Hangeshashinto Improves the Completion Rate of Chemoradiotherapy and the Nutritional Status in Patients with Head and Neck Cancer

Author(s)
Hatakeyama, Hiromitsu; Takahashi, Hiroki; Oridate, Nobuhiko; Kuramoto, Rinnosuke; Fujiwara, Keishi; Homma, Akihiro; Takeda, Hiroshi; Fukuda, Satoshi

Citation
ORL-journal for oto-rhino-laryngology head and neck surgery, 77(2): 100-108

Issue Date
2015-05

Type
article (author version)
Hangeshashinto improves the completion rate of chemoradiotherapy and nutritional status in head and neck cancer patients.

Hiromitsu Hatakeyama M.D., Ph.D. \(^1\); Hiroki Takahashi M.D. \(^1\); Nobuhiko Oridate M.D., Ph.D. \(^2\); Rinnosuke Kuramoto M.D. \(^1\); Keishi Fujiwara M.D., Ph.D. \(^1\); Tomohiro Sakashita M.D., Ph.D. \(^1\); Satoshi Kano M.D., Ph.D. \(^1\); Takatsugu Mizumachi M.D., Ph.D. \(^1\); Akihiro Homma M.D., Ph.D. \(^1\); Hiroshi Takeda M.D., Ph.D. \(^3\) and Satoshi Fukuda M.D., Ph.D. \(^1\)

1) Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Sapporo, Japan

2) Department of Otorhinolaryngology and Head and Neck Surgery, Yokohama City University School of Medicine, Yokohama, Japan

3) Department of Pathophysiology and Therapeutics, Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo, Japan

Corresponding author: Hiromitsu Hatakeyama

Mailing address: Department of Otolaryngology-Head and Neck Surgery, Hokkaido University Graduate School of Medicine, Kita 15, Nishi 7, Kita-ku, Sapporo 060-8638, Japan
Phone: +81-11-706-5958
Fax: +81-11-717-7566
E-mail: htkym@med.hokudai.ac.jp
Keywords: Mucositis, Hangeshashinto (TJ-14), Chemoradiotherapy, Head and Neck Cancer,
Nutrition
Short title: TJ-14 improves the completion rate of CRT in HNC
COI: The authors declare that they have no conflict of interests
Funding: H.H. and A.H. were supported, in part, by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science and Culture of Japan
Abstract

Purpose: Severe oral and pharyngeal mucositis is one of the most critical toxicities known to lead to the discontinuation of chemoradiotherapy (CRT) for head and neck cancer (HNC). Hangeshashinto (TJ-14) is a Kampo medicine that relieves chemotherapy-induced oral mucositis. We investigated the effect of TJ-14 on mucositis, nutritional status and completion rate of CRT.

Methods: The study group comprised patients with advanced HNC who treated with concomitant weekly cisplatin administration and 70 Gy of radiotherapy. The primary end point was the completion rate of chemotherapy, and the secondary end points were the grade of mucositis, and nutritional status.

Results: Total 57 patients were included in this study. The completion rate of CRT among patients who treated with TJ-14 was 91.4%. There was a significant difference in the completion rate of CRT between the groups with and without TJ-14. (p=0.0452) The reduction in body weight was significantly improved from 10.89% to 5.89 % with TJ-14 administration (p=0.003) and the reduction in serum albumin was also significantly decreased from 17.37% to 8.73 %. (p=0.024)

Conclusion: This therapy allowed a high completion rate of CRT as well as significant benefits in terms of nutritional status. We plan to carry out a further large-scale study of TJ-14.
Introduction

Concomitant chemotherapy with radiation for HNC provides a favorable prognosis as well as a significantly higher rate of organ preservation in comparison with radiation alone. [1] [2] Radiation with high-dose cisplatin every 3 weeks remains the most standard regimen in US Cooperative Group clinical trials. However, the toxicity of this regimen is too severe for most Japanese patients to complete; therefore, our institute has introduced a regimen of radiation with weekly 40 mg/m2 of cisplatin. [3] We have to date achieved good clinical outcomes with acceptable toxicity in terms of neutropenia and renal failure. [4] However, the completion rate of this regimen remains around 60 % and severe oral and pharyngeal mucositis sometimes causes the discontinuation of the CRT.

