management of moderate cancer pain: a comparative study

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Abstract
Introduction: *The treatment of pain in cancer patients following the guidelines outlined by World Health Organisation has been found to be feasible and effective. The guidelines recommend a sequential three-step analgesic ladder for treatment of pain but there is a lack of conclusive data regarding the management of moderate pain with step II weak opioids or low-dose step III strong opioids.*
Methods: *In total, Eighty two adult patients with moderate cancer pain were included in this randomised controlled study to receive either low dose morphine or high dose tramadol. The primary outcome was the number of responder patients where the response was defined as patients with a 20% reduction in pain intensity on the numerical rating scale.*
Results: *The primary outcome occurred in 85.8% of the low-dose morphine and in 57.8% of the tramadol group (odds risk, 4.41; 95% CI,P<.001). The percentage of responder patients was found to be higher in the low-dose morphine group in this study. Clinically meaningful (>30%) and highly meaningful (>50%) pain reduction from baseline was significantly higher in the low-dose morphine group (P <.001). Due to inadequate analgesia a change in the treatment process occurred more frequently in the tramadol group. The general condition of patients, which was based on the Edmonton Symptom Assessment System (ESAS) overall symptom score, was better in the morphine group. Adverse effects were similar in both groups.*
Conclusion: *Moderate cancer pain can be managed significantly better by low dose morphine than tramadol with early onset of action and similar level of adverse effects.*
Keywords: *Moderate cancer pain, tramadol, morphine.*

Introduction

The WHO guidelines on cancer pain management or palliative care are based on a sequential, three-step, analgesic ladder according to pain intensity: non-opioids (paracetamol or non-steroidal anti-inflammatory drugs) to mild pain in step I; weak opioids (eg, codeine or tramadol) to mild-moderate pain in step II; and strong opioids to moderate-severe pain in step III.[1-3] Whereas non-opioid analgesics and opioids for moderate to

severe pain are indisputable, the use of opioids for mild to moderate pain has been widely discussed. Several authors wish to abolish WHO step2 and to initiate early low-dose morphinetherapy.[4-6] Despite the widespread use of this ladder, unrelieved pain continues to be a substantial concern in patients with either solid or hematologic malignancies,[7-11] and a common reason is represented by the inadequacy of analgesic therapy, which may be influenced by multiple factors, including a nonspecific setting for cancer pain and opiophobia.[7,12,13] Tramadol is an opioid for mild to moderate pain and exerts additional analgesic effect by inhibition of serotonin and noradrenaline reuptake.[14] Oral tramadol 200–400 mg/d is effective and safe in the treatment of cancerpain[15-19]. The present evaluation compares the efficacy and safety of high doses of oral tramadol (≥300 mg/d) with low doses of oral morphine (≤60 mg/d).

Our study, a randomized controlled study designed to evaluate the efficacy and tolerability of low doses of morphine in comparison with standard doses of weak opioids in the treatment of moderate cancer pain in patients.

Patients and Methods

This study have been done in a tertiary care centre of West bengal for 28 days and patients have been randomly allocated into one of the two groups.

Study Population: Patients with cancer who are opioid naive, with moderate pain intensity (4-6 on the standard Numerical Rating Scale [NRS], range 0-10)[20]were included in the study after screening for eligibility criteria: age >18years; there is no cognitive impairment or psychiatric illness; and estimated survival of at least 3 months.

Study Treatments and Procedures: Patients were randomly allocated to receive either low-dose oral morphine (M) or a weak opioid (WO) from randomization until day 28.The WO group could receive oral formulations of tramadol alone or combinations with paracetamol. The minimum effective dose of WO was scheduled for a progressive increase, if necessary up to the maximum recommended dose 400 mg/day, or 300mg/day if patients were older than 75 years, for tramadol. The maximal daily dose of paracetamol was set at 4000 mg/day.

