Original Article

Efficacy and Safety of Transdermal Buprenorphine Patch for Cancer Pain Relief in Elderly Patients : A Retrospective Study from a Tertiary Care Centre of Eastern India

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Cancer is one of the leading causes of morbidity and mortality worldwide & cancer pain is experienced by patients with advanced, metastatic and terminal disease. Buprenorphine, a partial μ-receptor agonist and antagonist at the k-opioid receptor, shows no clinically relevant accumulation of active metabolites, and pharmacokinetics remain unchanged in renal insufficiency. In elderly cancer patients, the use of opioids for control of cancer pain is a therapeutic challenge, as these group of patients often associated with renal and hepatic comorbidity that limited the use of strong opioids like morphine.

Methods : A retrospective observational study was conducted in elderly patients to estimate the efficacy of transdermal buprenorphine patch for controlling of cancer pain as well as to assess the safety of the patch. For pain control Numerical Rating Score (NRS) was used & for safety assessment Grade 3 or 4 toxicity were recorded.Hepatic & renal toxicity were measured at baseline, at 1st month & at 3rd month of treatment & lastly at 6th month of treatment.

Results : Majority of the patients showing good to excellent global satisfaction with Buprenorphine patch and 57% of patients suffered from constipation along with 38% nausea & vomiting. It was found that there was a significant reduction in pain intensity from baseline with a p value of <0.05. There was no significant hepatic or renal toxicity found in the study.

Conclusion : Transdermal buprenorphine patch is effective and safe in elderly cancer patients for pain control. Further studies should be performed in order to find safe and effective opioid methods necessary to give greater insight into the difficult balance between analgesia and toxicity.

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Key words **: Buprenorphine, Cancer pain, Elderly.**

Cancer is one of the leading causes of morbidity and mortality worldwide, responsible for 19.2 million new cases and 9.9 million deaths in 2020 globally (Globocan 2020). InIndia, more than one million new cases of cancer are diagnosed each year and it is estimated that the cancer burden in India will almost double during the coming 20 years[1].

Pain is experienced by 55% of patients undergoing anti-cancer treatment and by 66% of patients who have advanced, metastatic and terminal disease (WHO). It was also shown that over 38.0% of all cancer patients experienced moderate-to-severe pain[2]. With the advances in preventive, diagnostic& therapeutic measures, the life expectancy of cancer patients have increased considerably. With high prevalence of advanced & metastatic disease in our country the prevalence of acute & chronic pain amounts to almost 70% of cancer patients.

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Editor's Comment :

- Cancer related pain is the most common cause of morbidity in cancer patients. Among various opioids buprenorphine is one of the most common & efficacious method to control pain evident by various study. In our study it showed similar results in elderly population. So we may conclude that buprenorphine transdermal patch can effectively reduce the pain and alleviate quality of life, though a large scale prospective study may be needed.

The World Health Organization (WHO) recommended 'a three-step analgesic ladder' for management of cancer pain based on pain intensity. A wide variety of medications ranging from acetaminophen & NSAIDs to strong opioids like morphine, buprenorphine is available now. The use of morphine may be complicated by accumulation of morphine metabolites, leading to dose reduction or opioid rotation in renally impaired, elderly or high-dose patients[3]. By contrast Buprenorphine shows no clinically relevant accumulation of active metabolites[4], and pharmacokinetics remain unchanged in renal insufficiency[5]. Buprenorphine therefore might be used as an alternative in these compromised patients[6].

Buprenorphine, a partial μ-receptor agonist and antagonist at the κ-opioid receptor[7], has been available

since 1981 in sublingual and parenteral formulation, and has a well-established efficacy and safety profile[8].

A transdermal patch is a medicated adhesive patch, is placed on the skin to deliver a specific dose of medication through the skin and into the blood stream. The advantage of transdermal drug delivery route over other types of medication delivery route like oral, topical, intra-venous or intra-muscular is that the patch provides a controlled release of medication into the patient. Buprenorphine transdermal formulation was introduced in Europe in 2001, and the patches of different releasing rates are available now.

Transdermal patch is non-invasive, effective & well accepted formulation accepted by cancer patients who have gastrointestinal problems and difficulties in oral medication (esophageal,gastric, intestinal, maxillofacial cancer) either due to cancer or due to side effects of oral or parenteral concomitant medications[9].