Hangeshashinto (TJ-14) is a Japanese traditional medicine (Kampo) that includes 7 natural extracts: Pinelliae Tuber, Scutellariae Radix, Zingiberis Rhizoma, Ginseng Radix, Glycyrrhizae Radix, Zizyphi Fructus, and Coptidis Rhizoma. TJ-14 has been reported to regulate prostaglandin E2 in in vivo colitis models and to reduce chemotherapy-induced severe oral mucositis in gastric cancer patients. [5] [6] [7] The degree of severity of oral and pharyngeal mucositis varies during CRT for pharyngeal cancer, and new agents are needed to improve completion rates and to limit pain in these patients.

This study evaluates the effect of TJ-14 on the completion rate of CRT in patients with cancers of the oropharynx and hypopharynx through the regulation of CRT-induced oral and pharyngeal mucositis.
This is the first trial to use TJ-14 as a gargle to prevent mucositis induced by chemoradiation. In this study we investigated the compliance of TJ-14 for CRT in oro- and hypopharyngeal cancer and the complete rate. Furthermore, nutritional status, grade of mucositis and pain were estimated in comparison with the patient treated without TJ-14.

Patients and Methods

Patients

The study group comprised Japanese patients who were diagnosed with advanced oropharyngeal and hypopharyngeal squamous cell carcinoma and treated with CRT at Hokkaido University Hospital, Japan. Written informed consent was obtained from all patients before entry into the study. This study was approved by the Institutional Review Board of Hokkaido University Hospital (UMIN000006461).

CRT and TJ-14 administration

All patients were treated with a total dose of 70 Gy of radiation in 35 daily fractions. After the initial dose of 40 Gy had been administered, an additional dose of 30 Gy was given with a shrunken field in 15 fractions over 3 weeks.

Weekly cisplatin was administered at a dose of 40mg/m2 on week 1, 2, 3, 4, 6 and 7 of radiation
therapy. The intended maximum total dose of cisplatin was 240mg/m2.

Patients received 2.5g of TJ-14 as a gargle three times a day as follows: 1) 2.5g of TJ-14 was dissolved in 40ml of drinking water and the patient rinsed the oral cavity and pharynx with the solution, without swallowing, for more than 5 seconds, 2) TJ-14 was expelled out after rinsing and was not to be swallowed, and 3) patient were advised not to consume any food or drink within 30 minutes after rinsing with TJ-14. CRT and TJ-14 administration schedules are shown in Figure 1.

**Evaluation of mucositis, pain, and nutritional status**

Oral and pharyngeal mucositis were graded as according to CTCAE v4.0. The maximum dose of morphine was defined as that on day 57. Body composition of all patients was estimated by bioelectric impedance analysis using an InBody S20 body composition analyzer with InBody 3.0 software (BioSpace) on Day 0 and Day 57. [8] Nutritional intake was assessed by the Nutrition Support Team of Hokkaido University Hospital, by measuring the weight of each dish before and after every meal. Furthermore, the calories of all additional foods, snacks, and drinks were added to the measured food intake. Total oral intake of calories and protein were recorded as the average of 3 days on 1st, 3rd, 6th and 8th week. The serum levels of albumin, pre-albumin and retinol binding protein were used as nutritional status markers and were estimated on day 1, 22, 43, 57.
Statistical Considerations

The primary endpoint was the completion rate of CRT. Complete chemoradiation treatment delivery was defined as the administration of full dose of 70 Gy radiation within 63 days, and the completion of at least five of six courses of cisplatin. Complete administration of TJ-14 was defined as more than 7 weeks treatment without interruption. The secondary endpoints were oral and pharyngeal mucositis grade, nutritional status and maximum dose of morphine.

