INTRODUCTION

Cancer is the common condition in which addressing pain relief is often the leading concern for the patient and palliative care team at end-of-life care.\[^1\] Every year, approximately 4.5 million patients die from cancer, and 3.5 million suffer from cancer pain daily, with only a limited number of them receiving adequate pain treatment.\[^2\]

The pain in cancer patients may be caused by direct tumor involvement, diagnostic or therapeutic procedures, side effects, or toxicities of cancer treatment. Regardless of its source, uncontrolled pain can affect every aspect of a patient’s quality of life, causing suffering, interference with sleep, and reduced physical and social activity and appetite.\[^3\] Though specialist palliative care teams are available for treating cancer pain, the deaths due to cancer pain are alarmingly at 28%.\[^4\]
In India, in a study cohort of 156 patients who were receiving radiotherapy for their cancer pain, 61% had incidence of pain.\(^5\) Bisht \textit{et al.}\(^6\) found that pain was the most common prevalent symptom (96% of 100 patients assessed) among cancer patients attending a palliative care unit in Uttarakhand, India.

World Health Organization (WHO) analgesic ladder management is currently the most accepted and widely employed pain management strategy in patients with cancer pain. Despite their well-known adverse effects ranging from local to general in bodily distribution, opioids are still the most recommended drug therapy of choice for patients with cancer pain.\(^7\) Despite great advances in the fields of pain management and palliative care, pain directly or indirectly associated with a cancer diagnosis remains significantly undertreated.\(^8\)

Nonpharmacologic methods used in conjunction with analgesics have as their goal to help the patient with cancer gain or maintain functionality and restore a sense of psychological control over their pain and their circumstances. These approaches ordinarily have no negative side effects.\(^9\) Physical interventions form a part of nonpharmacological interventions that include a variety of therapeutic methods for pain relief in palliative care, administered by physical therapists.\(^10\)

One of the recent developments in conceptualization of physical therapy management for pain relief in palliative care is the mechanism-based classification of pain.\(^11\) Identification of a cancer patient’s clinical presentation and its relationship to symptoms is essential for initiation of appropriate therapeutic strategy for pain relief.

There are five operating mechanisms in pain perception that are categorized under mechanism-based classification (MBC) of pain by Kumar and Saha,\(^11\) who described in detail the individual mechanisms, their clinical features, assessment findings, and probable physical therapy (mechanism-based physical therapy-MBPT) treatment techniques. Recently, Kumar\(^12\) described the application of MBC and MBPT to cancer pain. The five mechanisms are:

- Central sensitization/central neurogenic mechanism/central nociceptive mechanism
- Peripheral sensitization/peripheral neurogenic mechanism
- Peripheral nociceptive mechanism
- Sympathetically maintained pain/sympathetically dependent pain mechanism and
- Cognitive–affective (psychosocial) mechanism.

The recent paradigm shift toward mechanisms of musculoskeletal pain\(^13\) and MBPT indicates a comprehensive therapeutic decision-making process\(^14\) by identifying the predominant pain mechanism and future mechanism-specific physical therapy treatments. Although the WHO analgesic ladder is the most widely recommended treatment of choice for cancer pain,\(^15\) controlled clinical trials are lacking.\(^15,16\) A recent position statement of British Pain Society endorsed by the UK Association of Palliative Medicine and the Royal College of General Practitioners on physical, interventional, and complementary therapies emphasized a more comprehensive model of managing cancer pain was needed that was mechanism-based and multimodal, using combination therapies including interventions where appropriate, tailored to the needs of an individual, with the aim to optimize pain relief with minimization of adverse effects.\(^17\) The objective of this study was to detail the efficacy of MBPT in addition to standard intervention of WHO analgesic ladder prescription, for pain in patients with cancer.

**MATERIALS AND METHODS**

**Study design**

Observer-blinded prospective case series.

**Study location**

Department of physiotherapy, Kasturba medical college (Manipal University), Mangalore.

**Study setting**

KMC hospital, Attavar, Mangalore – an in-patient ward and out-patient physiotherapy unit in a multispecialty, university-affiliated teaching hospital.

**Sampling**

Convenient sampling.

**Subjects**

Hospitalized or out-patient adult patients of either gender medically diagnosed with cancer as a primary diagnosis, which were referred for rehabilitation and symptom palliation to physical therapy.