In elderly cancer patients, the use of opioids for control of cancer pain is a therapeutic challenge, as these group of patients often associated with renal and hepatic comorbidity that limited the use of strong opioids like morphine. Transdermal buprenorphine has been found to be effective and safety for elderly patients. However, there is a lack of sufficient data or literatures on this specific topic specially in eastern part of India. So, a study was conducted to find out the safety and efficacy of transdermal buprenorphine patch in elderly cancer patients.

Materials and Methods

We have conducted a retrospective observational study & have retrieved medical records of 120 elderly cancer patients from Dept. ofRadiotherapy, R G Kar Medical College & Hospital, Kolkata, registered from January 2018 to December 2020. All the patients received Buprenorphine Patch of '20µg' strength,as only patches of that strength were supplied in our institute at that period of time. The inclusion criteria were cancer patients with age 65 years or more. The patients who used concomitant other analgesic medications were excluded from the study.

The primary end point of the study was to estimate the efficacy of transdermal buprenorphine patch for controlling of cancer pain as well as to assess the safety of the patch for the elderly patients.

To estimate the efficacy of pain control, we looked at the Numerical Rating Score (NRS) and Visual Rating Scale (VRS) of the patients suffering from cancer pain at different time interval specifically at the beginning of treatment, at the 1st month ,3rd month and lastly at the 6th month of treatment.

To assess the safety of the drug for elderly patients we looked at the number of patients suffering from grade 3/4 toxicity or adverse events during their treatment with transdermal buprenorphine patch.

The retrieved data were then tabulated and analysis made accordingly to assess the efficacy and safety of the drug.

Results

We have collected data of a total of 120 patients for this study. Out of them 68 were male and 52 were female.Most of the cases were either in ECOG PS 3 or 2 in our study.

- **Age Distribution :**

The median age of the population was 69 years with a range from 65 years to 86 years.

- **Primary site of the tumors (Fig 1):**

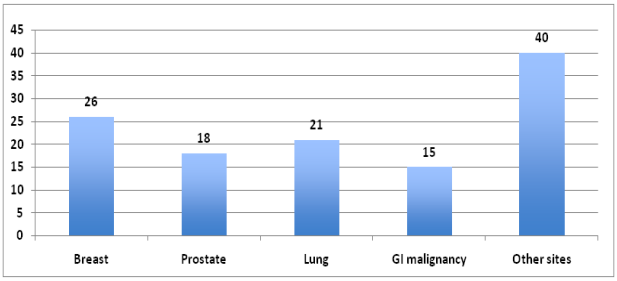

Fig 1 — Bar Diagram showing different primary sites distribution

It was observed that in majority of the cases, the primary was in breast followed by lung & prostate.

- **Metastatic Sites :**

From our patients' data sheet, it was seen that majority of them had skeletal metastasis (Table 1).

Table 1 — *Metastatic site wise patients' distribution*

Site of Metastasis	Number of patients	Percentage
Skeletal	46	52
Liver	12	14
Bulky nodes	16	18
Other	14	16

- **Adverse events :**

All patients were treated with buprenorphine transdermal patch 20 µg/hour in our study. Out of them constipation being the most common adverse event experienced and motor and cognitive impairment being the lowest (Fig 2).

- **Global Satisfaction with treatment :**

All patients were categorized according to their global satisfaction with the prescribed treatment with

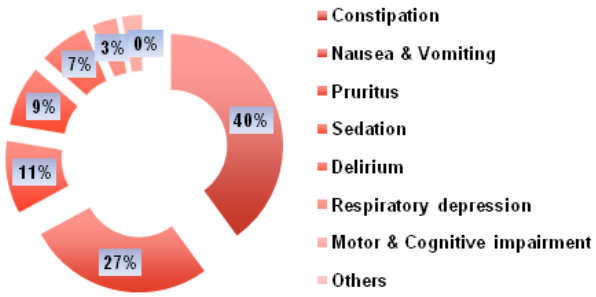

Fig 2 — Doughnut Chart showing various adverse events

buprenorphine transdermal patch into 5 distinct categories, having "excellent" as the best outcome & "poor" as the worst outcome (Table 2).

Table 2 — *Global satisfaction of treatment*

Global Satisfaction	No. of patients	Percentage
Excellent	18	15
Very good	44	37
Good	31	26
Fair	17	14
Poor	10	8

- **Pain intensity score :**

Pain intensity was measured using Numerical Rating Scale of all the participated patients at baseline, at 1st month & at 3rd month of treatment & lastly at 6th month of treatment. Only patients with moderate and severe pain were considered for the patch and on follow up most of the patients shifted from higher pain score to lower pain score or became painless. The patients were scored '0' having no pain; '1-3' having mild pain; '4-6' having moderate pain & '7-10' having severe pain (Table 3).

