Is Sublingual Buprenorphine A Succour for Cancer Pain Patient in Centres where Narcotic Licence is Not Permitted

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ABSTRACT

Introduction: Chronic pain occurs in 70-80% of cancer patients. The concerned about the development of dependence, tolerance, addiction, respiratory depression and severe constipation led to the growing interest in the use of analgesics which have antagonist properties. The aim of this study was to assess whether buprenorphine is associated with superior, inferior or equal analgesic potency and tolerability as compared to morphine.

Material and Methods: 40 patients with moderate to severe pain were randomized into two equal groups of 20 each. Group-A received sustained release 30 mg oral morphine one tablet 12 hourly and group B received sublingually tab buprenorphine 0.2 mg 8 hourly. VAS, number of rescue doses, compliance and adverse effects were noted. The duration of study was 12 weeks.

Results: The VAS score in both the groups was comparable in moderate pain group. The VAS score and number of rescue doses were more in buprenorphine group in severe pain patients. Compliance in buprenorphine group was better due to absence of constipation in moderate cancer pain patient.

Conclusion: In moderate cancer pain S/L Buprenorphine was appreciated by the patients due to less constipation while in severe pain morphine was found to be better.

Keywords: Sublingual Buprenorphine, Cancer Pain, Narcotic Licence

INTRODUCTION

Chronic cancer pain is difficult to manage due to associated medical and psychosocial problems. The goal of treating chronic cancer pain is to eliminate or reduce pain, to improve patient's quality of life and to minimize medication side effects. ASCO (American Society of Clinical Oncology) had published its guidelines for screening, comprehensive assessment, treatment and care options.

These goals may be achieved by use of longer acting medication or dosage forms that will provide stable analgesia, increased patient compliance and minimal adverse events and better pain control with lower risk of physical and psychological dependence.

Opioid analgesics are the primary therapeutic agents used for moderate to severe cancer pain. The initiation of treatment with opioid should be based on titration rule. To find out the optimal opioid dose to provide effective and well tolerated analgesia we carried out a pilot study on 12 indoor patients. Based on this pilot study, the present study was conducted in tertiary care cancer hospital. The study was initially done with morphine and later on continued with buprenorphine as due to imposition of numerous regulatory provisions and lack of universal availability of morphine thereof. This made buprenorphine an attractive option for pain relief in cancer patients. Since the drug was available in the institute and the response being more encouraging in the pilot study, we chose to expand our initial study.

Due to its unique pharmacology of antagonism buprenorphine has a low physical dependence and absence of constipation. The aim of this study was to assess whether buprenorphine is associated with superior, inferior or equal analgesic potency and tolerability as compared to morphine.

MATERIAL AND METHODS

After institutional ethical committee approval and written informed consent from the patient. 40 patients with moderate to severe chronic cancer pain were included in the study. Patients were randomized into two groups of 20 each. Group A received 30 mg sustained release morphine tablet on scheduled 12 hourly bases at 8 AM and 8 PM and group B received 0.2 mg sublingual buprenorphine tablet 8 hourly. The dosing frequency was kept constant throughout the study period. Dosage adjustment were not permitted during the trial. The patients were requested to strictly respect the dosage schedule of treatment as prescribed. Break through pain was managed with immediate release morphine 10 mg in both the groups with locking period of 4 hours. Buprenorphine was not used as rescue dose because of its long half life.

Patient having hepatic and renal insufficiencies, nausea, vomiting and true allergy were excluded from the study. By the time patient reach our pain clinic they had already received step I and Step II of WHO analgeisc ladder[2] drugs. Thus for starting opioid therapy we used conversion factor of 5 for converting dose of tramadol to morphine which came out to be 300÷ 5 = 60 mg/day.

The patients were assessed for pain intensity four times a day by one fixed person who was attending the patient at home. 10 cm visual analog scale (VAS) and Numerical scale

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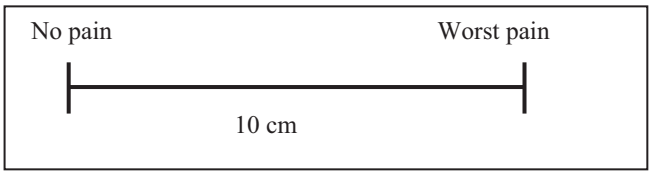

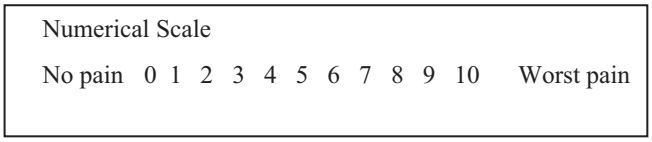

Figure–1: Visual Analogue Scale

WHO analgesic ladder	
Step 1 (pain <3/10)	Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs)
Pain persisting or increasing?	
Step 2 (pain < 3-6/10)	Weak opioid for mild-to-moderate pain + paracetamol and NSAIDs +/- adjuvant analgesic.
Pain persisting or increasing?	
Step 3 (pain >6/10)	Strong opioid for moderate-to-severe pain + paracetamol and NSAIDs +/- adjuvant analgesic.
Objective: freedom from pain.	

