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Original Research Article

Compliance, efficacy and quality of life for oral morphine versus transdermal fentanyl patch in management of cancer pain

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ABSTRACT

Background: A randomized, open, two-period, crossover study was done on cancer patients requiring strong opioid analgesia (n=104, mean age 63.5, range18-83 years) recruited from State Cancer Institute, Gauhati Medical College and Hospital, comparing transdermal fentanyl with oral morphine.
Methods: Patients received one treatment for 15 days followed immediately by the other for 15 days.
Results: Transdermal fentanyl provided good pain relief and it was also was associated with less constipation when compared to oral morphine($p<0.05$). Of those who were able to express a preference, significantly more preferred fentanyl patches.
Conclusions: Transdermal fentanyl patch provided good pain relief, equivalent to that provided by oral morphine, required lesser rescue doses, improved quality of life and is associated with less constipation when compared to morphine, and was preferred more by patients.

Keywords: Transdermal fentanyl, Morphine, Chronic pain, Cancer, Opioid analgesics

INTRODUCTION

More than 1 million new occurrences of cancer are diagnosed in India annually.[1] Among patients with cancer, pain is one of the most common symptoms and often has a negative impact on patients' functional status and quality of life (QOL). Despite increased attention on assessment and management, pain continues to be one of the most prevalent symptom in patients with cancer.

In our country, more than 75% of patients are in the advanced stage of cancer when first diagnosed. Pain is the most common symptom in 70-90% of people with advanced cancer. Approximately 30-50% of people with cancer experience pain while undergoing treatment.[2]

This study aims to compare the compliance, analgesic efficacy and impact on quality of life of patients on transdermal fentanyl patch and oral morphine for relief of moderate to severe pain.

Morphine, the prototypical opioid analgesic, is primarily metabolized in the liver by the uridine 5'-diphosphoglucuronosyltransferase isozyme (UGT2B7) possibly (and to a small extent by UGT1A1)22 to M3G and M6G.[3] In humans, approximately 60% of a morphine dose is converted to M3G and 10% to M6G.[4] M6G is predominantly eliminated from the body by renal excretion.[5]

Fentanyl is a strong opioid (approximately 75–100 times more potent than morphine), highly lipophilic and binds strongly to plasma proteins.[6,7] Its volume of distribution is large (3.5–81 kg−1) and its clearance relatively high (30–72 l h−1. Fentanyl is thought to be predominantly metabolized in the liver by cytochrome P450 iso-enzyme 3A4 (CYP3A4)-mediated N-dealkylation, resulting in the

inactive metabolite norfentanyl. Less than 1% is metabolized by alkyl hydroxylation, N-dealkylation or amide hydrolysis to the inactive compounds hydroxyfentanyl, hydroxynorfentanyl and despropionylfentanyl.[8,9] Unknown metabolic routes may be responsible for a significant part of fentanyl metabolism.[10]

METHODS

The present study was conducted in the department of pain and palliative medicine, State Cancer Institute, Guwahati Medical college after getting approval from Institutional Ethical Committee from January 2021 to September 2021. It is randomized open two period crossover study conducted on 104 patients with moderate to severe pain, requiring strong opioids. The inclusion criteria are patients with moderate to severe pain requiring strong opioids, aged above 18 years. The exclusion criteria are any patient who refuses to give consent, with known allergy to the study drugs, unable to take orally or history of opioid abuse. All the patients enrolled for the study were explained about the procedure and proper written and informed consent were taken.

Patients were divided in 2 groups, Group A and Group B, of 52 each. Group A received oral morphine tablets 10 mg 4 hourly and Group B received transdermal fentanyl patch 25 mcg/hour every 72 hours for the first 15 days.

For the next 15 days, Group A received transdermal fentanyl patch 25mcg/hour every 72 hours and group B received oral morphine tablets 10 mg 4 hourly.

At the beginning, all patients had a medical examination. Baseline assessment of performance status, pain score and quality of life (QOL) was done. Pain score was measured on Visual Analogue Scale (VAS) and QOL assessment was done using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ –C30). Further assessment was done on day 15 and day 31 using VAS and EORTC QLQ-C30.

