PEDIATRIC CANCER PAIN MANAGEMENT
AT A REGIONAL CANCER CENTER:
IMPLEMENTATION OF WHO ANALGESIC LADDER

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Abstract

Purpose: To collect data on the prevalence of various types of cancer pain in a sample of children with cancer, and to implement the WHO Analgesic Ladder in the management of pain in pediatric cancer.

Methods: Eighty four pediatric patients suffering of cancer pain were studied during the period 2001-2006. Patients were requested to rate their global intensity of pain on 0-100 mm visual analogue scale (VAS 0 = no pain 100 = maximum pain). Pain management was performed in accordance with the WHO Analgesic Ladder for cancer pain. Patients were followed up weekly for three weeks.

Results: Of the 84 pediatric children with cancer, pain was nociceptive in 26 (31%), neuropathic in 12 (14.3%) and mixed in 46 (54.8%). Almost 7 (8.3%) of patients were on WHO step 3 at baseline. Thereafter the WHO step 3 increased; first week visit 36 (43%) patients; second week visit 58(69%), and third week 69 (82.1%). At baseline, 40 (47.6%) patients took NSAID only, 2 (2.4%) patients took adjuvant, while 38 (45.2 %) patients took combination of NSAID and adjuvant treatment. There was statistically significant (p = 0.000) reduction in VAS as time progressed.

Conclusion: Cancer pain in pediatric age group can be well managed in accordance with the WHO Analgesic Ladder. Aggressive symptoms and control of treatment of related side effect are also needed to ensure successful implementation and the WHO Analgesic Ladder.

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Introduction

The provision of pain management to the pediatric oncology population presents special challenges. The pediatric oncology population is chronically ill, often young with a doubtful prognosis, labile disease course, receiving aggressive therapy with a debilitating side effects. Patients and their families experience severe disruption to their daily lives with frequent clinic visits, scheduled and unscheduled admission. Although there have been major advances in the treatment of childhood cancer with on overall survival rate of more than 70%, cancer continues to be the leading cause of death in children resulting from disease.

Pain control is an integral component of pediatric palliative care. Children may experience many different types of pain from invasive procedures, cumulative effects of toxic therapies, progressive disease or psychological factors.

The pain is often complex with multiple sources, comprised of nociceptive and neuropathic components. Children’s perception of pain is defined by their age and cognitive level; their previous pain experiences, against which they evaluate each new pain; the relevance of the pain or disease causing pain; their expectation for obtaining eventual recovery and pain relief and their ability to control the pain themselves.

In this study the pediatric cancer pain was managed in accordance to the WHO analgesic ladder. The aim was to collect data on the prevalence of different types of cancer pain in a sample of children with cancer pain and report on pain management in pediatric cancer with respect to the WHO ladder approach at a regional cancer set up.

Keywords: Cancer pain, Pediatric cancer pain, Palliative care, WHO analgesic ladder.

Materials & Methods

The present study was conducted on outpatients in the Pain and Palliative Care Clinic at Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi. India. 84 pediatric patients 5-15 years (mean 11 yrs), (73% males, 27% females) suffering of cancer pain were included in this prospective study during the period 2001-2006.

Initial work up of patients in the Pain Clinic included general medical and neurological examination and a specific examination of the site of pain and surrounding anatomic regions. Patient who were lost to follow up after single visit, were excluded from this study. Patients were followed up weekly for three weeks. Patients were asked to rate their global intensity of pain on 0-100 mm visual analogue scale (VAS 0 no pain and 100 mm is maximum pain).

Pain treatment was performed in accordance to the WHO analgesic ladder for cancer pain:

- NSAIDs for mild pain (WHO Step 1),
- Weak opioids and NSAIDs for mild to moderate pain (WHO Step 2),
- Morphine for moderate to severe pain (WHO Step 3).

Every step was accompanied by various adjuvant drugs for various indications (Table 1). All patients were followed up weekly for three weeks.

<table>
<thead>
<tr>
<th>Types of Drugs</th>
<th>Drugs</th>
<th>Doses (mg/kg/day)</th>
<th>Various Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant</td>
<td>Amitriptiline</td>
<td>0.2-0.5</td>
<td>Neuropathic pain</td>
</tr>
<tr>
<td>Anticonvulsant</td>
<td>Gabapentin</td>
<td>5-30</td>
<td>Neuropathic pain</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Dexamethasone</td>
<td>4-16 mg/day</td>
<td>Neuropathic pain, Bone pain, brain metastasis, Poor quality of life</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>Metoclopramide</td>
<td>10-30 mg/day</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td>Ondansetron</td>
<td>0.5-0.15</td>
<td>Nausea and vomiting</td>
</tr>
<tr>
<td></td>
<td>Granisetron</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Antihistamine</td>
<td>Promethazine:</td>
<td>0.5-2</td>
<td>Pruritus, Nausea/vomiting</td>
</tr>
<tr>
<td></td>
<td>Diphenhydramine</td>
<td>1-4</td>
<td></td>
</tr>
<tr>
<td>Laxatives</td>
<td>Bisacodyl</td>
<td>5-15 mg/day</td>
<td>Constipation</td>
</tr>
<tr>
<td></td>
<td>Sodium picosulphate</td>
<td>5-15 mg/day</td>
<td></td>
</tr>
</tbody>
</table>