Table 3 — *Pain Intensity Score of patients.*

Timeline	No of patients have scored '0' (No pain)	No of patients have scored '1-3' (mild pain)	No of patients have scored '4-6' (moderate pain)	No of patients have scored '7-10' (severe pain)
At beginning	0	0	52	68
At 1st Month	11	16	38	55
At 3rd Month	18	28	36	38
At 6th Month	20	40	32	28
p value			<0.05	

Among 120 patients having moderate to severe pain 60 of them had mild or no pain after six months of use. None of the patient suffered from increase in Pain Intensity Score during the treatment period. So, from the above table it has been found that there is a significant reduction in pain intensity from baseline with a p value of <0.05.

- **Toxicity profile :**
- **Renal Toxicity :**

Renal toxicity was measured by using creatinine clearance level at beginning, at 1st month, at 3rd month & at 6th month on buprenorphine transdermal patch.

There is no significant renal toxicity found with using buprenorphine transdermal patch in our study (Table 4).

Table 4 — *Renal toxicity in term of creatinine clearance (Crcl) occurring in patients*

Timeline	No Patients having Crcl >80ml/min	No Patients having Crcl 50-80ml/min	No Patients having Crcl 30-50ml/min	No Patients having Crcl <30ml/min
At beginning	9	58	46	7
At 1st month	8	56	48	8
At 3rd month	7	53	48	12
At 6th month	7	54	47	12
p Value			0.2	

- **Hepatic Toxicity :**

Hepatic toxicity was measured according to liver dysfunction level at beginning, at 1st month, at 3rd month & at 6th month on buprenorphine transdermal patch (Table 5).

Table 5 — *Hepatic Toxicity occurring in patients using Buprenorphine patch*

Timeline	No Patients having no liver dysfunction	No Patients having mild liver dysfunction	No Patients having moderate liver dysfunction	No Patients having severe liver dysfunction
At beginning	82	30	6	2
At 1st month	80	31	7	2
At 3rd month	77	31	9	3
At 6th month	76	30	12	2
p Value			0.1	

There is no significant liver dysfunction found with using buprenorphine transdermal patch in our study.

Discussion

Strong opioids are recommended for treating severe cancer pain in the advanced stages of the disease. Few data are available concerning the efficacy of buprenorphine in cancer pain. The European Medicines Agency (EMEA) guidelines on chronic pain recommend comparison of active treatment versus placebo to prove efficacy. In cancer, it is difficult to expose patients to placebo to prove the efficacy of analgesic methods, owing to ethical constraints. In addition, cancer is frequently progressive and this results in methodological limitations to pain assessments. In elderly cancer patients, the use of opioids for control of cancer pain is a therapeutic challenge, as these group of patients often associated

with renal and hepatic comorbidity that limited the use of strong opioids like morphine. Transdermal buprenorphine has been found to be effective and safety for elderly patients.

It has been observed that majority of the cases primary was in breast followed by lung & prostate in our study. It was also noted that 62 patients out of 120 elderly patients showed global satisfaction as "excellent" or "very good" after using transdermal buprenorphine patch which was also evident in various international papers.

Finally, when we compare pain intensity of those patients from beginning, at 1st month, at 3rd month & at 6th month using numerical rating scale we have found a significant trend towards reduction of pain intensity with a p value of 0.01. Similar data was found by research work done by Poulain Philippe, *et al* which showed a significant difference in the number of treatment responders was observed: 70 BUP TDS (74.5%, 65.7-83.3) *versus* 47 placebo (50%, 39.9-60.1) (P =0.0003)[10].

It has also observed there is no significant hepatic or renal impairment found when using buprenorphine transdermal patch in our study, which makes itto be an easier convenient method to reduce pain intensity in geriatric population.

Conclusion

In conclusion, we think that further studies should be performed in order to find safe and effective opioid methods necessary to give greater insight into the difficult balance between analgesia and toxicity. It is also important to consider individual variables, such as psychological distress in cancer patients, as these are important as prognostic factors since they affect the therapeutic results.

Limitations of the Study :

1. There was no comparator arm in our study from which the efficacy of buprenorphine patch was ascertained.
2. This is a single institutional study.
3. Sample size was small.
4. There was provision for subjective bias as the study didn't follow any blinding methods.

Disclosure : The authors report no conflict of interest in this work.

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