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MORPHINE CONSUMPTION IN CANCER PATIENTS VISITING PAIN CLINIC OF TERTIARY CARE SMHS HOSPITAL: A RETROSPECTIVE OBSERVATIONAL STUDY

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Abstract

Background: Morphine has been used for many years to relieve cancer pain. Oral morphine (in either immediate release or modified release form) remains the analgesic of choice for moderate or severe cancer pain. The dose of oral morphine is titrated up to achieve adequate relief from pain with minimal side effects. **Aim:** To assess the amount of opioid uses in cancer patients at our tertiary care unit. **Methods:** A profile of 30 outpatients aged ≥18 years diagnosed with cancer, who received opiod prescriptions between May 2022 and May 2023 over a period of one year at pain clinic of SMHS hospital which is one of the associated of Government Medical College Srinagar. Oral morphine equivalents (OME) were calculated using the standard conversion factors and the OME trend during the study period was assessed by a generalized additive model. Factors affecting the morphine equivalent daily dose (MEDD) were assessed using multiple linear regressions. Data were analyzed using the SPSS 21 (SPSS Inc., Chicago, IL, USA) package program. Continuous quantitative data were presented as number, mean ± standard deviation. The paired sample test was applied to non-parametric data for the statistical evaluation of repeated measurements. $P<0.05$ was considered significant. **Results:** The mean overall MEDD for all study patients was 28.9 ± 21.9 mg per day per patient. The bone and articular cartilage cancer patients had the highest MEDD. Patients with stage 4 cancer received a higher average MEDD of 5.05 (95% CI: 0.40-8.62) as compared to those with stage 1 cancer. Patients with bone metastasis received an average higher MEDD of 4.07 (95% CI: 0.72-8.19) compared to those without bone metastasis. Age was inversely associated with the MEDD. Patients aged 42-58, 59-75 and >76years old received MEDDs of 5.02 (95% CI: 3.21-8.17), 6.19 (95% CI: 4.03-8.42) and 7.89 (95% CI: 7.05-12.01) compared with those aged 18-42 years old. Brain metastasis was inversely associated with MEDD of 5.21 (95% CI: 1.01-8.39) compared to those without brain metastasis. **Conclusion:**Oral morphine use has increased over time in Kashmir but remains substantially lower than estimated need. Opioid use in cancer patients in this study was lower than the average global usage. There is significant geographic variation of use. Efforts are needed to improve palliative care in Kashmir and to reduce regional disparities in access to opioids.

Keywords: Cancer, Opioids, Oral Morphine Equivalent, Pain, Metastasis

Introduction:

Lack of access to palliative care is a global issue, with an urgent need for scale-up of services in low and middle- income countries (LMICs). [1,2]This is of increasing relevance in many LMICs, where cancer has emerged as a major threat to public health. Relief of cancer pain is considered by many organizations to be a basic human right, yet 66%of the world's population has virtually no access to opioids for pain, and only 8% of the global population has consumption levels that are considered adequate.[3]

More than 1 million new cases of cancer are diagnosed annually in India, which has a population of more than 1.2 billion.Because most patients in India are diagnosed with advanced disease, the cancer mortality rate is high, at 68% of the annual incidence. [4]Estimates suggest that up to 80% of patients with advanced cancer will develop significant pain. [5]

For cancer pain, oral opioid analgesic is the mainstay of treatment.[6-8] When weak opioids like tramadol, codeine fail to achieve satisfactory pain relief, strong opioids should be incorporated in the treatment plan in accordance with World Health Organization (WHO) guidelines for cancer pain relief. Consequently, morphine administration should be titrated in each individual to a dose sufficient to provide stable pain relief with an acceptable level of side effects.[9,10]

A number of reports have described access to opioids in India at a national level. [1,3,10]Several studies have also explored barriers to opioid use in India. [12-14]However, to our knowledge, there are no published studies that have described details of opioid use and delivery at the state or regional level. Although country-level opioid use statistics are helpful for national policy, promotion of system change requires access to granular data for clinicians, educators, and policymakers on the ground.

