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TO ASSESS AND COMPARE THE ANALGESIC EFFICACY AND SAFETY OF COMBINATION THERAPY OF TRAMADOL WITH DICLOFENAC VERSUS CODEINE WITH DICLOFENAC IN CANCER PAIN MANAGEMENT IN HALDWANI, KUMAUN REGION

KEYWORDS: efficacy, adverse drug reaction.

DR ATUL BUNDELA
Pg Resident, Department of pharmacology, Government medical college, haldwani

DR REENA BHARDWAJ
Associate Professor, Department of Pharmacology, Government medical college, haldwani

DR BHAVANA SRIVASTAVA
Professor and Head, Department of Pharmacology, Government medical college, haldwani

DR KAILASH CHANDRA PANDEY
Associate Professor and Head, Department of radiotherapy, Government medical college, haldwani

DR SWAROOP R
Assistant Professor,Department of Radiotherapy,Goverrnment medical college,haldwani

ABSTRACT **Objectives:**To assess the efficacy and safety of combination therapy of Tramadol with Diclofenac versus Codeine with Diclofenac in cancer pain management. **Methodology:** Total 60 number of patients recruited (30 in tramadol group and 30 in codeine group) and followed up at 2nd week and 4th week. **Results:** It was seen that both drugs were effective in cancer pain management as there was 28.26% decline in mean pain score in group I and 35.84% decline in group II after 4th week. A total of 72 adverse drug reactions were found and observed that group I had more number of reactions (41reactions) than group II (31 reactions). **Conclusion:** This study confirms that effective pain management can be achieved with the use of oral Tramadol with Diclofenac and Codeine with Diclofenac. Combination of Codeine with Diclofenac causes more adverse effects in comparison to Tramadol with diclofenac.

INTRODUCTION

Cancer is the leading causes of death worldwide, with approximately 14 million new cases and 8.2 million cancer related deaths in 2012 according to the WHO report[1] .According to WHO 2015-report of India crude incidence rate is $73.6/10^5$ and crude mortality rate is $49.1/10^{5(2)}$.

The primary goal of cancer therapy is to cure the cancer and increase the lifespan of patient, however improving patient's quality of life is also an important aspect of treatment. Cancer pain is the most debilitating symptom so to improve quality of life palliative care is done to treat the symptoms caused by cancer pain.

Cancer pain requires specialized treatment and before treatment, proper assessment of pain in cancer is also very important because it's failure can lead to under-treatment .The critical role of the assessment of cancer pain was highlighted in a 1993 study by Von Roenn JH et al [3], in which poor pain assessment was found to be the greatest barrier to the effective cancer pain management. To assess pain The Visual analog scale and "Ten point" numeric scales are used for evaluation.Pain treatment is done by World Health Organization (WHO) step ladder approach which was introduced in 1986 [4].

In First step use of Acetaminophen, or other NSAIDs for mild to moderate pain is done.

In Second step an opioid such as codeine or Hydrocodeine should be added to the NSAID.

In Third step more potent opioid or higher dose of opioid are used.

Tramadol is a new, centrally acting analgesic shows dual mechanism of action with selective interaction with 'mu' opioid receptors, which are responsible for nociception and weak pharmacodynamic activity on other opioids receptors.While codeine or 3-methylmorphine is a weak opioid to treat moderate to severe cancer pain and is given along with other NSAIDS generally. There are very few studies done to compare the efficacy and safety of Tramadol and Codeine in India further the prevalence of cancer in Uttarakhand is increasing, so safety and efficacy of drugs in cancer pain is an important subject to study.

So the present study shows an insight into the pain aspect of cancer with comparison of combination therapy of Diclofenac with Tramadol and Diclofenac with Codeine in cancer pain management.

Methodology:

This study was conducted in Department of Pharmacology, Government medical college, Haldwani and Department of Radiotherapy Swami Rama Cancer Institute, attached to Dr. Susheela Tiwari Government Hospital, Haldwani, Uttarakhand to compare the efficacy and safety between Tramadol and Codeine with Diclofenac. The study population involved consenting patients, diagnosed with cancer and registered for treatment. Total duration of the study was 4 weeks. After taking informed consent and applying inclusion and exclusion criteria patients were divided into two groups. Patients were evaluated for pain by ten point numeric scale and in each follow up adverse drug reactions were noted and reported to the higher centre. patients were followed for 4 weeks.

Observation and Results:

Patients meeting the inclusion and exclusion criteria and consenting to participate in the study were subsequently divided into two groups: group I (Tramadol + Diclofenac) and group II (Codeine + Diclofenac).

Ten point numeric scale was used to measure the efficacy of both the drugs (Tramadol with Diclofenac and Codeine with Diclofenac) in group I and group II. Measurement of efficacy was done at 0 week, 2 week and 4 week. Mean pain score at 0 week in group I and group II was 7.43±1.135 and 7.733±0.78 respectively. After first follow up at 2 weeks pain score showed decline with value of 5.60±1.069 and 5.233±1.006 in group I and group II respectively which was statistically significant ($p<0.05$).