M group patients underwent a 3-day titration phase with normal-release oral morphine up to 30 mg daily[21], and, thereafter, continued with slow-release morphine. Both the group switch to a strong opioid in the WO group and the switch to another strong opioid in the M group were allowed only when the therapeutic dose was reached and were considered as an end-point, at the end of study observation. On days 7, 14,21, and 28 patients were monitored after randomization. The frequency of adverse effects was assessed at every follow-up visit. This included presence of vomiting, constipation, dry mouth, itch, dizziness, somnolence, cognitive impairment, pseudohallucinations, myoclonic jerks, and other expected opioid-related toxicities.

A responder patient was defined as a patient who was experiencing a reduction of pain intensity of 20% or more from baseline[22], and the number of responder patients at 28 days or at the end of observation, whichever came first, was set as the primary end point. The proportion of pain reduction was calculated by the following formula: (pain intensity at final time -pain intensity at initial time)/ (pain intensity at initial time) × 100. Secondary outcomes included improvement in physical symptoms and overall well-being as assessed with ESAS[23-25]; number of patients with a clinically meaningful (>30%) and highly meaningful (>50%) reduction of pain intensity from baseline[26]; mean increase of opioid dosage calculated as opioid escalation index percentage according to the formula (OMD-OSD)/OSD/days ×100, where OSD is the opioid starting dose and OMD the opioid maximal dose[22]. Type and incidence of adverse effects, and therapy discontinuation, were evaluated at each visit.

Results

A total of 82 opioid-naive patients with cancer with moderate pain (NRS, 4 to 6) were enrolled on to the study, of 82 patients, 41 patients (50%) were assigned to low-dose oral morphine (M) and 41 (50%) were assigned to weak opioids (WO).

The primary end point of pain reduction of 20% or more from baseline was achieved in 85.8% of patients (35 of 41) in the M group and in 57.8% of patients (23 of 41) in the WO group (odds ratio, 4.41; 95% CI, P <.001). At the end of 28 days , a satisfactory pain control was found in both groups, although with a statistically and clinically significant advantage for M (median NRS score, 1; IQR, 0 to 2) compared with WO (median NRS score, 2; IQR, 0 to 4; P = .02). The linear mixed-model analysis to evaluate the time course of pain intensity score in each group showed that over time there was a greater reduction in pain intensity in the group treated with morphine (interaction P = .001). The findings related to the other measures of outcome are strictly consistent with the main results. A clinically meaningful (> 30%) and highly meaningful (>50%) pain reduction was found more frequently in patients treated with M than in those treated with WO, with proportions and statistical significance mirroring the broader estimate obtained for the primary end point.

Adverse Events: Both drug treatments were well tolerated. The intensity and frequency of opioid-related symptoms were same between the two groups.

Characteristics of patients at baseline

Characteristics	Weak Opioid group (WO)	Morphine group (M)
Male sex	23(55.7%)	19(47.5%)
ESAS overall symptom score		
Median	21	19
Interquartile range	14-33	12-29
Pain Intensity		
Median	5	5
Interquartile range	4-6	5-6

Outcome

	Weak Opioids (WO) (n=41)	Morphine(M) (n=41)	Odds Ratio	*P*
Primary outcome responders	23(57.8%)	35(85.8%)	4.41	<0.001
Secondary outcomes				
Meaningful pain reduction	19(46.3%)	33(80.5%)	4.46	<0.001
Highly meaningful pain reduction	15(36.6%)	30(73.1%)	4.92	<0.001

ESAS at end of study

ESAS item	Weak Opioids (WO)	Morphine(M)	*P*
Pain	4(1-6)	1(0-3)	<0.001
Tiredness	3(2-6)	2(1-3)	<0.001
Nausea	1(0-3)	1(0-1)	.03
Depression	2(1-4)	1(0-2)	<0.001
Anxiety	2(0-4)	1(0-2)	<0.001
Drowsiness	3(1-4)	1(0-2)	<0.001
Appetite	2(1-5)	1(0-2)	<0.001
Well-being	3(1-5)	1(0-2)	<0.001
Shortness of breath	0(0-1)	0(0-0)	.01
ESAS overall symptom score	19(10-17)	10(6-15)	<0.001

ESAS: Edmonton Symptom Assessment System

Discussion

In this study, low-dose morphine significantly reduced pain intensity, as compared with weak opioids in moderate pain among cancer patients, as early as 7 days after treatment. Constipation, dizziness, and other opioid related adverse effects

were almost same, in terms of either intensity or frequency, in the low-dose morphine group. The delayed and lower effect of treatment with weak opioids led to a more frequent switch to step III strong opioids.

