A Retrospective Study on the Influence of Nutritional Status on Pain Management in Cancer Patients Using the Transdermal Fentanyl Patch

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It is unknown whether nutritional status influences pain intensity in cancer patients receiving a transdermal fentanyl patch (FP). This study aimed to determine whether nutritional status is associated with pain intensity and to evaluate the influence of changes in nutritional status on pain intensity in cancer patients receiving transdermal FP treatment. We included 92 patients receiving transdermal FP treatment for the first time with switching from oxycodone. The patients were classified into low- and normal-nutrition groups based on their nutritional status, which was assessed according to the Nutrition Risk Screening 2002 (NRS 2002) parameters. The pain intensity of each patient was evaluated by a numeric rating scale (11-point scale from 0 to 10). NRS 2002 score and pain intensity were obtained on day 3 after the FP was applied to the skin. Pain intensities were significantly higher among patients in the low-nutrition group than among patients in the normal-nutrition group. NRS 2002 scores showed a significant positive correlation with the pain intensities. In 52 of 92 patients, who were evaluated using the NRS 2002 score and pain intensity on day 30 after FP application, the changes in NRS 2002 scores were significantly related to changes in pain intensities (odds ratio, 30.0; 95% confidence interval, 4.48–200.97; p=0.0005). These results suggest that an increase in the NRS 2002 score is a risk factor for an increase in pain intensity in cancer patients receiving FP treatment. Malnutrition may lead to poor pain management in cancer patients receiving FP treatment.

Key words fentanyl patch; nutritional status; Nutrition Risk Screening 2002; pain control

The transdermal fentanyl patch (FP) provides pain relief and has improved the quality of life of many cancer patients living with chronic pain. The high lipid solubility and low molecular weight are characteristics that make fentanyl suitable for transdermal administration.1,2 Currently, the transdermal FP therapeutic systems that are available in Japan are Durotep® MT patch (Janssen Pharmaceutical K.K.), Onduro® patch (Janssen Pharmaceutical K.K.), and Fentos® tape (Hisamitsu Pharmaceutical Co., Inc.). The FP should be replaced every 72 h (Durotep® MT patch) or 24 h (Onduro® patch and Fentos® tape), and it is particularly useful for patients with dysphagia. However, it has been reported that the duration of the analgesic effects of the FP are often decreased because of incomplete adherence to the skin at the application site, and that pain control is impaired in cancer patients who have switched from an oral sustained-release morphine preparation to the FP. Thus, some cancer patients receiving the transdermal FP may have unsuccessful pain control.3 In addition, some factors such as fever and body mass index (BMI) have been reported to influence the residual fentanyl content of used patches,4,5 suggesting that these factors may affect the transdermal absorption of fentanyl from the patch.

We previously reported that low body fat and poor nutritional status may decrease transdermal fentanyl absorption in cancer patients,6,7 which may affect pain management. However, thus far, there have been no studies examining if nutritional status influences the intensity of pain in cancer patients receiving the transdermal FP. To evaluate the nutritional status in cancer patients, we used the screening tool, Nutritional Risk Screening 2002 (NRS 2002), which is a comprehensive scoring system that evaluates a hospitalized patient’s nutritional status according to disease severity, BMI, percent weight loss, and changes in food intake.8,9 This study was aimed at determining whether nutritional status was associated with pain intensity and at evaluating the influence of changes in nutritional status on pain intensity in cancer patients receiving transdermal FP treatment.

METHODS

Patients Japanese adults who were in-patients of the Iwate Medical University Hospital between January 1, 2011 and December 31, 2012 and who were undergoing initial treatment for management of chronic cancer-related pain with the transdermal FP (Durotep® MT patch or Fentos® Tape) for the first time and who were switched from oxycodone were included in the present study. Patients with fever (≥40°C) and a change in cancer stage, and those who had been prescribed medication that influenced pain intensity, such as anticancer drugs and analgesic adjuvants (except for non-steroidal anti-inflammatory drugs (NSAIDs), were excluded from the analysis. This study was reviewed and approved by Iwate Medical University Ethics Committee. As this is a retrospective study, the patients did not provide written informed consent.

