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To Compare the Efficacy of Sublingual Buprenorphine and Oral Morphine in the Treatment of Moderate to Severe Cancer Pain of Malignant Origin -A Prospective Randomised Controlled Trial.

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Abstract
BACKGROUND: *Pain is a prevalent symptom of cancer of malignant origin affecting 70% of the patients in the advanced stages and almost all patients in the end stage disease. Opioids have been the main stay of treatment. But the fundamental issues of Opioid addiction, development of dependence, tolerance and severe constipation led to the ongoing search for better analgesics with minimal adverse effects. The aim of this RCT was to evaluate the effectiveness of Sublingual Buprenorphine for chronic pain analgesia.*
MATERIAL AND METHODS:*.Patients with moderate severe pain were randomised in to two equal groups of 25 each.*
Group A received Oral Tab Morphine 30mg Sustained released formulation 12th hourly and Group B received Sublingual Tab Buprenorphine 0.2mg 12th hourly. The measures of physical pain i.e. Visual Analog Scale, number of rescue doses compliance of the patients and any adverse events like nausea, vomiting and constipation were taken into consideration.
RESULTS*: 50 Patients were analysed using the student's 't'test. The VAS score in both the groups were comparable in moderate pain intensity group. Mental health and vitality was better in Buprenorphine group. Compliance was good and adverse events were less in Buprenorphine group. The VAS score and number of rescue doses were higher in the Buprenorphine group for severe pain patients.*
CONCLUSION*: Sublingual Buprenorphine was readily accepted by the Cancer patients due to less adverse effects of constipation and can be considered as an alternative to Morphine especially in the areas of Narcotic restrictions.*
Key Words*: Sublingual Buprenorphine, Cancer Pain, Narcotic licence.*

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I. Introduction

Pain is a predominant symptom of cancer affecting approximately 75% of the people with advanced stages and almost all with end stage disease. The World Health Organisation (WHO) pain ladder is the corner stone of pain management with Opioid analgesics being the primary therapeutic agent used for moderate to severe cancer pain. The goals of treating chronic cancer pain is to eliminate pain or reduce pain, to improve quality of life and to minimise the medication side effects[1].

The initiation of the treatment with Opioids should be based on titration rule. To find out the optimal Opioid dose to provide effective and well tolerated analgesia, a pilot study was carried out in 10 indoor patients. Based on that the present study was conducted in tertiary care cancer hospital. It was initially done with Morphine and latter on continued with Buprenorphine due to imposition of numerous regularity provisions and lack of universal availability of Morphine thereof.

Buprenorphine is a newly developed semisynthetic Opioid derivative of thebaine having Morphine like pure " μ" agonistic and antagonistic properties at "κ" Opioid receptors. As the drug was easily available and was an attractive alternative to Morphine in our pilot study we went ahead to expand our initial study.

AIMS AND OBJECTIVES: A randomised prospective study was done at a palliative care pain clinic of a tertiary care medical college with the following objectives.

1. To compare the efficacy of sublingual Buprenorphine with oral Morphine
2. To compare the adverse effects of Buprenorphine with oral Morphine.

II. Materials And Methods:

Inclusion criteria: Patients with solid tumour malignancies suffering from moderate to severe cancer pain, VAS score greater than 4.0 attending our palliative care clinic were included in our study. Patients in the age group 18 to 70 years with duration of pain greater than 3 months were included. Hospital records and physician prescriptions were scrutinised.

Exclusion criteria : Those patients with minimum life expectancy less than two months, those with neurological deficits, those with prolonged respiratory diseases and patients with hepatic, renal insufficiency and patients with severe nausea, vomiting and true allergy were excluded.

After ethical committee approval, all the patients recruited were entitled to give consent along with patient's care givers who were also counselled regarding the potential toxicities arising from drug administration and their remedies.

Patients were randomised in to two groups using computer based randomisation with 1: 1 ratio. The patients in group A received Oral Morphine (Sustained formulation) 30mg / Tab. In 12^{th} hourly doses.