Results

Patient characteristics

Demographic and clinicopathological data, including age, gender, tumor site, TNM stage, smoking and alcohol abuse of all patients are shown in Table 1. Twenty three patients with oropharyngeal cancer and 34 patients with hypopharyngeal cancer were included in this study. Forty patients had Stage IV disease, 6 had Stage III disease and 10 had Stage II. Of 57 patients, twelve patients (11 male and 1 female) who received TJ-14 treatment were enrolled in the study and were evaluated from January 2012 through September 2013. Other 45 patients treated without TJ-14 from June 2006 through January 2011. The patients treated with TJ-14 ranged in age from 40 to 70 years (median = 60 years) and the patients treated without TJ-14 ranged from 40 to 75 years (median 59 years).

All patients received oral care from the Dental Care Team of Hokkaido University Hospital during
CRT.

TJ-14 compliance

A total 9 of the 12 patients completed 7 or 8 weeks of treatment with TJ-14. Three patients could not continue to use TJ-14, but they could complete the CRT. One patient discontinued TJ-14 on day 6 due to its bitter taste. One patient could not keep himself from eating or drinking for 30 minutes after gargling with TJ-14, and stopped the study on day 16. The third patient discontinued TJ-14 on day 38 due to vomiting and nausea. No patients interrupted TJ-14 treatment due to oral and pharyngeal mucositis.

Chemoradiotherapy completion rate

Completion rate of chemoradiotherapy were summarized in Table 2. All patients who treated with TJ-14 received the full dose of RT (70Gy) without interruption. A total of 11 (91.6%) patients completed five (5 patients) or six (6 patients) courses of chemotherapy. One patient could not receive a 5th course of chemotherapy due to fever. Eight of 9 (88.9%) patients who completed treatment with TJ-14 also completed CRT. Eighteen of 45 patients treated without TJ-14 interrupted the CRT. The cause of Chemotherapy interruption were neutropenia in 4 cases, fever in 4, renal failure in 3, liver dysfunction in 1, mucositis in 1, tumor bleeding in 1, and the rejection by 2 patients. The
radiation course was extended in 2 cases by holidays and machine maintenance. [9]

There was a significant difference in the completion rate of CRT between the groups with and without TJ-14. (p=0.0452, Fisher’s exact test)

**Mucositis and Pain**

There were no significant differences in the maximum grade of mucositis and the maximum dose of morphine between with and without TJ-14. (Table 3). Grade 3 mucositis were developed in 5 (41.7%) patients and Grade 4 mucositis was absent in the TJ-14 administration group, whereas Grade 3 mucositis were developed in 25 (57.8%) patients and one of Grade 4 mucositis occurred in TJ-14 non-administration group. Significant difference was not observed in mean maximum dose of morphine between Grade 1-2 mucositis and Grade 3-4.

**Body composition analysis and nutritional status**

We investigated the body composition index of the patients treated with TJ-14 to reveal their nutritional status and the results were summarized in Table 4. The median body weight of the patients was significantly decreased after chemoradiation (p=0.006) with a median decrease in body weight of 5.89 %. (Maximum 11.7% and minimum -2.8%). Median fat and bone mass did not change during CRT, but the muscle mass and total body water were significantly decreased by 5.7%
and 5.5%, respectively (Muscle mass: p=0.045, Body water: p=0.049). The median metabolic rate also decreased by about 4.0% during CRT. Table 5 shows the changes in median oral intake calories and nutritional status markers in the serum. The median total oral intake of calories drastically decreased after the 4th week. Seven patients had used PEG before CRT, and 4 of the 7 patients started to used PEG due to oral feeding difficulties on day 21, 36, 45 and 47, respectively. The median level of albumin and pre-albumin in the serum gradually decreased throughout the course of CRT, but the changes were not statically significant. The mean serum concentration of retinoid-binding protein increased on the 3rd week, but decreased again after the 6th week.

