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RESEARCH ARTICLE

AUDIT OF EFFICACY AND ADVERSE EVENTS OF ANALGESICS USED TO MITIGATING CANCER PAIN: OBSERVATIONS FROM A TERTIARY CARE HOSPITAL

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ABSTRACT: **Introduction:** Analgesics are the main stay in the mitigation of pain in cancer patients. However, depending on the type of analgesics, adverse events which at times can be severe are also observed. In this study an attempt has been made to understand the beneficial and adverse effects of the standard analgesics recommended for mitigating cancer pain. **Materials and methods**: This is a cross sectional prospective observational study with 150 cancer patients requiring analgesics and was conducted at the oncology ward of a tertiary care hospital. The prescription pattern, the mitigation of pain and the adverse events were recorded. **Results**: The results indicate that morphine injection was the most effective followed by morphine tablets, ultracet, tramadol and paracetamol. With regard to the adverse effects it was observed that 70.7% of the patients had one or other symptoms and that constipation (9.3%; 14/150) followed by nausea (8%; 12/150) and drowsiness (5.3%; 8/150) were the most common. **Conclusion**: The results of the study indicate that in spite of administering protective/ preventive drugs analgesic-induced adverse effects are common in cancer patients.

KEY WORDS: Analgesics, cancer, morphine, ultracet, tramadol, paracetamol, WHO three-step ladder, adverse events.

INTRODUCTION:

In people afflicted with cancer, pain continues to be a prevalent and distressing symptom in most patients. Reports indicate that nearly 25% of all newly diagnosed cases, 33% of patients undergoing curative treatment, and 75% of the people with advanced disease experience pain[1]. Cancer pain is often unpredictable and the intensity variable and affects the quality of life of the patients[2]. From an anatomical perspective, cancer pain is directly associated with tissue damage and when it persists and worsens indicates that the disease is progressing[1-3]. Prom a physiological perspective, pain due to cancer may be because of the tumor, due to

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metastasis and or owing to physical impact of tumor pressing on to a nerve root [1; 4]. Cancer pain is recognized to be multidimensional and due to somatic, visceral or neuropathic[3; 5]. In addition, pain can also be caused by treatment, general debility, and by unrelated co-morbidities [5;6].

Ascertaining the exact cause for the initiation and perpetuation of the pain is vital for effective cancer pain management. The management of cancer pain depends on a systematic assessment that considers the stage of the disease, age and general health of the patient and the physiological cause for the pain[5,6]. Considering this, in the year 1986, WHO developed a three-step "ladder" and the guidelines for analgesics are as follows: 1 for mild pain, nonopioids (like paracetamol/ acetaminophen or aspirin with or without "adjuvants" such as COX-2 inhibitors; 2 for Moderate pain, weak opioids such as codeine, dihydrocodeine or tramadol; and 3 for severe pain strong opioid, such as morphine, diamorphine, fentanyl, buprenorphine, oxymorphone, oxycodone, hydromorphone, with concomitant continuation of the non-opioid therapy and also increasing the dose of opioid till the patient is free of pain and does not develop adverse effects[5,6]. The present study was undertaken to understand the prescription pattern of analgesics, the degree of pain relief afforded and the adverse effects of the analgesic in cancer patients undergoing pain palliation.

MATERIALS AND METHODS:

The study was conducted at the oncology ward of Father Muller Medical College Hospital, Mangalore, from January 2012 to December 2013. The inclusion criteria included Cancer patients above the age of 18 years admitted in the oncology wards. The exclusion criteria included patients with co morbidities like severe diabetes, AIDS and those with diminished mental competence, deafness, visual disturbances which would prevent them from comprehending the numeric rating scale (NRS). The study was approved by the institutional ethics committee.

The cancer patients admitted for pain palliation care were explained about the study objective in the presence of the caregiver. The willing volunteers were explained in their own language about the numeric rating scale and were shown how to use it. A brief history about the case was noted and pain was confirmed to be only due to cancer. A written informed consent was obtained from the patient in the presence of the care giver.