**Selection criteria**

The patients were considered for participation in this study if they had the following inclusion criteria:

- Cancer as a primary diagnosis for a minimum of 6 months and pain as a primary symptom for a minimum of 3 months.
The patients with following presentations were excluded from the study:
Secondary comorbid diagnoses of neurological, musculoskeletal, psychiatric, cardiopulmonary disorders, skin disorders, which would affect physical therapy examination and treatment.

**Procedure**

All patients were required to provide a written informed consent prior to participation and screening.

**Categorization of pain in patients with cancer**

At the first level, cancer pain will be categorized under three broad categories, by referring physician or medical oncologist and/or radiation oncologist, respectively, into each of the following.\[13\]

- Pain unrelated to cancer (noncancer pain) – pain in areas anatomically unrelated to the region of carcinoma; intermittent pain aggravated/relieved by positions and/or movements; pain that was present much before the diagnosis of cancer; and, pain that do not respond to cancer treatments.

- Cancer-related pain (primary cancer pain), which will be further subgrouped into breakthrough (refractory/incidental) pain and nonbreakthrough pain. Cancer-related pain – pain in the region of carcinoma; pain that started after cancer diagnosis; constant pain of high intensity that usually responds to anticancer treatments.

- Cancer treatment-related pain (secondary cancer pain) – pain after initiation of anticancer treatments such as chemotherapy (e.g., neuropathy), radiation therapy (e.g., mucositis), or surgery (e.g., postoperative pain).

**Categorization of patients’ pain into five mechanisms**

A qualified physical therapist would classify the patient’s pain into following five mechanisms and also rate and rank the predominant mechanism operating for pain in the patient. The detailed description of MBC for cancer pain is provided elsewhere.\[12\]

**Intervention**

**Mechanism-based physical therapy**

The following mechanism-specific treatments were administered by a physical therapist and a clinical psychologist.

**Cognitive-affective**

Pain education emphasizing on pain–disability interrelationship, stress and pain, pacing, graded activity training, and cognitive-behavioral therapy. An attempt to explore the patient’s own understanding of pain and related symptoms into locus of control was done to improve coping behavior and positive self-monitoring approach to pain.

**Central sensitization**

Pain neurophysiology education and low-frequency transcutaneous electrical nerve stimulation (TENS) applied to the painful area.

**Peripheral sensitization**

Sciatic nerve press technique, peripheral nerve massage, and peripheral nerve slider techniques.

**Sympathetically maintained pain**

Sympathetic slump technique performed for the thoracic region with the patient in long sitting position. Thoracic spinal mobilization was performed additionally if restricted mobility was found on passive motion testing of the spine.

**Nociceptive**

High-frequency TENS, soft tissue mobilization/massage, passive/active-assisted/free-active/resisted exercises.

The intervention was administered once weekly for a period of five weeks, with each session lasting 30 min.

All patients were also on WHO analgesic ladder for their cancer pain, which was first proposed in 1986 as a guideline and later updated in 1997,\[19\] which was later validated\[20\] and recommended by palliative care associations and associations of radiation oncologists\[21\] and endorsed by guidelines\[22\] for its use as an effective therapeutic strategy in management of pain in patients with cancer.

**Outcome measures**

**Pain**

Brief pain inventory for cancer pain (BPI-CP)\[23\] consisting of pain severity and pain interference subscales was used as a self-report measure for evaluating pain and associated activity limitations due to cancer pain. The Brief Pain Inventory (BPI) is recommended as a pain measurement tool by the Expert Working Group of the European Association of Palliative Care.

The first part of the BPI measures pain severity using four different 11-point numeric scales anchored by 0 representing “no pain” and 10 being “pain as bad as you can imagine.” Patients are instructed to rate their pain now and worst for the past 24 h, least for the past 24 h, and average pain. The second part of the BPI
measures how pain interferes with general activity, mood, walking, normal work, relationships with others, sleep, and enjoyment of life. Similar to pain severity, each functional item is ranked on an 11-point numeric scale, where 0 represents “Does not interfere” and 10 denotes “completely interferes.” The sum of the scores of the pain intensity items represents the summed pain intensity score, and the sum of the scores on the pain interference items represents the summed interference score. Because BPI has no validated method for handling missing values, the summed scores were not calculated for patients with missing values.