The morphine equivalent daily dose (MEDD) is a common measurement that is widely used to estimate and compare opioid usage among countries and settings. [15] Decreasing trends of MEDD in the US and European countries have been reported in various studies since opioid restriction acts were initiated in 2014 , [16] while the MEDD trends in Asian countries have been increasing [17,18] but are currently at levels that are much lower than in the US and UK.

Methods:

A retrospective study was carried out on 30 patients including both male and female over a period of one year treated at the at pain clinic of SMHS hospital which is one of the associated of Government Medical College Srinagar. All had pain due to advanced cancer. The All patients were treated with oral morphine when their pain was no longer controlled with "weak" opioids and NSAID administration, following the WHO sequential ladder. [19,20]

Patients selected for study underwent morphine treatment for more than one week. Data for this study were collected daily basis. A pain evaluation form has been in use which integrates the information contained in the pain clinical file, where pre-codified and descriptive information are recorded. Data are recorded from the first examination to death, or until the end of oral morphine administration. A daily recording form is completed at the home of the patient, with the help of relatives, if necessary. This form records: the daily duration of pain at five different levels of intensity, hours of sleep, performance status; hours standing, hours sitting; and presence or absence of major side effects.

Patients were excluded if they had known morphine intolerance, decreased gastrointestinal uptake of oral medications, or were using two different opioid drugs. Patients with reduced cognitive function and patients otherwise unable to complete the questionnaires were excluded.

Oral morphine equivalents (OME) were calculated using the standard conversion factors and the OME trend during the study period was assessed by a generalized additive model. Factors affecting the morphine equivalent daily dose (MEDD) were assessed using multiple linear regressions. Data were analyzed using the SPSS 21 (SPSS Inc., Chicago, IL, USA) package program. Continuous

quantitative data were presented as number, mean ± standard deviation. The paired sample test was applied to non-parametric data for the statistical. Results were considered statistically significant at P value<0.05.

Conflict of interest: Nil
Funding: Nil

Results:

A retrospective observational study was carried out on 30 patients (16 male and 14 female) treated at our pain clinic SMHS hospital. The average age of the patients was 59.9±13.54 years [Table 1]. Clinical data of the study population are listed in [Table 2].

Table 1: Demographic profile of the study population

Age (years)	Frequency	%
18-40	03	10.00
41-55	04	13.33
56-70	11	36.66
71-80	07	23.33
≥80	05	16.66
Sex M/F	16/14	53.3/46.6
Mean age =59.9±13.54		

Table 2: Primary Cancer Type

Primary Cancer Type	Frequency	%
Ca rectum	6	20.0
Ca colon	5	16.6
Ca urinary bladder	5	16.6
Ca prostate	5	16.6
Ca lung	3	10.0
Ca breast	2	6.6
NHL	2	6.6
Gynecological	2	6.6

Overall, the mean MEDD was 27.8 ± 21.9 mg per day per patient during the study period [Table 3]. Patients with stage 4 cancer received higher MEDD of 4.04 (95% CI: 0.30-7.62) as compared to those with stage 1 cancer [Fig 1]. The mean MEDD was significant higher in patients with high cancer stages and metastases of the bone, brain, lung, liver, and peritoneum [Fig 2].

Table 3: Characteristic of cancer patients visiting the outpatient department and the opioid consumption

Age (years)	Mean ±SD	P value
18-40	10.03±5.23	<0.05
41-55	5.02±2.43	<0.05
56-70	6.19±3.01	<0.05
71-80	7.89±3.09	<0.05
≥80	8.91±4.01	<0.05
Male	9.49±5.01	<0.05
Female	8.21±4.09	<0.05
Mean =28.9 ± 21.9		