In intergroup comparison of efficacy between both the groups mean value of pain score was 7.43±1.135 and 7.73±0.78 (p=0.239) for group I and group II respectively at 0. Mean value of pain score at 2 weeks was 5.60±1.069 and 5.23±1.006 (p=0.177) for group I and group II respectively which was not statistically significant and mean value of pain score at 4 weeks was 5.33±0.099 and 4.96±0.927 (p=0.145) for group I and group II respectively which was again not statistically

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significant (p< 0.05) (table 1)

TABLE 1: Intergroup efficacy comparison by ten point numeric pain scale at 0, 2 week and 4 weeks

WEEKS	Group-I (tramadol+diclofenac) Mean ± SD	Group-II (codeine+diclofenac) Mean ± SD	p value
0 week	7.43±1.135	7.73±0.78	0.239
2 week	5.60±1.069	5.23±1.006	0.177
4 week	5.33±0.099	4.96±0.927	0.145

(p≤0.05=significant)

After first follow up at 2nd week there was a decline in pain score which was 5.60±1.069 (p=0.001) and 5.233±1.006 (p=0.008) for group I and group II respectively.

After second follow up at 4 weeks pain score decline was more from 2nd week follow up,which was 5.33±0.99(p=0.001) and 4.96±0.927(p=0.004) for group I and group II respectively and which was statistically significant(p<0.05)

MEASUREMENT OF SAFETY PROFILE

In study adverse drug reactions were found in 44(73.33%) patients out of all 60 patients and total number of adverse drug reactions were 72 in number (31 in group I and 41 in group II).

Constipation, nausea and sedation were very common in both groups. Nausea was more common in group I(Tramadol), whereas constipation and sedation were predominant in group II(Codeine). The incidence of constipation in group I and group II were 16.7% vs 43.36% and the difference is statistically significant (P=0.0242). The incidence of nausea in group I and group II were 40% and 33.36% respectively, the difference is statistically significant (P=0.5921). There was a trend towards a greater incidence of sedation in group II .The difference between group I and group II was 33.36% vs 53.3%, however in view of the small sample size, statistical significance could not be defined (P=0.118).

After WHO-UMC assessment 73.61% drug reactions were classified as probable, 18.05% were possible, 8.3% were unlikely. No reaction was labeled as certain in WHO-UMC classification.

Discussion:

The incidence of new cancer patients in India is about 10 lakh every year. The incidence of pain in advanced stages of cancer approaches 70 percent to 80 percent. One of the major symptoms and fears of patients with cancer is pain, which can occur as a result of the cancer itself or its treatment, or from other causes.[5-8]According to a report published by Regional Cancer Centre, Thiruvananthapuram, Kerala and WHO India Office, New Delhi in India there are around 8 lakh new cases/year and 24 lakh prevalent cases with crude incidence rate of $66.2/10^5$ in male and $81.6/10^5$ in female for all ages.[9]

The incidence rate of cancer in our study was more in male patients (in group I 66.7% and in group II 53.34%) and the world cancer scenario states that the overall age standardized cancer incidence rate is almost 25% higher in men than in women, with rates of 205 and 165 per 100, 000 respectively [9].

In intergroup comparison of present study the mean pain score in group I and group II at 0 week was 7.43±1.135 and 7.733±0.78 (mean ±SD) p=0.239 respectively. After first follow up at 2nd week pain score was 5.60±1.069 and 5.233±1.006 (mean ±SD) p=0.177 for group I and group II respectively and after second follow up at 4th week mean pain score was 5.33±0.99 and 4.96±0.927 (mean ±SD) p= 0.145 for group I and group II.

These data shows that in intergroup comparison there was no significant difference in both the groups after 2nd and 4th week of treatment (group I, p=0.177 and group II, p=0.145). These results are comparable with the several studies like Smith AB et al, Pluim M et al, Jeffrey HM et al [10-12] which states that there is no significant difference in the analgesic efficacy of oral tramadol tablet and oral codeine tablet combined with NSAIDS[13] also one study done by Toms L et al revealed that in cancer pain codeine with NSAIDS provides better analgesics than other drug combination like tramadol with NSAIDS.[14]

In our study 43.33% of group II patients complained of constipation due to medicine while in group I 16.67% patients complained of constipation. Other drug reactions found were nausea (40% group I, 33.34% group II), sedation (33.34% in group I and 53.34% group II) and others (palpitations) was found in 13.34% and 6.7% patients of group I and group II respectively, these data supports the results of studies done by Arbaiza D et al and Straube C et al which states that incidence of nausea and sedation as adverse drug reaction by codeine in cancer pain management is more, in comparison to other opioids[.[15]

In our study out of all the 72 drug reactions found, 53 (73.61%) reactions were classified as probable under the WHO-UMC causalty assessment, 13 (18.05%) adverse drug reactions were classified as possible under WHO-UMC causalty assessment, and 6 (8.3%) reactions were classified as unlikely.

Summary and Conclusion:

Total 65 patients were recruited according to the inclusion and exclusion criteria and were divided into two groups following which baseline investigations and pain assessment was done with the help of ten point numeric scale and patients with moderate to high intensity of cancer pain (5 to 10) were included in the study. Patient was followed up at 2nd week in which 5 patients were lost to follow up and next follow up was done at 4th week. At the end of the study it was seen that both the drugs were effective in cancer pain management as there was 28.26% decline in mean pain score in group I(Tramadol) and 35.84% decline in mean pain score in group II(Codeine) after 4th week of study. At every follow up adverse drug reaction monitoring was done and total 72 adverse drug reactions were found(18 constipation, 22 nausea, 26 sedation and 6 others) all the drug reactions were noted and sent for further evaluation to higher centre. It was observed that group I had more number of reactions (41reactions) than group II (31 reactions).

Therefore we observed in our study that both the drug combinations are equally efficacious although adverse reaction profile was different for both the drugs.

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