Patients were explained about Visual Analogue Scale (VAS) and the score was recorded as per their response on day 1. They were further asked to maintain a diary and record their pain score, VAS, on day 7. On the 15th day, both the group of patients were called for review, their VAS recorded and drug was changed from morphine to fentanyl and vice versa. Both group of patients were then asked to record their VAS on day 23 and they were finally called for evaluation on day 31.

Statistical analysis

The null hypothesis was that equal proportion of patients would prefer each treatment. Patient preference was tested using a chi-square test to compare those who expressed a preference with those who did not, and a binomial test to determine a difference in preference between the two treatments. Data from VAS were expressed as a percentage maximum area under the curve (AUC). The McNemar test was performed to compare data on constipation and other side effects. For all statistical tests, a p value less then 0.05 was taken to indicate a significant difference at 95% confidence level.

RESULTS

A total of 104 patients entered the study. Their mean age was 63.5 years (range, 18-83 years) and 67 (64%) were men. There were no significant differences between the groups that received fentanyl in the first phase (n = 52) and the group that received morphine first (n=52) in terms of age, gender, baseline VAS and EORTC QOL ratings. 66 patients completed the study, further details given in table 1.

Table 1: Pain attrition during trial.

	Treatment groups	
	Fentanyl/ morphine	**Morphine/fentanyl**
Patients entered	52	52
Patients completed	39	27
Reasons for withdrawal		
Death	2	3
Withdrew consent	3	8
Others	8	14

Table 2: Assessment of pain and its relief.

Pain control recorded by patients as	Fentanyl	Morphine
Successful	50 (63.3%)	43 (47.3%)
Unsuccessful	29 (36.7%)	48 (52.7%)
EORTC pain score, mean (95% CI)	45.5 (43.3, 47.7)	42.0 (36.9, 47.1)

Pain control

Pain control was assessed using VAS. Details in table 5.

During the study, patients were asked to record when they took additional medication for breakthrough or incident pain. During the morphine phase, patient needed more rescue medication than in the fentanyl phase. Rescue medication was used, on an average for 49.5% of days during morphine treatment, compared to 35 % of days for fentanyl, throughout the whole of the phases.

43% of patients required upward titration on morphine compared to 23% of patients receiving fentanyl to maintain analgesia.

Table 3: Bowel function.

	Fentanyl	Morphine
Constipation	19	47
Diarrhoea	8	3
Normal	55	54
Details from patients who reported predominantly constipation		
N	19	47
Painful or difficult passage of stools	8 (42.2%)	36 (76.5%)
Stools hard in consistency	9 (47.3%)	36 (76.5%)
Stools passed on < 3 days per week	10 (52.6%)	26 (55.3%)
Details from patients who reported predominantly diarrhoea		
N	8	3
Loose movements >2 per day	5	1

Table 4: Adverse events.

Event	Fentanyl	Morphine
Constipation	19	47
Diarrhoea	8	3
Nausea	33	25
Vomiting	7	8
Dyspnoea	8	7
Drowsiness	7	10

Table 5: VAS at different times.

	Fentanyl Morphine		Morphine Fentanyl	
	Mean	**Median**	**Mean**	**Median**
Day 1	8.4	8	8.3	8
Day 7	3.9	3	3.4	2.5
Day 15	2.8	3	2.9	2
Day 23	3.1	3	3.1	2
Day 31	2.6	2	1.7	2

Sedation and sleep

Fentanyl appeared to be less sedative than morphine both in the daytime and at night. Data from the EORTC questionnaire showed significantly less sleep disturbance with morphine [mean % AUC=35.6 (95% confidence intervals 31.3,39.9) versus 25.3(19.6,31) for fentanyl and morphine, respectively. There was no difference in nighttime waking between the treatments.

Bowel function

Fentanyl treatment was associated with significantly less constipation than morphine. Out of 79 patients that received fentanyl patches, 19 (~25%) had constipation compared to 47 (~51%) out 91 who took morphine tablets.

Diarrhea was seen in 8 (~10%) in those that received fentalyl patches compared to 3 (~3%) in those that received morphine tablets. Details in table 3.

Performance status

Measurement of WHO performance status revealed a slight overall deterioration during the course of the trial, which would be due to the clinical stage of the disease of the study population and the setting from which the patients were recruited. Out of the 83 patients that provided performance status data, 17 (~20%) deteriorated, 13 (~15%) improved and the rest 53 (~64%) showed no change. No significant treatment effects were detected.