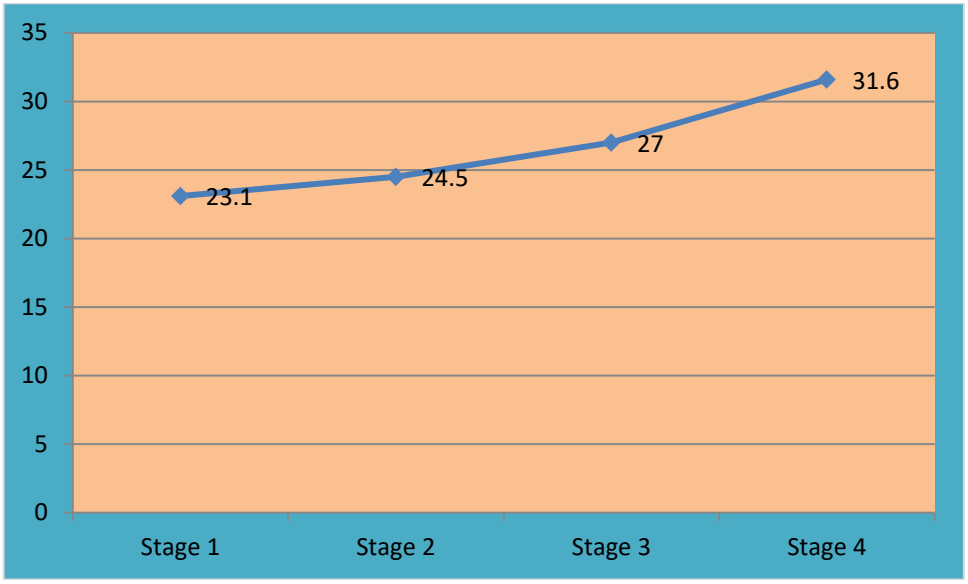

Fig 1

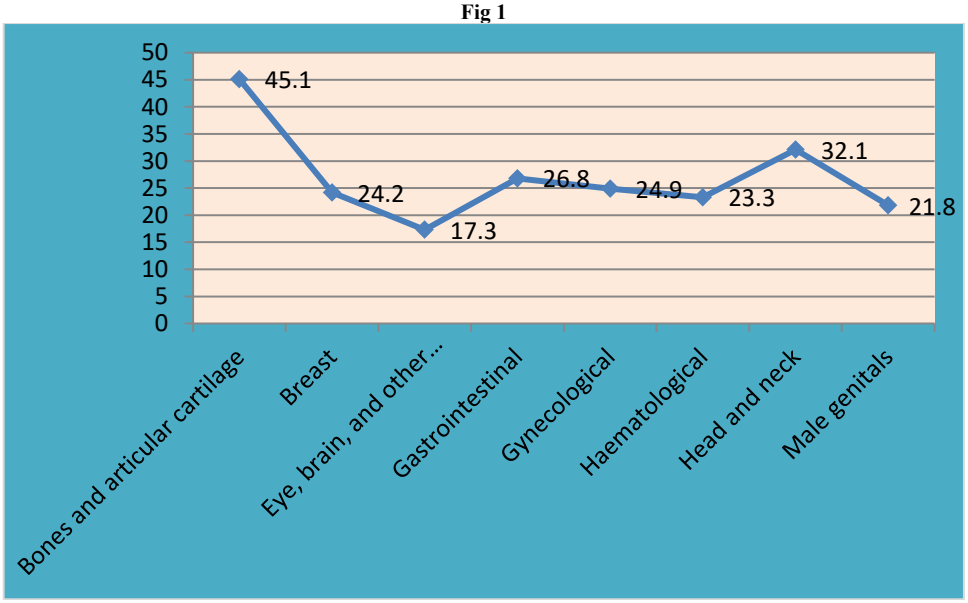

Fig 2

Discussion:

Cancer pain is a common and devastating symptom. In patients with advanced cancer, pain is described as moderate to severe in approximately 40%e50% and as very severe or excruciating in 25%e30%. [21]Morphine is recommended for cancer at Step 3 of the World Health Organization (WHO) ladder. [22]The Expert Working Group of the Research Network of the European Association for Palliative Care (EAPC) has listed 20 recommendations for the treatment of moderate to severe pain in cancer patients. [22]