The median reduction in body weight during CRT without TJ-14 was 10.72% and the reduction in serum albumin was 17.37%, whereas the reduction in body weight was significantly improved up to 5.89 % with TJ-14 administration (p=0.003) and the reduction in serum albumin was also significantly decreased to 8.73 % in this study. (p=0.024) (Figure 2)

Discussion

Toxicities with CRT often lead to treatment interruptions that are invariably associated with a poorer outcome.[10] [11] To improve the completion rate of CRT for HNC, we modified the regimen and improved the management program in terms of the hydration protocol and the adequate administration of G-CSF to avoid severe leucopenia, neutropenia and renal failure.[4] Although
nausea and vomiting were one of the most severe side effects of cisplatin administration, it was dramatically improved with the administration of dexamethasone and serotonin 5-HT3 receptor antagonists. [12] On the other hand, the pain and the dysphagia associated with severe oral and pharyngeal mucositis have been a critical factor in completion rate. Most patients with oropharyngeal and hypopharyngeal cancer undergoing CRT receive direct irradiation to oral cavity and pharynx, so it is easy to assume that therapy-induced mucositis is more severe than in other digestive cancers. Severe direct irradiation-induced mucositis led us to apply TJ-14 for oropharyngeal and hypopharyngeal cancers at first, with the gargle therapy involving TJ-14 achieving good compliance with a 75% completion rate. Only one patient had an early interruption of treatment with TJ-14 due to its bitter taste, and no patient discontinued treatment due to oral mucositis or pain.

The pilot study of TJ-14 for chemotherapy-induced oral mucositis in gastric cancer showed a significant effect. [13] However, a double-blind, placebo-controlled, randomized phase II study of TJ-14 did not show any difference in oral mucositis grade, but a tendency for TJ-14 to reduce the duration of chemotherapy-induced oral mucositis from 17 days to 9 days was observed. [7] We previously reported that the rate of grade 3-4 mucositis induced by the same regimens of CRT for HNC were 39.6%. [4] If limited to oropharyngeal and hypopharyngeal cancers, the rate of grade 3-4 mucositis was 51.6%. [9] In this study, no patients had grade 4 mucositis, and the rate of grade 3
mucositis decreased to 41.6%. Unlike the study on gastric cancer, no statistical significant effect of TJ-14 in terms of mucositis grade could be observed. However, no patient interrupted CRT due to mucositis and almost grade 2-3 mucositis were occurred at late phase of CRT in TJ-14 administrated group. These facts might be induced the beneficial change in the complete rate of CRT and the nutrition status. No statistical difference in oral mucositis might be caused from the fuzzy grading system. The grading in oral mucositis of CTCAE v4.0 has only 5 grades and lacks the clarity, and the real extent of mucositis was different in the same grade. Therefore, a more extensive method of evaluation mucositis in place of CTCAE v4.0 is needed.

Molecular targeted therapy using cetuximab, an epidermal growth factor receptor monoclonal antibody, has recently been investigated in conjunction with radiation therapy for advanced HNC patients, and has shown promising results. [14] [15] Radiation therapy with cetuximab does not cause toxicity leading to leucopenia, neutropenia or renal failure, and is relatively-safe compared to platinum-based CRT. However, severe mucositis occurs more often during radiation therapy with cetuximab, so a new agent to prevent radiation-induced mucositis is needed. TJ-14 may be a promising option for use in combination with cetuximab treatment for HNC.

One of the reasons for the improvement in completion rate of CRT with TJ-14 is the good outcome in terms of nutritional status. Recently, several studies have suggested that early and intensive nutritional support improved the quality of life and outcome of patient with HNC undergoing RT or
Capuano et al. showed that a weight reduction of more than 20% significantly increased CRT-induced toxicity, risk of early mortality and hospital readmission rate.