The patients in group B received Sublingual Buprenorphine 0.2mg 12^{th} hourly, scheduled at 8AM & 8PM. Additional drugs allowed were Paracetomol 1gr every 6hours maximum of 4gr daily dose in individual with normal liver function tests. Diclofenac sodium (50mg QDS), Lorazepam 1 mg and short course Dexamethasone (8mg) and other adjuvants such as Pregabalin or Amitryptilline as per requirement.

The patients were assessed with VAS Scores.

The dosing frequency was kept constant throughout the study period without any dosage adjustments. Break through pain was managed with oral Tramadol tablets maximum of 200mg/day.

The patients had already received Step I and Step II of WHO Analgesic ladder drugs. Hence for starting Opioid therapy we used conversion factor of 5.. Tramadol to Morphine 300mg/5 = 60mg/day.

The patients were assessed for pain intensity four times a day by fixed person who was attending the patient at home after giving adequate training to their attendants regarding the VAS score.

VAS score 0 to 10, a Numerical rating scale starting as "0", No Pain and 10 as Worst pain was used to note the intensity of pain. Number of rescue doses was calculated in both the groups and adverse effects were noted.

STATISTICAL ANALYSYS

The results were expressed as Mean ± Standard deviation (SD)

Student "t'' test was used for testing the significance between the two study groups.

III. Results

Study was conducted between August 2019 to February 2020. A total of 50 participants fulfilling our selection criteria were analysed base line parameters regarding the demographic data were comparable.

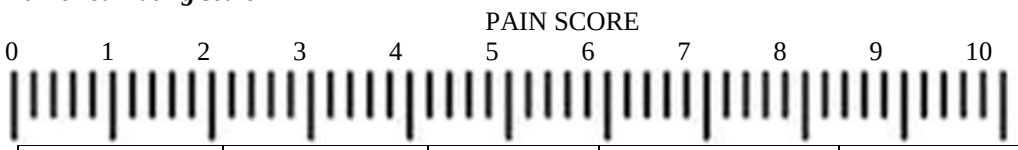
Demographic data comparision between two study groups

DEMOGRAPHIC	GROUP A- ORAL MORPHINE			GROUP B- S/L BUPRENORPHINE		
DATA	Number		Column,n%	Number		Column,n%
Gender						
Female	13		52	11		44
Male	12		48	14		56
Age in Years						
Median		54.00			56	
Mean +/- SD		50.6+/- 11.8			49.8+/-12.9	
Primary Sites						
Head and Neck	8		32	8		32
Breast	4		16	3		12
Cervix	7		28	10		40
Pancreas	5		20	2		8
Others	1		4	2		8
TNM Staging						
II	4		16	6		24
III	14		56	13		52
IV	7		28	6		24

TABLE I

Demographic data were comparable in both the groups and clinically insignificant.

Numerical rating scale



PAIN SCORE	0	1 TO 3	4 TO 6	7 TO 9	10
INTENSITY	No Pain	Mild Pain	Moderate Pain	Severe pain	Worst pain

Table II Visual Analog scale.

Moderate pain patients.

The base line VAS Scores were comparable in both the groups. The initial VAS score in the patients with moderate pain.

N=20 in group A was 5.5 ± 0.76

N = 19 In group B it is 5.5± 0.77

After administration of medication in both these groups i.e. Group A Morphine orally and Group B Buprenorphine Sublingually over 24 hour duration the mean VAS scores were,

N=20 in group A was 1.1± 0.57

N = 19 In group B it is 0.96± 0.54

P Value 0.42 showing that it is clinically not significant.