During the study period, all cancer patients in our pain clinic SMHS hospital received a total OME of approximately 1.51- 1.67 mg per day per patient. The MEDD per prescription was the highest in patients with bone and articular cartilage cancer. Even after adjusting for covariates, including age, duration of cancer, and staging, the MEDD of patients with bone and articular cartilage cancer was still higher than those of patients with other types of cancer. Overall, male cancer patients received higher dose of opioids than female patients throughout the study period. However, after adjusting for covariates including age, year of prescription, and primary cancer site, the difference in MEDD between male and female patients became not statistically significant. This might be partially explained by the fact that larger proportions of male patients were in advanced cancer stages and

had been diagnosed with cancers with higher incidences and more severe pain, including bone and articular cartilage cancer, compared to female patients.

In patients with bone and articular cartilage cancer, pain can be caused by either direct pressure from the tumor on the nerves surrounding the bone or various cytokines released around the area, including interleukin-1b, tumor necrosis factor a, interleukin-6, epidermal growth factor, and platelet-derived growth factor.[23,24]

In our study the MEDD exhibited slightly increasing trend over the study period; however, the magnitude of the changes in MEDD was relatively small, especially when compared with the changes in MEDD in our study. One study reported that the MEDD in the US decreased from 150 mg/day in 2008 to 83 mg/day in 2014, [16] while the overall MEDD in this study slightly increased from 26.8 mg/day during 2016–2018 to 29 mg/day during 2018–2020. This level is much lower than the recommended dosage limit of 90 mg/day and well under the limit of 100 mg/day, which is the normal level indicating an overdose . [25]

According to a report from the Thai Food and Drug Association (FDA), the prescription of FDA-approved opioids modestly increased each year during 2012–2018, similar to the findings of this study. [26] However, the utilization of opioids in Thailand was still much lower than the annual allocated quota. Opioid accessibility issues have been found with morphine IV, oral methadone, and oxycodone. [26]In our study, young age, years with cancer, advanced-stage cancer, bone metastasis, and adjuvant treatment were significant positive predictors of opioid prescription. In terms of age, MEDD was highest in young adult patients, under 42 years of age. Previous studies have reported a decrease in opioid use in older patients. [27, 28] However, the association between age and pain perception remains uncertain. Some studies have reported decreased pain perception in older patients due to the degeneration of neurological systems, while other studies have reported decreases in the pain threshold in older patients, thus increasing pain perception .[29] “Opiophobia,” a term introduced in the 1980s, might explain this phenomenon. This refers to the fear that some physicians have that the use of opioids might lead a patient to become addicted to the drug or develop severe side effects.[30] Morevover, fears of overdose resulting in deep sedation or respiratory depression are also widespread among healthcare providers and the general population. [31,32] A lack of appropriate education is one of the significant barriers for adequate opioid prescriptions for pain control . [33] These concerns can lead to the under-prescription of pain-relieving drugs, leading to the under treatment of severe pain, especially inelderly patients. [34] Improved education on the safe and effective use of opioids might relieve those exaggerated risk perceptions resulting in opiophobia.In our study longer duration and cancer stage were associated with increased MEDD. This might be related to various factors, including increased pain caused by cancer progression, larger tumors, irritation of nerves and tissues around the tumors, distant metastases, or therapy .[35]In the present study bone metastases were found to be associated with higherMEDDs. Bone is a connective tissue containing a large number of sensitive neurons in both the periosteum and the bone marrow which mediate acute and chronic bone pain. [36] Bone metastasis can stimulate these neurons leading to an increase in pain severity, eventually resulting in an increase in opioid consumption to control pain. In one study 75% of cancer patients with bone metastases reported having bone pain.[47]

Oral administration of morphine could not be maintained for the majority of patients to the last ours of life due to their aggravated clinical condition. Parenteral infusion of morphine was then necessary.

Conclusion: Oral morphine use has increased over time in Kashmir but remains substantially lower than estimated need. Opioid use in cancer patients in this study was lower than the average global usage. There is significant geographic variation of use. Efforts are needed to improve palliative care in Kashmir and to reduce regional disparities in access to opioids.

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