To improve nutrition, we introduced oral care, a PEG prior to treatment and a pain management program based on the combined efforts of dentists and supportive-care staff. Despite the introduction of a PEG and oral care, the median reduction in body weight during CRT remained around 10%. It is interesting to note that most of the body weight loss involved the loss of body water and muscle mass, so that the control of dehydration and muscle maintenance may improve nutritional status. Although this study was a single-arm trial, not a controlled randomized trial with a placebo, these results suggest that improved nutritional status might contribute to a higher completion rate of CRT.

TJ-14 has been known as an agent for enhancing digestive activity, and it was originally used for acute and chronic gastritis, heartburn, and diarrhea. Patients often swallowed TJ-14 after gargling, so the possibility that it had an effect on digestive activity cannot be totally excluded. The anti-inflammatory effect of TJ-14 has been explained by its direct regulation of PGE2 and COX-2, but the mechanism by which it enhances digestive activity remains to be clarified. The effects of Kampo drugs has been known historically and confirmed empirically, and their mechanisms have been gradually revealed both biologically and pharmacologically. One of the advantages of Kampo drugs is their limited side effects, and several Kampo drugs have been used for supportive treatment for various cancers. Although most Kampo drugs are composed and used according to
traditional strategies, we should accumulate the cases and provide clinical evidence for their effective utilization. Seven components are included in TJ-14 and these interact with each other. Therefore, to reveal the mechanism of TJ-14, we need to investigate not only the function of all components, but also their cross-reactions.

In conclusion, the feasibility of TJ-14 for HNC CRT-induced oral mucositis was confirmed. Treatment with TJ-14 was shown to benefit the completion rate of CRT as well as nutritional status. Next, a large-scale, randomized prospective controlled study is needed to define the effects of TJ-14 on the completion rate of CRT, nutritional status, and survival benefits for patients with HNC.

Acknowledgement: This work was supported by Nutrition Support Team of Hokkaido University Hospital and a Health and Labour Sciences Research Grant for Clinical Cancer Research (H26-141) from the Ministry of Health, Labour and Welfare of Japan and the National Cancer Center Research and Development Fund (26-A-4) of Japan.
Figure Legends

Figure 1 Chemoradiation and TJ-14 administration schedules

Figure 2 Comparison between TJ-14 administration group and non-administration group

A, Reduction in total body weight

B, Reduction in the level of serum albumin

Table 1 Clinical characteristics of all patients.

Table 2 Completion rate of chemoradiotherapy

Numbers shown in parentheses are the number of patients who completed the treatment of TJ-14 and the completion rates

Table 3 Mucositis grade and maximum dose of morphine

Numbers shown in parentheses are the number of patients who interrupted the TJ-14 treatment

Table 4 Changes in total body weight and body composition during chemoradiotherapy in TJ-14 administration group

Table 5 Changes in oral intake and nutritional status markers in TJ-14 administration group


Valentini V, Marazzi F, Bossola M, Micciche F, Nardone L, Balducci M, Dinapoli N,


Figure 1

Radiation
70Gy/35fr/7wk

Cisplatin
(40 mg/m²)

Hangeshashinto
(7.5g/day)
Figure 2

A

Body Weight

Reduction Rate (%)

TJ-14
Control

p = 0.003

B

Albmin

Reduction Rate (%)

TJ-14
Control

p = 0.024
<table>
<thead>
<tr>
<th>Clinical Characteristics</th>
<th>TJ-14(n=12)</th>
<th>No TJ-14(n=45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>40-70</td>
<td>40-75</td>
</tr>
<tr>
<td>Median</td>
<td>60</td>
<td>59</td>
</tr>
<tr>
<td>Sex ratio(M/F)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11</td>
<td>42</td>
</tr>
<tr>
<td>Female</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Tumor Site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharynx</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>Hypopharynx</td>
<td>9</td>
<td>25</td>
</tr>
<tr>
<td>Tumor Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>10</td>
</tr>
<tr>
<td>III</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>IV</td>
<td>9</td>
<td>32</td>
</tr>
<tr>
<td>Performance Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>10</td>
<td>44</td>
</tr>
<tr>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Heavy use of Alcohol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>5</td>
<td>21</td>
</tr>
<tr>
<td>No</td>
<td>7</td>
<td>24</td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>PEG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>7</td>
<td>32</td>
</tr>
<tr>
<td>No</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>
Table 2. Completion Rate of CRT