The volunteers were asked to rate the severity of the pain on the numeric rating scale provided to them. The NRS score was noted before administration of the analgesic and subsequently at 15 min, 30 min, 1 hr, 2 hr, 3 hr. The patients were followed up for a period of 2 months and the adverse effects attributable to the analgesics were noted in a preformatted data collection sheet.

Statistical analysis:

The collected data was analyzed by mean, standard deviation, frequency percentage, demographic evaluation, sex distribution, chi square test. Multiple comparisons were analyzed by ANOVA and the level of significance is measured. SPSS version 17 was used for analysis.

RESULTS:

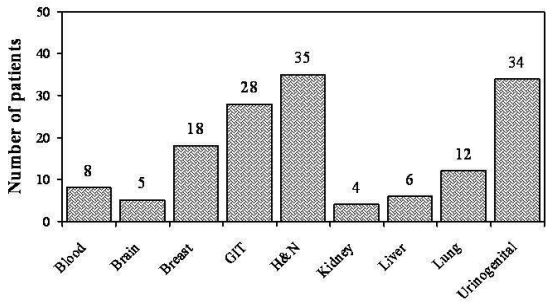

Figure.1 Detail on the type of cancer affecting patients

This cross sectional prospective observational study and a total of 150 patients were enrolled in the study during the time point. The results indicate that 47% were males and 53% were females (Table 1) and that the cancers of the oral cavity was the most common in males and cervical the most prevalent in the females (Figure 1). The age of the patients enrolled in this study varied from 25 to79 years and that a maximum number of patients were in the age group of 50-60years (Figure 2).

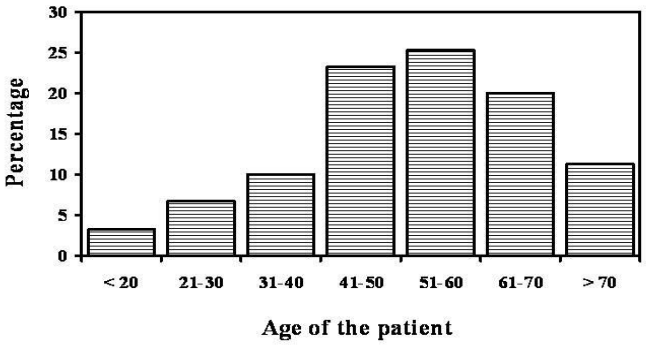

Figure.2 Detail on the cancer patients age

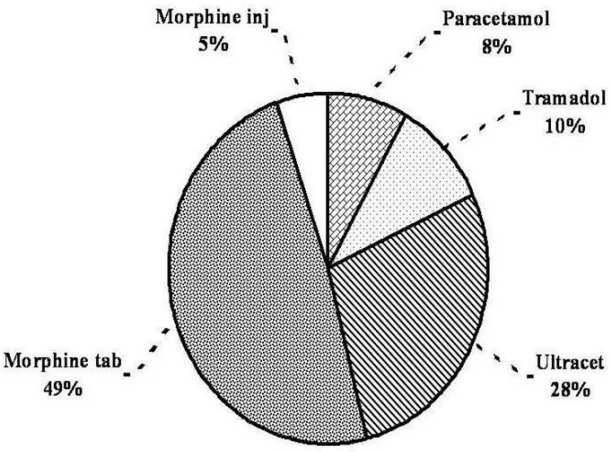

Figure.3 Detail on the analgesic use in study

With regard to the use of analgesics, data indicates 12 patients received tab paracetamol (500 mg 8th hourly), 15 patients received tab tramadol (50 mg 8 th hourly), 42 patients received ultracet (a combination of tramadol and paracetamol 32.5 mg+325 mg 8th hourly), 73 received morphine tablets (10 mg orally every 4 hrs), and that 8 patients who were in very severe pain received morphine 10 mg iv every 4th hourly (Figure 3).