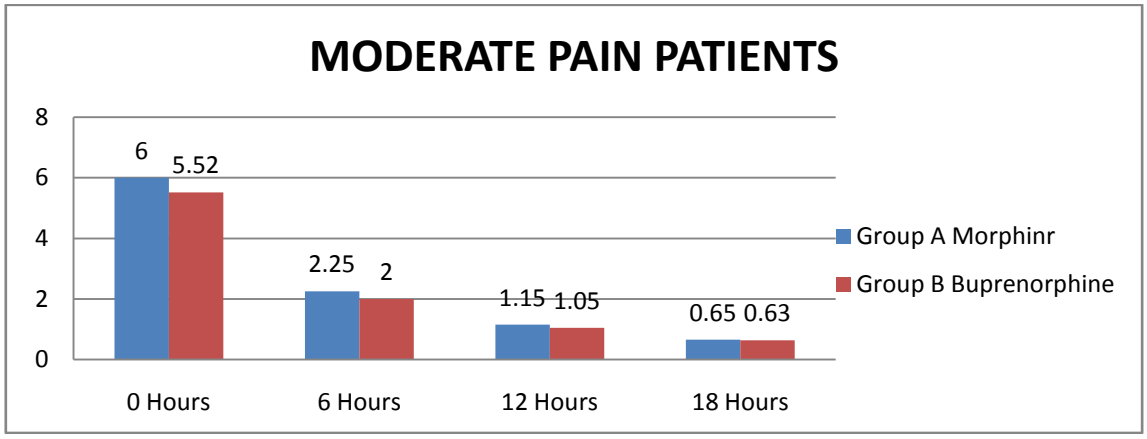


Table 1

Interpretation: The VAS scores were comparable in both the groups.

Severe pain patients:

The initial VAS score in the severe pain patients of Group A and Group B were 8.0±1.414 and 8.3±0.816 respectively.

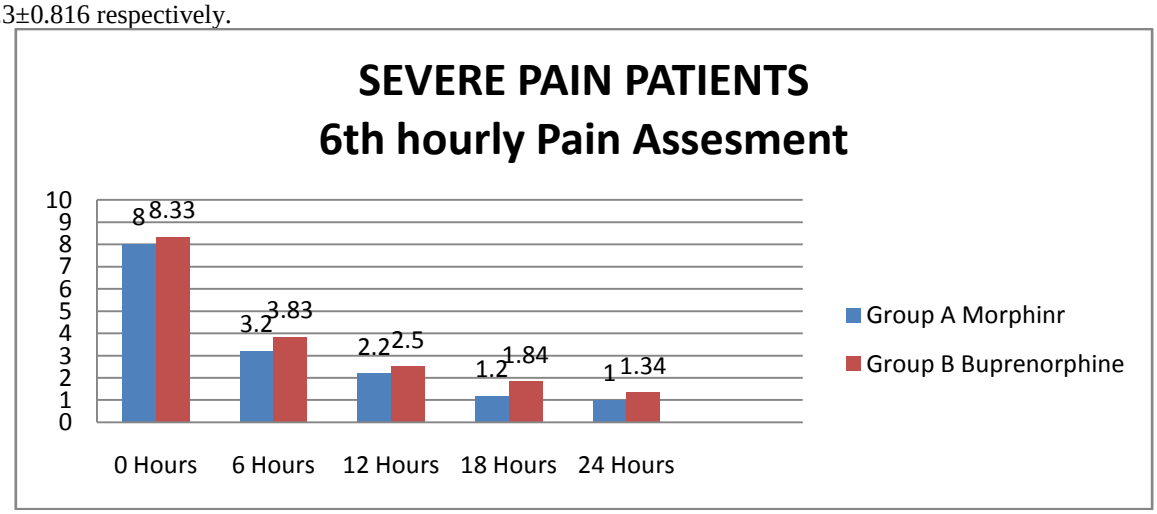


Table 2

Interpretation: The VAS score in the patients with severe pain in Group A is, N=5 in group A was 1.9± 0.706 which was less than that in Group B i.e. N = 6, which is 2.375± 0.947
P =0.37., it was comparable in both the groups and statistically not significant.