Figure–2: WHO analgesic ladder

starting at zero as no pain and 10 as excruciating pain was used to note the intensity of pain. (Fig1 and Fig 2)
Number of rescue doses of morphine were calculated in both groups and adverse effects were noted in both groups.

STATISTICAL ANALYSIS

The results were expressed as mean ± standard deviation. Student's 't' test was used for testing the significance between the two study groups.

RESULTS

The demographic profile of age, sex, weight and type of malignancies were comparable in both the study groups. Most common malignancies were oral, breast, cervix, lungs and gallbladders.
The VAS score in patients with moderate pain N=16 in group A was 0.94±0.68 and in group B 1.00±0.73 (P= 0.804), which was comparable in both the groups.
The VAS score in patients with severe pain N=4 in group A was 2.00 ±0.81 which was less than that in group B 3.00 ± 1.41, P=0.267.
Number of rescue doses were significantly more in buprenorphine group 2.25±1.11 especially in severe pain patient as compared to morphine group 1.20 ±0.83, P=0.002.
Compliance was good in buprenorphine group because of less side effects. Adverse effects like constipation was almost absent in buprenorphine group.

DISCUSSION

Itiology of pain is related to the site of origin of cancer staging and treatment when the intensity of pain is moderate to severe there is a consensus that opioid therapy is the first line of treatment of cancer pain.
Most opioid drugs are mu receptor agonist which may be divided into pure agonist like morphine and fentanyl and agonist antagonist like buprenorphine. The success of opioid therapy requires individualization of the dose by using a process of dose titration by which increments in dose are undertaken to identify a stable dose associated with favorable balance between analgesia and adverse effects.
Oral morphine is usually considered as first line in treatment of cancer pain.[3] After administration the peak plasma levels reach at 30-90 min.[4] absorption is mainly from duodenum[4] Bioavailability[4] of morphine is low owing to extensive first bypass metabolism in the liver. The peak plasma levels of controlled release morphine occur at 150 min.
Bioavailability of controlled release morphine is 85% to 90% that of immediate release morphine. The metabolites of morphine are M3G and M6G. M3G a major metabolite has no analgesic potency and may influence the development of morphine tolerance. M6G has higher analgesic potency.[4]
Morphine act on opioid receptors located in periaqueductal and periventricular grey matter, medulla and spinal cord.[5]
Buprenorphine is an agonist antagonist especially considered good for neuropathic pain.[6] The antagonist properties of buprenorphine avoids social problems of addiction. It is mostly used sublingually or transdermal, oral bioavailability is 15% due to extensive first pass metabolism[8]. Buprenorphine does not accumulate in renal and hepatic failure.[6]
Breakthrough pain - This is a transient pain described as brief exacerbation of pain that occurs in the background of stabilized pain management adequately controlled by round the clock opioid therapy. The rescue dose should be prescribed from the start of maintenance treatment as break through pain can occur at any moment. The rescue dose should be 1/6th of the total daily dose as recommended by NICE (National Institute for Health and Care Excellence). If more than 2 doses are required for breakthrough pain over a 24 hours period in order to achieve adequate pain control once steady state has been reached, then clinicians may consider increasing the dose of opioid by 25% to 33% but in our study in buprenorphine group the incidence of breakthrough pain was 2.25±1.11 only so we did not increase the total dose. The locking period was kept at 4 hours.
In our study the VAS score in patient with moderate pain were comparable in both the groups. But in patient with severe to excruciating pain the VAS score was more in buprenorphine group as compared to morphine group.
The requirement of rescue dose in buprenorphine group was significantly more than that in morphine group. This increase in rescue dose was because 4 patients had severe to excruciating pain.
The compliance in buprenorphine group was better than in morphine group and patients were happy due to the absence of adverse effects like constipation. Drowsiness was acceptable as we used low dosages and patients were able to carry out their normal routine indoor and outdoor activities.

CONCLUSION

Sublingually administered buprenorphine seems to be a valuable addition to the range of opioids available for

chronic cancer pain. It has great practical and theoretical advantage of being a morphine antagonist with minimal abuse potential. The only main side effect was acceptable drowsiness. Constipation in buprenorphine group was almost absent. Although in severe excruciating pain morphine was found to be better than buprenorphine. Buprenorphine was found to be equal in analgesic potency in moderate pain but in severe to excruciating pain it is found to be inferior to morphine but better tolerated.

We look forward for sublingual buprenorphine for succor to cancer patients in centers where narcotic license is not available.

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