As pain scale for each individual was different (at the beginning of the study) the value was converted in to relative grades. The numerical values got for each patient with the NRS score was converted in to percentile score with the first value being considered as 100 and then the appropriate decrease was deduced for each time point (Figure 4).

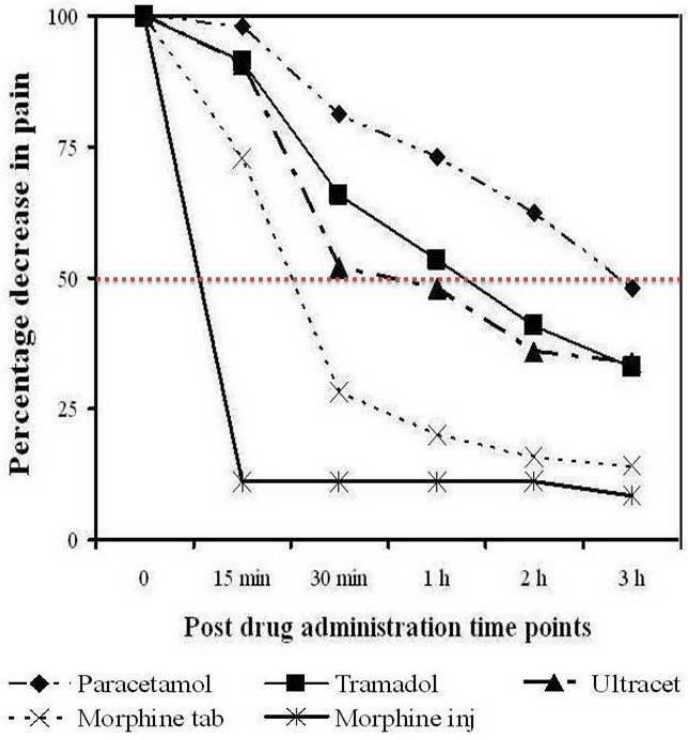

Figure.4 Percent reduction in pain post treatment with the analgesics (0 to 3 hrs)

The results indicate that morphine injection was the most effective followed by morphine tablets, ultracet, tramadol and paracetamol. The analgesic effect was calculated and 50% reduction in pain was observed as follows paracetamol (2.45 h), tramadol (1.5 h), ultracet (55 min), morphine

tablets (25 min) and morphine injection (12 min) (Figure 4).

Table 1: Details of analgesics used based on the pain in the cancer patients

	Analgesic Group					Total
	Paracetamol	Ultracet	Tramadol	Morphine (Oral)	Morphine I.V.	
Females Count (%)	9 (75.0%)	21 (50.0%)	10 (66.7%)	35 (47.9%)	5 (62.5%)	80 (53.3%)
Males Count (%)	3 (25.0%)	21 (50.0%)	5 (33.3%)	38 (52.1%)	3 (37.5%)	70 (46.7%)
Total (%)	12 (100.0%)	42 (100.0%)	15 (100.0%)	73 (100.0%)	8 (100.0%)	150 (100.0%)

The administration of the analgesics caused adverse effects in 70.7% of the patients (106/150) Table 2. The most common side effect was constipation (9.3%; 14/150) followed by nausea (8%; 12/150) and drowsiness (5.3%; 8/150) (Table 2). With respect to the individual analgesics in the cohorts that received paracetamol, nausea (25%) and epigastric pain (16.7%) were observed (Table 2). In the patients administered with tramadol, constipation were the major adverse effect (13.3%) followed by nausea and drowsiness (Table 2). In the ultracet group drowsiness was the foremost unpleasant effect (11.9%) followed by nausea (7.1%), constipation (7.1%), insomnia and headache (Table 2). While in patients provided with of oral morphine, constipation (9.6%) followed by nausea (6.8%) were the most frequent (Table 2). The other adverse effects observed were euphoria, anxiety and hallucinations. In patients administered with morphine injection, constipation was the chief complain (Table 2).

