parents [15]. These programs suggest the need to explore the types of psychosocial support that might be provided in Japan.

There are several limitations to this study. First, we used figures obtained at the NCCH to make national inferences using PBCR cancer incidence data from patients in the same strata of age, gender, and cancer type. Therefore, if the number of the children within the same stratum in our study is different from that of the entire cancer patient population in Japan, our estimates may be biased. Another limitation arises from the use of PBCR data, which does not have a mandatory reporting system and does not capture all incidences of cancer in Japan. This may have resulted in an underestimation of our findings. Lastly, we did not include data from cancer patients who were very young or very old. However, we obtained similar results to those of a study in Norway that used cancer registry and national birth cohort data of cancer patients between 17 and 70 years of age. They report that annual incidence of parental cancer for children under 18 years of age was 0.3%. Future studies should include data from various hospitals so that a more representative estimate is obtained.

5. Conclusion

To our knowledge, this is the first study to estimate the nationwide incidence of cancer among patients who have minor children in Japan. Our finding showed that a substantial number of children are likely to be experiencing the hardships of having their parents diagnosed with cancer. Greater attention should be paid to these children by both service-providers and policy-makers. The cancer parent also faces the added burden of child-rearing while undergoing cancer treatment. More research on the demographic and socioeconomic characteristics of these patients will be helpful in understanding the needs of the patients and in planning effective support programs for both cancer patients and their children.

Authors' contribution

I declare that all authors participated sufficiently in this research. All authors participated in drafting the article or revising it critically for important content, and gave final approval of the version to be submitted and any revised version.

Specific contributions were made by:

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Acknowledgement

This research was supported by a grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan (JSPS 25282227).

References

[1] S. Mellon, L.L. Northouse, Family survivorship and quality of life following a cancer diagnosis, Res. Nurs. Health 24 (6) (2001) 446–459.
[2] T. Krattenmacher, et al., Parental cancer: factors associated with children's psychosocial adjustment—a systematic review, J. Psychosom. Res. 72 (5) (2012) 344–356.
[3] National Statistics Center, Special report of vital statistics. Japan. http://www.e-stat.go.jp/SG1/estat/eStatTopPortal.do, 2009 (accessed August 2015).
[4] Center for Cancer Control and Information Services, National Cancer Center, Japan. http://ganjoho.jp/public/statistics/pub/statistics01.html (accessed March 2014).
[5] Lifetime Risk (Percent) of Being Diagnosed with Cancer by Site and Race/Ethnicity: Males, 18 SEER Areas, 2009–2011 (Table 1.16) and Females, 18 SEER Areas, 2009–011 (Table 1.17). http://seer.cancer.gov/csr/1975_2011/results_merged/topic_lifetime_risk_diagnosis.pdf (accessed August 2015).
[6] Cancer Research UK, http://www.cancerresearchuk.org/health-professional/cancer-statistics/risk/lifetime-risk (accessed August 2015).
[7] A. Syse, G.B. Aas, J.H. Loge, Children and young adults with parents with cancer: a population-based study, Clin. Epidemiol. 4 (2012) 41–52.
[8] K.E. Weaver, et al., Parental cancer and the family, Cancer 116 (18) (2010) 4385–4401.
[9] A. Matsuda, T. Matsuda, A. Shibata, K. Katanoda, T. Sobue, H. Nishimoto, The Japan Cancer Surveillance Research Group, Cancer incidence and incidence rates in Japan in 2008: a study of 25 population-based Cancer Registries for the Monitoring of Cancer Incidence in Japan (MCIJ) Project, Vital Statistics Japan (Ministry of Health, Labour and Welfare), J. Clin. Oncol. 44 (4) (2013) 388–396.
[10] Ministry of Health, Labour and Welfare. Vital Statistics Japan. http://ganjoho.jp/pro/statistics/en/table_download.html (accessed 05.03.14).
[11] M.E. Nilsson, et al., Mental health, treatment preferences, advance care planning, location, and quality of death in advanced cancer patients with dependent children, Cancer 115 (12) (2009) 2896–2905.
[12] G.A. Huizinga, et al., Family-oriented multilevel study on the psychological functioning of adolescent children having a mother with cancer, Psychooncology 20 (7) (2011) 730–737.
[13] M. Watson, et al., Factors associated with emotional and behavioural problems among school age children of breast cancer patients, Br. J. Cancer 94 (1) (2006) 43–50.
[14] A. Visser, et al., Parental cancer, Cancer 106 (5) (2006) 1178–1187.
[15] M. Niemelä, H. Hakko, S. Rissanen, A systematic narrative review of the studies on structured childcentred interventions for families with a parent with cancer, Psychooncology 19 (5) (2010) 451–461.