Retrospective Survey Data on sex, age, height, weight, type of cancer, stage of cancer, fentanyl dose, concomitant drugs, laboratory test results (levels of alanine aminotransferase [ALT], aspartate aminotransferase [AST], γ-glutamyl transpeptidase [γ-GTP], and serum creatinine [Cr]), dietary intake, and pain intensity (numeric rating scale: 11-point scale

The authors declare no conflict of interest.

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Table 1. The NRS 2002 Screening System

(1) Impaired nutritional status score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal nutritional status</td>
</tr>
<tr>
<td>1</td>
<td>Weight loss of &gt;5% in 3 months or food intake below 50–75% of normal requirement in the preceding week</td>
</tr>
<tr>
<td>2</td>
<td>Weight loss of &gt;5% in 2 months or BMI of 18.5–20.5+ impaired general condition or food intake of 25–60% of normal requirement in the preceding week</td>
</tr>
<tr>
<td>3</td>
<td>Weight loss of &gt;5% in 1 month (&gt;15% in 3 months) or BMI &lt;18.5+ impaired general condition or food intake of 0–25% of the normal requirement in the preceding week</td>
</tr>
</tbody>
</table>

(2) Severity of disease score

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal nutritional requirements</td>
</tr>
<tr>
<td>1</td>
<td>Hip fracture, patients with chronic conditions, in particular with acute complications: cirrhosis, chronic obstructive pulmonary disease, chronic hemodialysis, diabetes, oncology</td>
</tr>
<tr>
<td>2</td>
<td>Major abdominal surgery, stroke, severe pneumonia, malignancy</td>
</tr>
<tr>
<td>3</td>
<td>Head injury, bone marrow transplantation, intensive care patients</td>
</tr>
</tbody>
</table>

(3) Nutritional evaluation (1(1)+(2)) (if ≥70 years, add 1 to total score)

<table>
<thead>
<tr>
<th>Total Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3</td>
<td>Normal-nutrition group</td>
</tr>
<tr>
<td>≥3</td>
<td>Low-nutrition group</td>
</tr>
</tbody>
</table>

Table 2. Patients’ Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Male/female</th>
<th>Age (years)</th>
<th>Initial dose of FP (as release rates; µg/h)</th>
<th>Concomitant medications</th>
<th>Primary cancer location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>55/37 (n=92)</td>
<td>64.6±10.6 (40–91, mean±S.D.)</td>
<td>74 (DP 49, FT 25)</td>
<td>NSAIDs 92 Hypnotics 31</td>
<td>Esophagus 11 Bladder 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>18 (DP 11, FT 7)</td>
<td>Antilulcer drugs 85 Antiemetics 40</td>
<td>Lung 9 Colon 5</td>
</tr>
<tr>
<td>Initial dose of FP</td>
<td></td>
<td>12.5</td>
<td>25</td>
<td>Antianxiety drugs 17 Cathartics 79</td>
<td>Pancreas 9 Ovary 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>74</td>
<td>12.5</td>
<td></td>
<td>Stomach 9 Pharynx 4</td>
</tr>
<tr>
<td></td>
<td></td>
<td>74</td>
<td>25</td>
<td></td>
<td>Breast 8 Uterine cervix 3</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td></td>
<td>74</td>
<td>25</td>
<td></td>
<td>Biliary tract 8 Uterine body 2</td>
</tr>
<tr>
<td>Primary cancer location</td>
<td></td>
<td>74</td>
<td>25</td>
<td></td>
<td>Liver 6 Others 9</td>
</tr>
</tbody>
</table>

RESULTS

Characteristics of the Patients During the study period, 153 patients had used the transdermal FP for the first time. During the study, the administration of the FP was discontinued for 24 patients, 26 patients had not provided the necessary information for evaluating the nutritional status and pain intensity, 5 patients were taking medications that influenced pain intensity, and 1 patient had a fever (≥40°C), 5 patients experienced a change in their cancer stage. Thus, 61 patients were excluded from the analysis. The characteristics of the remaining 92 patients observed on day 3 after the FP application are shown in Table 2. The release rates of the initial dose of the FP were 12.5 µg/h in 74 patients and 25 µg/h in 18 patients. Cancer stage was III in 24 patients and IV in 68 patients. All patients had taken one type of NSAID at the initial FP application (etodolac, 28; diclofenac, 4; naproxen, 14; flurbiprofen, 8; meloxicam, 3; lornoxicam, 3; and lornoxicam, 3). In 10 of these patients, medication route was changed from the oral to the rectal or intravenous route for NSAIDs because of dysphagia; NSAID use remained unchanged in other patients until 1 month after the patch was applied to skin.