Quality of life
Was measured using generic and disease-specific components of European organization for research and treatment in cancer quality of life questionnaire 30-item (EORTC-QLQ C30).[24] Both patient- and caregiver-reported versions were taken. It has high reliability and validity in different groups of cancer patients and the test–retest reliability is optimal. The questionnaire consists of 30 items. It is composed of five functional scales (physical, role, emotional, cognitive, social), three symptom scales (fatigue, pain, nausea/vomiting), and eight single items (global health, global quality of life, dyspnea, appetite loss, sleep disturbance, constipation, diarrhea, and financial impact of the disease and treatment).

Data Collection
Outcome measures were taken pre- and post-treatment by an independent blinded observer who was a qualified physiotherapist.

Data Analysis
Sample size estimation was done through anticipated effect size, desired statistical power, and level of probability using an online sample size calculator.[25] Pre–post comparison for both outcome measures for total scores and subscores was done using Wilcoxon signed-rank test at 95% confidence interval using Statistical Package for Social Sciences (SPSS) version 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS
Sample size estimation
For an effective size of 1.5 (substantial) under a desired power level of 90% with a level of probability set at 5%, we calculated a priori sample size for this study to be 22 with a two-tailed hypothesis. Including a possible 10% dropout, we thus needed to recruit 24 patients.

Demographic characteristics
There was a series of 24 patients whose demographic characteristics are shown in Table 1.

Primary outcomes
The MBC findings for those patients are shown in Table 2 and the pre–post comparisons for the two measures (BPI and ERTC-QLQ-C30) with their subscales are shown in Table 3.

DISCUSSION
The study is the first of its kind, conducted on patients with cancer pain where the treatment was based on the identified predominant mechanism of pain. While mechanisms were found to play an important role not only in therapeutic responses but also in pathogenesis of pain per se, the notable changes in outcome measures of pain and quality of life measured using BPI-CP and EORTC-QLQ-C30 were much beyond the substantial effective sizes for both the measures. This change was associated with 100% statistical power, which adds to the external validity of this study’s findings. There were thus clinically significant improvements together with the statistical significance. The choice of these two outcome measures would have determined the accuracy of the observed change since they were chosen based on earlier reports of their established measurement properties and evidence-based recommendations on their use.[23,24] This study findings are based on a small sample size and hence caution is warranted prior to extrapolation of its findings into patient populations with cancer pain.

The decision making in MBPT is open for further scrutiny since the classification is recently under preliminary validation and is yet to be comprehensively established. However, other methods of clinical decision making[26] for management of patients with cancer pain are open for future research and comparisons between different approaches would yield better clinically relevant information.

One of the acceptable limitations and of probable consideration is the patient heterogeneity in the etiological diagnosis for cancer pain. This study included bone cancer, breast cancer, head and neck cancer, and lung cancer and inclusion of other types would yield different results, and
future research on MBPT could study homogeneous types of cancer patients and their therapy responses.

There were mixed findings obtained from patient history findings in terms of pain presentations as most of the patients had cancer treatment-related pain rather than cancer-related pain. Also it is important to note that all patients were already on analgesics prescribed on symptomatic basis as outlined by the WHO and hence MBPT effects could be opined better as an useful adjunct to drug therapy.

Some of the important observations of this study include: Prevalence of nociceptive mechanism was greater than peripheral sensitization and cognitive–affective mechanism in cancer pain. This trend was similar to findings in patients with musculoskeletal pain found earlier, hence there is a possibility that these patients’ pain was predominantly musculoskeletal in origin, which was evidenced by intermittent nature and mild irritability. Breakthrough pain was not considered in this study, which might not have responded to MBPT or was originally not intended to be used for.

Future controlled studies on comparison of individual versus mechanism-based treatments may be warranted in other medical and nonmedical therapeutic interventions. Another factor evaluated in this study was the effects and not the effectiveness, the latter needs to be evaluated using large-scale, population-based, pragmatic, randomized, clinical trials.

CONCLUSION

Mechanism-based physical therapy produced clinically and statistically significant change in BPI-CP and EORTC-QLQ-C30 scores among people with cancer pain in this study.