Laxatives were given prophylactically to all patients who were on opioids. In follow up visits, patients were asked about pain intensity, nausea/vomiting, sedation, constipation, generalized weakness, lack of appetite. Patients were asked to rate their symptoms on verbal rating score (VRS-1 not at all; 2 mild grades; 3 moderate grades; 4 severe grades).
Statistical Analysis

The appropriate descriptive statistics were used for presentation of each of the covariates. Exploratory exercise was also done for applying the appropriate statistical tools. One way analysis of variance was used to compare the VAS among the different types of pain. Kruskal Wallis test was used to compare the age among the different types of pain. Chi square test was performed to evaluate the association of various outcomes at baseline with different types of pain. Repeated measure of analysis of variance was used for seeing the changes in the VAS as time increases as well as effect of different types of pain (Neuropathic, mixed and nociceptive pain). Cochran Q test was used to look at the differences in proportion of nausea/vomiting, constipation, sedation and pruritus as the time increases. For seeing the changes in the generalized weakness and loss of appetite as the time changes, Friedman test was applied for each of the different types of pain. The p-values less than 5% were considered as a significant result. SPSS 11.5 was used for statistical analysis.

Results

Of the total 94 patients enrolled, 10 patients did not turn up after 1st visit so were excluded. 84 patients were followed up weekly for 3 weeks during the period 2001-2006.

52% of patients were referred from the medical oncology, 30% patients from radiotherapy and 2% patients from surgical oncology, whereas 16% patients were direct referred to pain clinic.

Of the pediatric cancer patients studied 38% had not taken any prior treatment 21% patients had taken chemotherapy only, 19% patients had taken chemotherapy and radiotherapy and 12% patients had taken surgery, chemotherapy and radiotherapy prior to referral.

26 (31%) patients had nociceptive pain (somatic, bony, and visceral). 12 (14.3%) patients had neuropathic pain, 46 (54.8%) patients had mixed pain (Table 2).

Almost 8.3% of pediatric patients were in the WHO step 3 at baseline. Thereafter the WHO step 3 steadily increased at first weekly visit 36 (43%) patients, second visit 58 (69%) patients, and third visit 69 (82.1%) (Fig. 1).

In addition, at baseline, 40 (47.6%) patients took NSAID only, 2 (2.4%) patients took adjuvant while 38 (45.2%) patients took combination of NSAID and adjuvant treatment. The proportion of patients taking combination of NSAID and adjuvant were increasing continuously as time increased. The median morphine dose at baseline, first and second weekly visits was same i.e. 30 mg. However, median morphine dose at third visit rose to 40 mg.

There was statistically significant (p = 0.000) reduction in VAS as time increased while no effect of different types of pain and no interaction effect of time and different types of pain could be found (Fig. 2).
At baseline the nausea/vomiting was moderate grade in 2 patients and severe grade in 1 patient. At second weekly visit no patient had severe grade nausea/vomiting while 6 patients had moderate grade nausea/vomiting. Similarly, none of the patients had severe grade constipation at any visit. 1 patient had pruritus at baseline, 2 patients had moderate grade pruritus and 1 patient had severe pruritus at first visit. One patient had moderate grade pruritus at second visit and no patients developed any type of pruritus at third visit (Fig. 3).

Since the number of patients presented with nausea/vomiting or pruritus or constipation at any visit was not much, therefore the category with occurrence of symptom or no symptom was made for further analysis. However, in case of generalized weakness and loss of appetite, the level of severe grade (VRS 4) patients was less so that patients were pooled with patients having VRS 3. The comparisons of baseline characteristics are shown in Table 2.

The significant deterioration \((p = 0.000)\) in nausea/vomiting was found as time increased. However no significant changes in the proportion of patients could be seen in constipation. In addition, the significantly increased changes in generalize weakness was found whereas no significant changes were for loss of appetite. There was no effect of different types of pain on any of the outcomes separately.

Discussion

Pain control is an intrinsic component of pediatric palliative care. Since children may experience complex pains due to myriad physical and psychological factors, pain control must be child centered rather than disease centered\(^5\).