In an early retrospective study by Ventafridda and colleagues,[27] the effectiveness of step II of the WHO method had a time limit of 30 to 40 days and, for most patients, the shift to step III was made mainly because of inadequate analgesia rather than adverse events. In current daily clinical practice, step II is often bypassed in favour of strong opioids, although the strategy is not supported by strong scientific evidence, because it was investigated by only two randomized controlled studies enrolling only 92 and54 terminally ill patients respectively,[28,29] and one prospective study[30]. In the study by Marinangeli and colleagues,[28] a significantly better pain relief was achieved in patients with mild-moderate pain treated with strong opioids, compared with those treated with step II opioids, with only nausea more frequent in the former group, whereas no differences in other opioid-related symptoms were observed. In a study by Maltoni and colleagues[29], patients receiving step III opioids had a significant advantage in terms of a reduction in the number of days with the worst pain, but more frequently showed grade 3 and 4 anorexia and constipation. In a prospective study by Mercadante and colleagues,[30] that enrolled only 110 patients with moderate-severe pain, treatment with low-dose morphine (starting dose of 15 mg/day and in patients >70 years 10 mg/day) was effective and well tolerated. However, these three studies reported inconclusive results because of the low number and representativeness of the patient sample and the low statistical power, leading to a weak recommendation for either a step II opioid or low doses of a step III opioid, as an alternative, in international guidelines[31-33].To the best of our knowledge, our study has provided the first formal proof that, although step II opioids are effective when used for limited time intervals, low-dose morphine can be usefully anticipated and can substitute for weak opioids in patients with cancer and moderate pain, more than half of whom are receiving active antitumor therapy , because of greater efficacy and a comparable toxicity profile.

The observed advantages in the clinical outcome coincide with the doubling of the estimates formulated in the original protocol and translate into a statistical significance ($P < .001$) of the difference, in the primary end point, already in a population which is a half of the one planned, in the original statistical design. The clinical reliability and significance are confirmed by the coincidence of similarly statistically significant findings in the secondary end points, and the ESAS results. The minimal clinical difference for improvement and deterioration of each of the nine ESAS symptoms is one point or more[34]. When the magnitude of symptom changes was assessed by ESAS in the two groups, treatment with low-dose morphine was associated with a significant improvement in either physical or emotional symptoms, providing a further argument in favour of its use in opioid naive patients with cancer with moderate pain. Support of the findings could be seen in the consistency between crude estimates and the results obtained in the fully adjusted multivariate analysis, which could, on the contrary, be rather sensible to the instability associated with the small numbers of the population. Despite confidence in the outcome of the study, we are aware of aspects of the trial, which could be considered structural, more than formal, weaknesses, namely, the lower and too long accrual of patients, assessed in an exploratory interim analysis which became (because of the surprising available evidence) a, somehow, mandatory stopping rule; the absence of pharmacologic quantification of rescue prescriptions; the open-label design. Relevant to this, opiophobia caused by the reluctance of patients and/or their families to accept strong opioids is a well-described cause of under treatment of pain and may result in a low compliance with the recommended doses.

Conclusion

Our study demonstrated that compared with step II opioids, low-dose morphine provided an earlier and a more adequate level of analgesia for moderate cancer pain, with a fairly good tolerability profile and a positive impact on overall well being. In most countries, strong opioids are highly regulated, and oncologists, family physicians, and internists may prefer to prescribe weak opioids because of lower regulatory requirements, including special prescriptions forms. However, our data show that this intermediate step may be less effective and more expensive. The current WHO recommendation has the three-step pain ladder as the basis for treatment of cancer pain. New guidelines, including that by the EAPC, describe a two-step approach as an alternative. To abolish the second step will simplify treatments and perhaps give patients with cancer better pain control. Whether the findings of this study, which are in favour of starting directly with a step three opioid, may contribute to changing the WHO guidelines must be confirmed by other studies.

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