In addition, 52 patients were followed-up for 1 month after the initial FP application.

Relationship between Nutritional Status and Pain Intensity According to the criteria of the NRS 2002, 92 patients were classified into a normal-nutrition group (36 patients, <3) or a low-nutrition group (56 patients, ≥3). The sex ratio, ages, FP dose, and levels of ALT, AST, γ-GTP, and Cr in the low- and normal-nutrition groups were not significantly different (Table 3). However, the mean pain intensity in the low-nutrition group was significantly higher than that in the normal-nutrition group (3.34±1.22 vs. 2.18±0.75, p<0.01) (Table 3). In addition, the mean NRS 2002 score was significantly and pos-
The intensity in patients receiving the FP was positively correlated to the pain intensity in all patients (Fig. 1).

**Influence of the Change in Nutritional Status on Pain Intensity**

When the difference between the NRS 2002 scores at the time of FP application and 1 month after FP application was +1 or more, the difference was categorized as an "increase." Similarly, when this difference was −1 or less, the difference was categorized as a "decrease." If this difference ranged from −1 to +1, it was recorded as "no change." Differences in the numeric rating scale were also categorized in the same manner as NRS 2002 scores.

Of the 52 patients, who were available for follow-up 1 month after the FP application, 42 patients had a decrease or no change and 10 patients had an increase in the NRS 2002 score. The sex ratio, ages, and levels of ALT, AST, γ-GTP, and Cr of the 2 groups were not significantly different (Table 4). However, the change in the NRS 2002 score was significantly related to the change in pain intensity (Table 4). The time course of an increase in the NRS 2002 score and pain intensity observed in 6 patients is shown in Fig. 2. In all 6 patients, the increase in the NRS 2002 score was followed by an increase in pain intensity. In addition, univariate logistic analysis revealed that the odds ratio was 30.0 (95% confidence interval, 4.48–200.97; \( p = 0.0005 \)), suggesting that an increase in the NRS 2002 score was a risk factor for increased pain intensity in patients receiving the FP.

**DISCUSSION**

The purpose of this study was to investigate the relationship between nutritional status and pain intensity and to evaluate the influence of changes in nutritional status on pain management in cancer patients receiving the FP. In this study, the NRS 2002 was used to estimate the patient’s risk of malnutrition. Some randomized clinical studies showed that NRS 2002 is able to effectively identify patients who require nutritional care. The mean pain intensities of patients in the low-nutrition group were significantly higher than those of patients in the normal-nutrition group (Table 3), and a

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**Table 3. Comparison of Patient Characteristics and Pain Intensity in the Normal- and Low-Nutrition Groups as Classified by the NRS 2002 (n=92)**

<table>
<thead>
<tr>
<th></th>
<th>Normal-nutrition group n=36</th>
<th>Low-nutrition group n=56</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male/female)</td>
<td>21/15</td>
<td>34/22</td>
<td>0.820 (^a)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.3±9.2</td>
<td>65.7±11.1</td>
<td>0.124 (^b)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>34.0±37.1</td>
<td>31.4±26.5</td>
<td>0.636 (^b)</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>35.3±36.6</td>
<td>39.2±39.6</td>
<td>0.646 (^b)</td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
<td>111.0±166.8</td>
<td>113.5±112.2</td>
<td>0.959 (^b)</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>0.75±0.44</td>
<td>0.86±0.77</td>
<td>0.473 (^b)</td>
</tr>
<tr>
<td>FP dose (µg/h)</td>
<td>14.6±4.8</td>
<td>15.1±5.1</td>
<td>0.648 (^b)</td>
</tr>
<tr>
<td>Pain intensity</td>
<td>2.18±0.75</td>
<td>3.34±1.22</td>
<td>&lt;0.01 (^a)**</td>
</tr>
</tbody>
</table>

The values were mean±S.D.; \( a \) Chi-squared test; \( b \) Student’s \( t \)-test; \( c \) Mann–Whitney \( U \)-test. **\( p < 0.01 \).”