Rescue doses

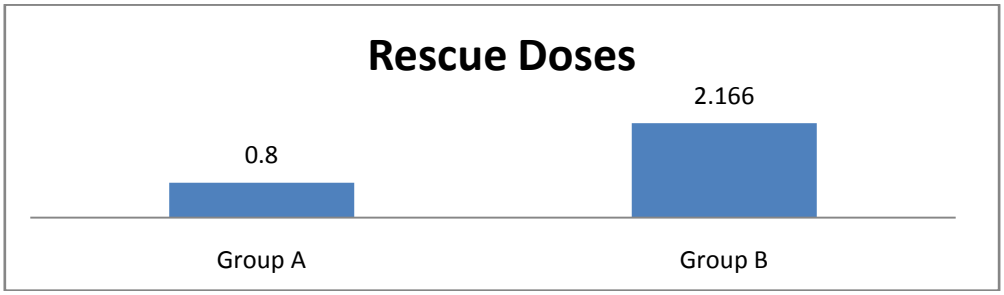


Table 3

Rescue doses needed were significantly more in the Buprenorphine group (Group B) than Group A ,i.e. 2.16 ± 1.169 over the Morphine Group ie.0.8 ± 0.447 especially in the CA patients with metastasis.
p – Value is 0.03 which is clinically significant showing that Morphine was superior to Sublingual Buprenorphine in the patients with very severe pain of metastasis.

Adverse effects

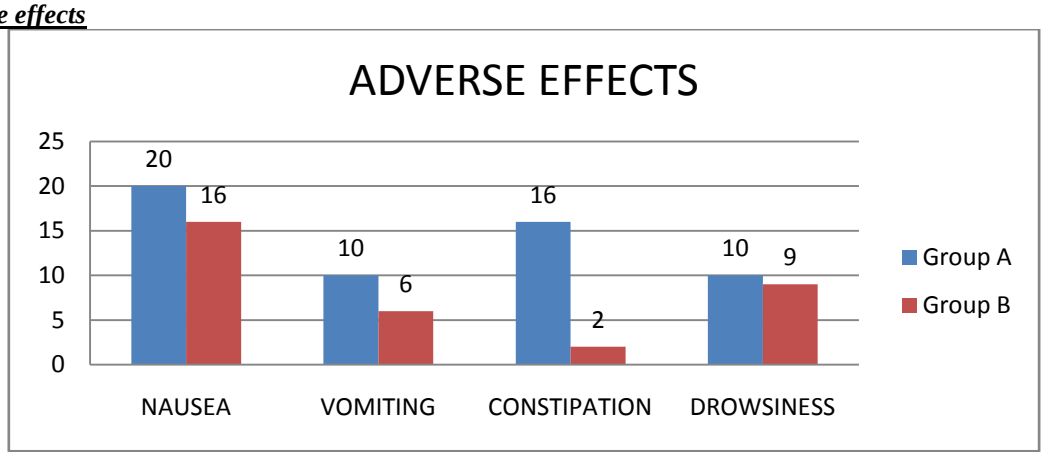


Table 4

Common side effects in both the groups were Nausea, vomiting, constipation and Drowsiness. Both Nausea, Vomiting and Constipation were clinically significant in Morphine Group compared to Buprenorphine Group. The incidence of constipation was remarkably low with Buprenorphine. The patient compliance was good who were taking Buprenorphine. However the toxicities were manageable and no patient was discontinued from the study due to toxicity.

IV. Discussion

Opioid are the market leaders for the treatment of moderate to severe malignant cancer pain. The etiology of the pain is related to site of origin of cancer, staging, as well as its treatment. Those individuals with metastasis have the worst pain.

Opioids act upon the '' μ '' receptors to exercise its analgesic effect. Certain drugs like Morphine and Fentanyl are pure agonist where as others like Buprenorphine[2] is partial agonist – antagonist. The rationale of Opioid therapy is individualisation of the dose by using a process of dose titration by which increments in the dose are undertaken to identify stable dose associated with favourable balance between analgesia and adverse effects.