The management of pain in the palliative care of children is somewhat different from that in adults. It also differs in approach from the management of other types of acute and chronic pain in childhood. But in this present study it was found that pain management

<table>
<thead>
<tr>
<th>Variables</th>
<th>Neuropathic ((n = 12))</th>
<th>Mixed ((n = 46))</th>
<th>Nociceptive ((n = 26))</th>
<th>p-values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean ± SD)</td>
<td>9.25 ± 4.49</td>
<td>10 ± 3.52</td>
<td>11.14 ± 3.03</td>
<td>0.256</td>
</tr>
<tr>
<td>Sex (M:F)</td>
<td>5:7</td>
<td>37:9</td>
<td>19:7</td>
<td>0.027</td>
</tr>
<tr>
<td>Visual analogue scale (VAS)</td>
<td>77.5 ± 18.64</td>
<td>83.26 ± 16.33</td>
<td>80.38 ± 22.53</td>
<td>0.163</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>5 (41.7%)</td>
<td>13 (28.3%)</td>
<td>12 (46.2%)</td>
<td>0.28</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (25%)</td>
<td>17 (37%)</td>
<td>12 (46.2%)</td>
<td>0.446</td>
</tr>
<tr>
<td>Sedation</td>
<td>2 (16.7%)</td>
<td>2 (4.3)</td>
<td>1 (3.8%)</td>
<td>0.237</td>
</tr>
<tr>
<td>Pruritus</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (3.8%)</td>
<td>0.323</td>
</tr>
<tr>
<td>Generalized Weakness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild Weakness</td>
<td>7 (58.3%)</td>
<td>19 (41.3%)</td>
<td>8 (30.8%)</td>
<td>0.302</td>
</tr>
<tr>
<td>Moderate Weakness</td>
<td>1 (8.3%)</td>
<td>2 (4.3%)</td>
<td>4 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>Loss of appetite</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>7 (58.3%)</td>
<td>20 (43.5%)</td>
<td>9 (34.6%)</td>
<td>0.182</td>
</tr>
<tr>
<td>Moderate</td>
<td>1 (8.3%)</td>
<td>10 (21.7%)</td>
<td>11 (42.3%)</td>
<td></td>
</tr>
</tbody>
</table>

\(n = \) Total number of patients.
in pediatric cancer pain according to WHO analgesic ladder, is as good as in adult patients.

In the present study 14.3% patients were having neuropathic, and 54.6% patients from mixed (nociceptive and neuropathic) and 31.1% from nociceptive pain. In adult patient’s the incidence of neuropathic pain ranged from 16-31%, as quoted by various authors6,7,8 but it is not clearly mentioned the component of nociceptive in their population.

 Mean pain intensity at base level in all types was insignificant. There was statistically significant reduction in VAS as time increased, while no effect of different types of pain and no interaction effect of time and different types of pain could be found. This study therefore demonstrated that neuropathic pediatric cancer pain can be relieved in most patients and the efficacy of pediatric cancer pain treatment following the WHO guideline was as good as in neuropathic and mixed, as in nociceptive pain. It has previously been thought that opioids were highly dangerous drugs unsuitable for use in children. However, opioids have now taken their place as the mainstay for provision of good analgesia to manage moderate to severe pain in malignant conditions9,10. Similar findings were observed in the present study where at the end 82.1% patients were on opioids as compared to 8.3% at base line, and the mean dose of morphine used at the end of study was 40 mg with statistically significant decrease in VAS as compared to base line.

 No extreme sedation or respiratory depression was observed in any of our patient, similar to others9. Itching was found in 2 children and out of these two one was having itching before coming to our clinic and another had itching after starting morphine which subsided following antihistaminic therapy. Total of 6 (7.1%) patients had nausea/vomiting but out of these six patients 2 patients had nausea/vomiting before coming to our clinic, findings similar to findings observed by Still et al9 but different from Kasai et al11, as incidence of nausea and drowsiness were 52.9% and 41.2% respectively. They proposed the two step Analgesic Ladder.

 Effective management of some difficult but common pain syndromes such as shooting or burning neuropathic pain, requires techniques “beyond the ladder”. These patients require different classes of drugs, such as tricyclic antidepressants and anticonvulsants. Unfortunately many of these nonopioid adjuvant drugs have not been studied in children and when prescribed, are “off label”12.

 The adjuvant analgesics comprise a diverse group of medications with different primary indications like antidepressants, anticonvulsants steroids13,14. Various adjuvant drugs used in our study; amitryptiline, gabapentine and corticosteroids, as was used by various authors and found to be effective, though it is not evidence based15,16. Future studies are therefore needed to determine the effectiveness of these adjuvant analgesics.

**Conclusion**

Cancer pain in pediatric age group can be very well managed in accordance with the WHO analgesic ladder. Aggressive control of related side effects, is needed to ensure successful implementation of the analgesic ladder.
References