**Table 4. Comparison of the Changes in the Patients’ Characteristics and Pain Intensity in the Normal- and Low-Nutrition Groups as Classified by the NRS 2002 (n=52)**

<table>
<thead>
<tr>
<th>Change in the NRS 2002 score</th>
<th>Decrease or no change n=42</th>
<th>Increase n=10</th>
<th>( p ) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (Male/female)</td>
<td>22/20</td>
<td>6/4</td>
<td>0.736 (^a)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63.1±7.7</td>
<td>63.1±8.5</td>
<td>0.991 (^b)</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>29.7±18.7</td>
<td>38.4±22.6</td>
<td>0.348 (^b)</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>34.8±22.0</td>
<td>45.0±31.6</td>
<td>0.537 (^b)</td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
<td>126.0±98.2</td>
<td>160.4±98.6</td>
<td>0.455 (^b)</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>0.82±0.34</td>
<td>0.66±0.14</td>
<td>0.428 (^b)</td>
</tr>
<tr>
<td>Change in pain intensity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease or no change</td>
<td>40</td>
<td>4</td>
<td>&lt;0.01 (^a)**</td>
</tr>
<tr>
<td>Increase</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

The values were mean±S.D.; \( a \) Fisher’s exact test; \( b \) Student’s \( t \)-test. **\( p < 0.01 \).”
significant positive correlation between the NRS 2002 scores and pain intensities was observed (Fig. 1). These results suggest that patients with poor nutrition status experience higher pain intensity than well-nourished patients. In this study, all 92 patients continued NSAID use until 1 month after FP application, and 10 of them required alterations in the administration route. However, medication changes did not result in deviations from the conventional dose range. Therefore, it was considered that altering NSAID use had little impact on the evaluations of pain intensity.

In the follow-up survey of 52 patients, a significant relationship between the change in the NRS 2002 scores and pain intensities was observed (Table 4). No patients with a decreased NRS 2002 score had increased pain intensity. In 6 patients who demonstrated increased NRS 2002 score and pain intensity, the increase in NRS 2002 score was followed by an in-

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**Fig. 2. The Time Course of NRS 2002 Score and Pain Intensity at 1 Month in 6 Patients Who Demonstrated an Increase in NRS 2002 Score and Pain Intensity**

NRS 2002 score of each patient was calculated by disease severity, BMI, percentage weight loss, and changes in food intake. Pain intensity was evaluated using a numeric rating scale (11-point scale from 0 to 10), and the mean of three measurements over a single day was regarded as pain intensity reading for each patient.
crease in pain intensity, suggesting that poor nutritional status increased pain intensity in patients receiving FP (Fig. 2).

These results show that a change in nutritional status influences pain intensity in cancer patients who received the FP. Furthermore, univariate analysis indicated that the increase in the NRS 2002 score was a risk factor for an increase in pain intensity, suggesting that malnourished patients receiving the FP are at risk of poor pain management.

Recently, we reported that body fat and BMI showed a significant positive correlation with the efficacy of transdermal fentanyl delivery, which was estimated based on the residual content of fentanyl in used patches. In addition, the efficiency of fentanyl delivery in patients in the low-nutrition group decreased by 10% compared to that in patients in the normal-nutrition group. Dry skin is a common physical sign in patients with advanced cancer with malnutrition. A preclinical study using FPs showed that the serum fentanyl concentrations in rats with dry skin were significantly lower than those in rats with normal skin. Furthermore, in a clinical study of patients experiencing cancer-related pain with or without cachexia and who were using FPs, transdermal fentanyl absorption was impaired in cachectic patients (mean BMI, 16 kg/m² vs. 23 kg/m²). Therefore, increased pain intensities in the low-nutrition group might be attributed to the inhibition of fentanyl absorption.

Our study had several limitations. This was a small retrospective study in a single center, and the criteria for increasing the FP dose might not have been applied correctly for all patients. In addition, performance status (PS) and transdermal fentanyl absorption were not evaluated in this study. PS is closely related to nutritional status, and may be a very important factor affecting pain control. Prospective studies evaluating a large number of patients are required to verify the results of this study.

In conclusion, a change in nutritional status affects pain intensity in cancer patients who receive transdermal FPs, and therefore, pain intensities of malnourished patients with cancer receiving FPs should be monitored carefully.

Acknowledgments Each of the authors has read and concurred with the content in the final manuscript. The authors greatly appreciate the participants of the study and acknowledge the assistance of staff members at Iwate Medical University.

REFERENCES