Morphine, an age old drug is considered to be the first line drug of moderate to severe cancer pain[3]. It acts on Opioid receptors located in peri aqueductal grey matter, peri ventricular grey matter, medulla and spinal cord. After the oral administration the peak plasma level reaches at 30 to 90 minutes, absorption occurs from the duodenum. Bio availability of Morphine is low owing to extensive first pass metabolism in the liver. The bio availability of sustained release formulation is 85% to 90%, that of immediate release Morphine[4]. The metabolites of Morphine are Morphine 3 Glucoronide and Morphine 6 Glucoronide.(M3G and M6G). M3G , a

major metabolite has no analgesic potency and might be responsible for development of Morphine tolerance. M6G has high analgesic potency.

Buprenorphine hydrochloride [2] is a partial '' μ '' receptor agonist, and oxidised low density lipoprotein receptor-1 agonist and Delta and Kappa receptor antagonist[4]. It is classified as a Schedule 3 controlled substance. It is used for managing acute surgical pain, Cancer and Non cancer pain[5]. It has a unique distinction of having the US – FDA approval for the three unrelated indications[6]. Opioid detoxification, Opioid maintenance and pain management. Buprenorphine is available for intravenous use, as rectal suppository, as a transdermal patch and as a sublingual preparation. (Tablet and film). Due to its extreme first pass metabolism, enzyme CYP-3A4 in the gastrointestinal tract when taken orally it is not effective by this route. When used sublingually there is 30% to 60% bio availability as hepatic first pass metabolism is avoided SL Buprenorphine is available as 200 micro grams tablet. It takes 10 mins to dissolve and around 60 to 90 minutes to achieve maximum plasma concentration. Other issues with commonly used Opioids such as addiction, abuse and tolerance are less with Buprenorphine as it is not a pure agonist [7,8,9]. Buprenorphine is also used in combination with Naloxone[10] for reducing Opioid dependence[11] for Opioid substitution therapy[12, 13]. It is started as 2mg sublingual tablet and gradually increased as tolerated up to 24 mg / day. Such a high dose is not indicated in Opioid naive patient. It is also considered for neuropathic pain. it has also been used for break through pain[14], which is defined as transient exacerbation of pain that occurs in the back ground of stabilised pain management adequately controlled by round the clock Opioid therapy. The rescue dose needs to be prescribed from the start of the therapy. It should be 1/6 of the total daily dose as recommended by NICE, (National Institute for Health and Care Excellence). If more than two doses are required over a period of 24 hours in order to achieve adequate pain control once study state has been reached then the clinician may consider increasing the dose of Opioid by 25% to 33%. But in our study the break through pain was 2.25 ± 1.11 only. So we did not increase the total dose. The requirement of the rescue dose in Buprenorphine group was significantly more than in the Morphine group as 4 patients had very severe excruciating pain. Compliance in the Buprenorphine group was better than the Morphine group as the patients did not have adverse effect like constipation. Drowsiness was acceptable as we used low doses and patients were able to carry out their normal routine activities.

Transdermal Buprenorphine patches[15] also found to be effective and tolerable in the moderate to severe cancer patients.

V. Conclusion

Buprenorphine administered sublingually appears to be a safe alternative to Morphine in the treatment of chronic pain of malignant origin[16]. Buprenorphine carries higher discriminatory profile verses '' μ '' agonist (Morphine, Fentanyl and Methadone). Safety of Buprenorphine[17] is much superior over the other marketed Opioids because of

1. Ceiling effect on respiratory depression.
2. Lower constipation.
3. Anti hyperalgesic profile and low tolerance.
4. Feasibility of the drug and ability to procure without Narcotic licence.

The only main side effect was acceptable drowsiness. Although in cases of very severe excruciating pain, Morphine was found to be better. Buprenorphine was found to be equipotent to Morphine in the treatment of moderate pain and better tolerated. So it can substitute Morphine in the centres where narcotic licence is not available.

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