<table>
<thead>
<tr>
<th></th>
<th>TJ-14</th>
<th>No TJ-14</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRT Complete</td>
<td>11(8)</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>CRT Failure</td>
<td>1(1)</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Completion Rate</td>
<td>91.6% (88.9%)</td>
<td>60.00%</td>
<td>0.0452</td>
</tr>
</tbody>
</table>

*Numbers shown in parentheses are the number of patients who completed the treatment of TJ-14 and the completion rates*
<table>
<thead>
<tr>
<th>Mucositis Grade and Maximum dose of morphine</th>
<th>TJ-14</th>
<th>No TJ-14</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>7 (2)</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>5 (1)</td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Grade 4</td>
<td>0</td>
<td>1</td>
<td>n.s.</td>
</tr>
<tr>
<td>Maximum dose of morhine (mg/day)</td>
<td>88.5±65.4</td>
<td>42.1±42.52</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

*Numbers shown in parentheses are the number of patients who interrupted the TJ-14 treatment*
### Table 4.

Body weight and Body composition of the patients treated with TJ-14

<table>
<thead>
<tr>
<th></th>
<th>1st week</th>
<th>8th week</th>
<th>( p )</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Body Weight (kg)</td>
<td>60.8±13.58</td>
<td>57.06±9.97</td>
<td>0.006</td>
<td>-5.89%</td>
</tr>
<tr>
<td>Body Fat Percentage(%)</td>
<td>19.05±6.34</td>
<td>20.62±5.74</td>
<td>0.494</td>
<td>8.20%</td>
</tr>
<tr>
<td>Total Body Muscle (kg)</td>
<td>46.13±8.81</td>
<td>43.52±6.35</td>
<td>0.045</td>
<td>-5.65%</td>
</tr>
<tr>
<td>Total Body Water (kg)</td>
<td>36.07±6.88</td>
<td>34.07±4.70</td>
<td>0.049</td>
<td>-5.54%</td>
</tr>
<tr>
<td>Total Body Bone (kg)</td>
<td>2.59±0.438</td>
<td>2.53±0.284</td>
<td>0.103</td>
<td>-2.32%</td>
</tr>
<tr>
<td>Basal Metabolic Rate(kcal)</td>
<td>1422.33±199.5</td>
<td>1364.33±137.16</td>
<td>0.046</td>
<td>-4.08%</td>
</tr>
</tbody>
</table>
Table 5. Nutritional Status

<table>
<thead>
<tr>
<th></th>
<th>1st week</th>
<th>4th week</th>
<th>6th week</th>
<th>8th week</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total oral intake (kcal/day)</td>
<td>2051.66±318.64</td>
<td>1701.3±676.96</td>
<td>1181.1±844.97</td>
<td>1108.71±671.51</td>
<td>0.013</td>
</tr>
<tr>
<td>Oral protein intake (g/day)</td>
<td>71.70±11.25</td>
<td>61.07±23.45</td>
<td>39.87±28.91</td>
<td>38.74±26.06</td>
<td>0.024</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.94±0.41</td>
<td>3.70±0.28</td>
<td>3.66±0.39</td>
<td>3.63±0.45</td>
<td>0.056</td>
</tr>
<tr>
<td>Pre-albumin (mg/dl)</td>
<td>29.76±6.85</td>
<td>27.94±5.34</td>
<td>25.94±6.94</td>
<td>23.32±6.89</td>
<td>0.053</td>
</tr>
<tr>
<td>Retinol binding protein (mg/dl)</td>
<td>3.29±0.98</td>
<td>3.54±0.88</td>
<td>3.08±0.58</td>
<td>2.96±0.91</td>
<td>0.284</td>
</tr>
</tbody>
</table>

Changes in oral intake and nutritional status markers.