Table 2: Details on the analgesics-induced adverse events in cancer patients

	Paracetamol	Ultracet	Tramadol	Morphine (oral)	Morphine IV	Total
ADR	7 (58.3%)	28 (66.7%)	11 (73.3%)	56 (76.7%))	4 (50.0%)	106 (70.7%)
Euphoria	0 (0%)	0 (0%)	0 (0%)	2 (2.7%)	0 (0%)	2 (1.3%)
Nausea	3 (25.0%)	3 (7.1%)	1 (6.7%)	5 (6.8%)	0 (0.0%)	12 (8.0%)
Anxiety	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (2.7%)	0 (0.0%)	2 (1.3%)
Constipation	0 (0.0%)	3 (7.1%)	2 (13.3%)	7 (9.6%)	2 (25.0%)	14 (9.3%)
Drowsiness	0 (0.0%)	5 (11.9%)	1 (6.7%)	0 (0.0%)	2 (25.0%)	8 (5.3%)
Epigastric pain	2 (16.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.3%)
Hallucinations	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (1.4%)	0 (0.0%)	1 (0.7%)
Headache	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Insomnia	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Seizures	0 (0.0%)	1 (2.4%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Total	**12 (100.0%)**	**42 (100.0%)**	**15 (100.0%)**	**73 (100.0%)**	**8 (100.0%)**	**150 (100.0%)**

DISCUSSION:

From a therapeutic viewpoint, the critical components in the management of pain are the assessment of pain and adopting a standard analgesic regime in accordance to the tenets of the World Health Organization's analgesic ladder[6]. In this study it was observed that depending on the intensity of the pain the use of analgesics differed and ranged from paracetamol to morphine injection[6]. Paracetamol which is a non-opioid analgesic with antipyretic effects is

arguably one of the most commonly used pharmacological agents in the world and is also a recommended drug in the WHO analgesic ladder for mild pain[6]. In this study, paracetamol was observed to be effective in reducing the pain in majority of the patients. However the efficacy was not as pronounced as the other analgesics [6].

When the pain was moderate, tramadol a non opoid, and ultracet [which is a combination of fixed amount of tramadol (37.5 mg) and paracetamol (325 mg)] were also observed to be effective in mitigating mild-to-moderate pain[7-9]. In severe pain depending on the intensity morphine tablets or injection or both were used. In most cases morphine was administered to people who have had severe pain as suggested in literature[6,10]. On a relative grade the analgesic effect of morphine injection was more effective than any other analgesics and is in agreement to the published literature [10,11].

With regard to the analgesic induced adverse effects the results indicated that 70.7% of the patients had one or other form of side effects (Table 2). A detail analysis indicated that all the side effects were the ones reported in the literature and no novel adverse effects were observed. In the paracetamol only group nausea (25%) and epigastric pain (16.7%) were noted and in agreement to the published reports[11,12]. In the ultracet group drowsiness was the main adverse effect noted (11.9%) other adverse effects being nausea (7.1%) constipation (7.1%), insomnia and headache as reported earlier[13-15] (Table 2). The tramadol group saw constipation as the main adverse effect (13.3%) with nausea and drowsiness being seen in 6.7% of the patients (Table 2). The most common analgesic-induced side effect in patients administered with morphine was constipation (Table 2) and in agreement to earlier reports [16].

The results of the present study indicate that in spite of administering suitable analgesic specific protective/preventive drugs like (like gastric H+/K(+)-adenosine triphosphatase inhibitors in paracetamol & ultracet; antiemetic for morphine, paracetamol & ultracet and laxatives for constipation), analgesic-induced adverse effects are common in cancer patients. Future studies should be aimed at understanding the effects of combination and control release formulations in mitigating the analgesics-induced adverse effects. The results of this prospective study will be very beneficial as it will mitigate the adverse effects and improve the quality of life of the patients. In cancer, quality of life is very important and a combined endeavor including use of suitable analgesic and other supportive drugs should be adopted as this will serve the purpose of palliation and relief to the patient and their care takers.

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