Medical Manuscript

American Journal of Hospice & Palliative Medicine®
1-8

DOI: 10.1177/1049909115608810
ajhpm.sagepub.com
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How Do Hospital Palliative Care Teams Use the WHO Guidelines to Manage Unrelieved Cancer Pain? A 1-Year, Multicenter Audit in Japan

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Abstract

It has been reported that pain relief for patients with cancer is suboptimal in Japan. This has been mainly attributed to inadequate dissemination of the World Health Organization (WHO) guidelines for cancer pain management. To better understand this problem, we reviewed how 6 hospital palliative care teams (HPCTs) used the WHO guidelines for unrelieved pain in a 1-year audit that included 534 patients. The HPCT interventions were classified according to the contents of the WHO guidelines. In our study, HPCT interventions involved opioid prescriptions in >80% of referred patients, and "For the Individual" and "Attention to Detail" were the 2 most important principles. Our study indicates which parts of the WHO guidelines should be most heavily emphasized, when disseminating them in Japan.

Keywords

palliative care team, cancer pain relief, WHO guidelines, opioid, audit, analgesics

Introduction

Unrelieved pain is a common fear among patients with cancer.[1] To address this issue, the World Health Organization (WHO) published guidelines for cancer pain relief in adults in 1986. One year later, the document was translated into Japanese by Fumikazu Takeda. The guidelines have been widely implemented in Western countries.[2-5] However, in 1999 and 2004, nationwide surveys in Japan[6] revealed that the majority of Japanese nonpalliative care physicians were unfamiliar with the WHO guidelines. In 2002, the Ministry of Health, Labour, and Welfare introduced insurance coverage of palliative care services that are provided by certified hospital palliative care teams (HPCTs).[7] In 2009, additional reimbursement for cancer pain management with strong opioids, in accordance with the WHO guidelines, was approved. Despite these efforts, medical opioid consumption, a potential indicator of nationwide cancer pain treatment adequacy,[8] has not increased in Japan. In fact, in one study Japan had one of the lowest medical opioid consumption rates among the Group of Seven countries examined.[9] This may indicate that many Japanese patients have cancer pain because of inappropriate pain management. To improve this situation, it is important to determine which parts of the WHO guidelines are not being used by nonpalliative care physicians when managing cancer pain in Japanese acute care hospitals.

The initial aim of the current study was to examine the parts of the WHO guidelines that the nonpalliative care physicians left unused but which were used by HPCTs that were well acquainted with the guidelines. We used an original protocol

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that we derived from the WHO guidelines. Using a collection sheet based on our protocol, we retrospectively reviewed the medical records of inpatients having cancer with pain who were referred to HPCTs, to learn which parts of the protocol corresponded with HPCT interventions, the frequency of interventions, and which interventions were prioritized by the HPCTs. We also evaluated the ability of HPCTs to relieve cancer pain using a patient-rating scale.