ACKNOWLEDGEMENT

The authors wish to thank patients and their family caregivers for their whole-hearted participation in the study.
Table 3: Pre–post comparisons of total and subscale scores of brief pain inventory and European organization for research and treatment in cancer quality of life questionnaire 30-item questionnaire

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>Subscales</th>
<th>Pre-treatment</th>
<th>Post-treatment</th>
<th>Statistical power (%)</th>
<th>Effect size (Cohen’s D)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brief pain Inventory-cancer pain</td>
<td>Pain severity subscale (PS)</td>
<td>28.25±2.71</td>
<td>15.12±2.35</td>
<td>-</td>
<td>5.17</td>
</tr>
<tr>
<td>EORTC-QLC-C-30 Questionnaire</td>
<td>Pain interference subscale (PI)</td>
<td>47.3±2.02</td>
<td>25.1±4.62</td>
<td>-</td>
<td>5.03</td>
</tr>
<tr>
<td></td>
<td>Total score</td>
<td>75.25±3.77</td>
<td>40.12±4.08</td>
<td>100</td>
<td>8.94</td>
</tr>
<tr>
<td></td>
<td>Global health status/quality of life</td>
<td>42.5±3.9</td>
<td>68.16±5.9</td>
<td>-</td>
<td>3.20</td>
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<tr>
<td></td>
<td>Physical functioning (a)</td>
<td>69.62±4.7</td>
<td>88.2±4.4</td>
<td>-</td>
<td>4.23</td>
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<tr>
<td></td>
<td>Role functioning (b)</td>
<td>57.1±4.7</td>
<td>86.87±9.4</td>
<td>-</td>
<td>4.05</td>
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<tr>
<td></td>
<td>Emotional functioning (c)</td>
<td>64.1±23.6</td>
<td>85.33±3.8</td>
<td>-</td>
<td>6.09</td>
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<tr>
<td></td>
<td>Cognitive functioning (d)</td>
<td>72.14±2</td>
<td>90.82±4.3</td>
<td>-</td>
<td>2.79</td>
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<tr>
<td></td>
<td>Social functioning (e)</td>
<td>68.87±4.42</td>
<td>87.87±6.72</td>
<td>-</td>
<td>3.34</td>
</tr>
<tr>
<td></td>
<td>Functioning subscale (a+…e)</td>
<td>331.6±109.75</td>
<td>438±112.04</td>
<td>100</td>
<td>9.71</td>
</tr>
<tr>
<td></td>
<td>Fatigue (f)</td>
<td>52.5±2.07</td>
<td>23.6±3.85</td>
<td>-</td>
<td>9.34</td>
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<tr>
<td></td>
<td>Nausea and vomiting (g)</td>
<td>45.51±0.6</td>
<td>13.5±2.9</td>
<td>-</td>
<td>1.00</td>
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<tr>
<td></td>
<td>Pain (h)</td>
<td>48±1.3</td>
<td>15.6±2.5</td>
<td>-</td>
<td>16.25</td>
</tr>
<tr>
<td></td>
<td>Dyspnea (i)</td>
<td>28.6±2.13</td>
<td>17.6±2.81</td>
<td>-</td>
<td>3.56</td>
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<tr>
<td></td>
<td>Insomnia (j)</td>
<td>37.2±7.77</td>
<td>17.1±1.3</td>
<td>-</td>
<td>6.43</td>
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<td></td>
<td>Appetite loss (k)</td>
<td>25.8±2.98</td>
<td>17.7±5.03</td>
<td>-</td>
<td>4.13</td>
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<td></td>
<td>Constipation (l)</td>
<td>23.8±11.45</td>
<td>17.1±11.35</td>
<td>-</td>
<td>4.81</td>
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<tr>
<td></td>
<td>Diarrhea (m)</td>
<td>10.7±2.49</td>
<td>5.±1.6</td>
<td>-</td>
<td>2.50</td>
</tr>
<tr>
<td></td>
<td>Financial difficulties (n)</td>
<td>28.2±2.31</td>
<td>13.8±7.23</td>
<td>-</td>
<td>6.33</td>
</tr>
<tr>
<td></td>
<td>Symptoms subscale (F1–n)</td>
<td>259.38±6.32</td>
<td>141.62±7.93</td>
<td>100</td>
<td>14.85</td>
</tr>
</tbody>
</table>

All values are in means and standard deviations; *<P values for all comparisons were significant at <0.0001 level; EORTC-QLQ-C-30, European organization for research and treatment in cancer quality of life questionnaire 30-item.

REFERENCES

Kumar, et al.: Mechanism-based cancer pain physical therapy


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