Treatment preferences

At the end of the trial, significantly more patients indicated that fentanyl patches caused less interruption to their daily activities, and the activities of family and caregivers and had been more convenient to take than the morphine tablets.

The percentages expressing preference were as follows: less interruption of daily activities: ~49% fentanyl, ~ 21 % morphine, less interruption to carers: ~48% fentanyl, ~22 % morphine, more convenient medication: ~60% fentanyl, ~23% morphine.

Side effects and adverse events

The most common adverse events are shown in table 4.

5 patients died during the course of the study, but this was not unexpected given the nature of the patient sample. No deaths were considered to be study related.

It is known that some patients transferring from morphine to fentanyl may experience acute symptoms of morphine withdrawal, in spite of adequate pain control. 3 specific cases of 'withdrawal effects' were reported in this study during fentanyl treatment, and other adverse experiences may have been associated with morphine withdrawal rather than fentanyl treatment, although this cannot be known for certain.

DISCUSSION

The main objective of this study was to record patients' preference between two distinctly different formulations of strong opioids. Therefore, a randomized but open crossover design seemed most appropriate.[11] It would be difficult for patients to express a preference if they were receiving both the delivery system at once. We acknowledge that the open design may have introduced bias in reporting of side effects, but the randomized

design was used to ensure that this effect would have been present in both the arms. From previous studies, pain control between the formulations was expected to be similar.[11,12]

Morphine has been considered the gold standard for treating moderate to severe pain. It is the drug of choice at whatever stage of the disease the patient experiences severe pain; not reserved only for the terminal stage.[2,13,14]

Morphine is the principal medical alkaloid of opium derived from poppy plant. It is a pure agonist and acts at the opioid receptors in the central nervous system.[2,13,14]

On the other hand, fentanyl is a selective mu receptor agonist. In India, it is available as a 72 hour transdermal patch (tdp) formulation.

Oral morphine is a very cheap and affordable drug whereas transdermal fentanyl is expensive. However, both the preparations are made available free of cost for all patients at our institute.

Conversion from oral morphine to tdp fentanyl was done as per guidelines.[2,13]

Patients were advised to take adequate doses of oral morphine for breakthrough pain. In light of this, the higher use of rescue medication on oral morphine is not surprising, given that 43% of patients required upward titration on morphine compared to 23% of patients receiving fentanyl to maintain analgesia.

The findings of this study re-established the fact that, while does equivalence tables provide guidance regarding the starting point when switching opioids, the actual dose needs to be carefully titrated according to individual patient's requirement.[15]

There was no significant difference in EORTC functioning scales between the treatments. This is not surprising given the relatively major impact in the patients' underlying condition compared with the impact of any improvement that may follow a change in symptom control.

The most common side effects of opioids are usually constipation, drowsiness, nausea and vomiting.[16]

Constipation is seen in most cancer patients who are on opioids for pain and about 90% need regular laxatives.[17] Opioids lead to constipation as they reduce the propulsive intestinal activity and increase the non-propulsive activity of small intestine and colon and increase the absorption of fluid and electrolytes. So we made sure to prescribe a laxative to each patient who were a part of the study, the dose of laxatives were titrated according to the individual's need. Along with this, patients were advised to maintain adequate hydration and encouraged to take a balanced diet.

Since this is one of the very few studies (by best of our knowledge), and it is limited to only a single centre, a multicentric study involving a larger number of patients will help to establish our findings.

Treating pain with quality pain management and palliative care involves assessments that define the most important pain mechanisms for each individual patient. Medical and physiological evaluations need to be combined with a psychosocial assessment, which includes an assessment of suffering. Pain diagnoses and therapies should be directed at medical diagnosis and psychosocial assessment.[18]

Patients' preference for a treatment will depend on a wide range of factors, including unwanted effects and ease of use. No one drug will be superior in all these parameters for every patient, but this study re-establishes the fact that, for whatever reasons, patients with advanced cancer can express preferences between different analgesics and this should be considered when individualizing patient care.

CONCLUSION

We conclude that, in this study, transdermal fentanyl patch provided good pain relief, equivalent to that provided by oral morphine, required lesser rescue doses, improved quality of life and was associated with less constipation, and was preferred by more patients as compared to morphine.

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