Materials and Methods

Design and Setting

This study was a multicenter, retrospective, 1-year review conducted in the 6 designated cancer care hospitals in Japan. These include the National Cancer Center Hospital (600 beds), Hokkaido University Hospital (946 beds), Chukyo Hospital (668 beds), Nagasaki Municipal Hospital (414 beds), Akita City Hospital (458 beds), and Ofunato Prefectural Hospital (489 beds). While none of these hospitals had dedicated palliative care units at the time of the study, they all had HPCTs knowledgeable in implementing the WHO guidelines. Based on the referring physicians' requests, the HPCTs followed patients every day and prescribed medications for symptom relief on their own.[7]

Patients

All inpatients initially referred to each HPCT for pain relief between January and December of 2009 were considered for inclusion in the analysis. Patients were excluded if they were under 13 years of age, died on the same day as the first HPCT visit, or were unable to confirm pain symptoms due to consciousness disturbance (eg, severe delirium) at the time of referral.

Data Collection Algorithm

Based on the WHO pain relief guidelines[10] and additional related publications,[11-13] we created a checklist algorithm to assist nonpalliative care physicians and inexperienced HPCTs. The algorithm contains 6 decision points and 4 checklists (Figure 1 and Table 1). The protocol was named "Algorithm with Lists for Palliation Helped by Analgesia" (ALPHA).

Data Collection Form

We created a structured form based on ALPHA—to uniformly obtain data from medical records. The form consisted of entry columns corresponding to each symbol and all the checklist items contained in the ALPHA. The 6 HPCTs were instructed to complete each column based on the medical records. First, if HPCT interventions corresponded to symbols (1) and (3), they placed a check mark in the appropriate entry column with the first date of intervention. Second, if HPCT interventions corresponded to symbols (2), (4), (5), or (6), they placed a check mark in the entry columns corresponding to the symbols and checklist items with the first date of intervention.

To properly represent patient pain, the data collection period was limited to the first week following HPCT referral,[7] in which the referral day was defined as day 0 and the last day of the week-long round was defined as day 7. Collected data fell into the following 5 categories: patient characteristics, frequency of intervention, priority of intervention, opioids and adjuvant analgesics, and pain relief performance, as detailed subsequently.

Patient Characteristics

Apart from age, gender, and primary cancer site, the patient characteristics analyzed included "medical condition" based on the Japanese version[14] of the Eastern Cooperative Oncology Group (ECOG) performance status (PS) and tumor modifying therapy. Based on ECOG PS (where 0 = no disability and 4 = totally bedridden), "poor" was defined as <2.[15]

Frequency of Intervention

The frequency of an HPCT intervention was defined as the proportion of patients with at least 1 check mark in the corresponding entry column.

Priority of Intervention

To explore the order of HPCT interventions, the dates on which HPCT interventions were recorded according to the 6 ALPHA symbols were analyzed. In addition, we defined "early intervention" as intervention implemented within the first 2 days (day 0 or day 1), indicating intervention priority.

Intervention With Opioids and Adjuvant Analgesics

The proportion of patients prescribed around-the-clock (ATC) opioids or adjuvant analgesics (eg, carbamazepine for neuropathic pain) was examined. All prescribed ATC opioid doses were converted to the daily oral morphine equivalent dosage (DOMED) for analyses. In opioid-naive patients without any history of opioid prescription on day 0, only the doses on day 7 were recorded. In opioid-tolerant patients with opioid prescriptions on day 0, the doses used on days 0 and 7 were recorded, and the opioid dose ratio (day 7 DOMED/day 0 DOMED) was calculated. The opioid conversion ratios employed to calculate the DOMEDs in this study were as follows[16-18]: oral morphine 100 = intravenous morphine 33 = suppository morphine 70 = transdermal/intravenous fentanyl 1 = oral oxycodone 70 = subcutaneous compound oxycodone 50 = suppository/intravenous buprenorphine 2. On days 0 and 7, information on whether or not adjuvant analgesic drugs had been prescribed was collected to determine prescription rates.

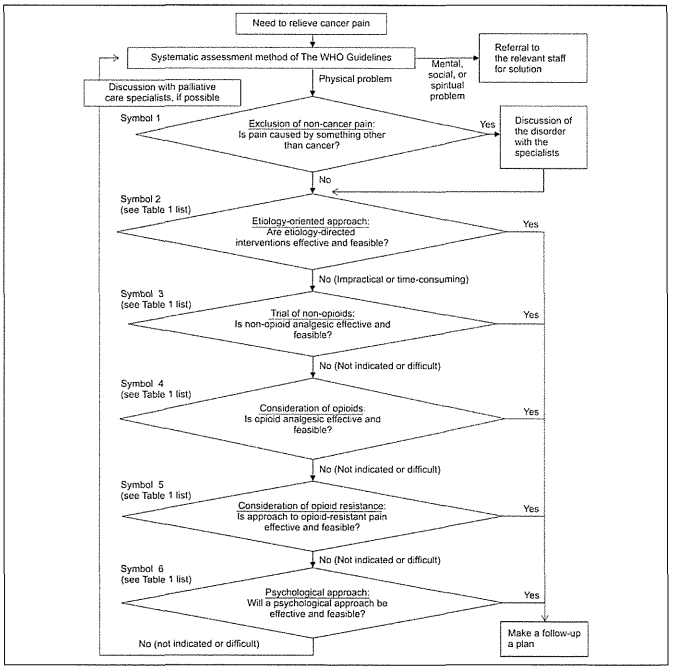

Figure 1. Draft protocol used in the Algorithm with Lists for Palliation Helped by Analgesia (ALPHA) survey: Query answers at each of the 6 decision symbols are shown in Table 1.

Outcome of Pain Relief Interventions

Pain intensity on days 0 and 7 was determined using a 4-point (none, mild, moderate, and severe) verbal rating scale (VRS). If the 11-point numeric rating scale (0 = no pain and 10 = worst imaginable pain) had been used, pain levels were converted to the VRS in the following manner: 0 = no pain, 1 to 3 = mild pain, 4 to 6 = moderate pain, and 7 to 10 = severe pain.[19] When patients complained of pain at multiple sites, the highest pain level reported was recorded. Intervention success was defined as at least 1 step down in VRS between days 0 and 7.[20]

Statistical Analyses

Comparisons were performed using Wilcoxon sign-rank tests, Kruskal-Wallis tests, or chi-square tests, as appropriate. Statistical software (SAS 9.1, SAS Institute, Inc, Cary, North Carolina) was used to perform analyses. Statistical significance was defined as $P < .05$.

Table 1. Frequency of Interventions by the 6 Hospital Palliative Care Teams (HPCT) in Each Algorithm with the Lists for Palliation Helped by Analgesia (ALPHA) Symbol.[a]

ALPHA Symbol Number	Intervention Category and Percentage of Patients[b]	
1	Diagnosis of pain from comorbid disease: 4.7	
2	Etiology-oriented intervention to relieve pain: 20.4	
	Decompression procedure: 8.1	Palliative radiation therapy: 3.9
	Immobilization or nonweight bearing device: 6.1	Antimicrobial therapy: 1.5
	Recalcification with biphosphate: 5.7	Oncology emergency identified: 0.7
3	Change or stop of nonopioid drugs: 4.5	
4	Opioid analgesic interventions (based on the 5 principles of the WHO guideline): 80.5	
	Opioid introduction, according to the *By the ladder* principle: 23.0	
	Route switch of opioid using the *By mouth* principle: 37.1	
	To oral: 12.2	To transdermal: 4.3
	To subcutaneous: 11.6	To rectal: 0.4
	To intravenous: 10.3	To spinal: 0.4
	Optimal scheduling of opioid administration along pain intensity pattern using the *By the clock* principle: 41.6	
	Introduction of rescue dose: 20.0	Dosage-interval adjustment: 13.5
	Continuous infusion with a syringe driver: 19.7	Rescue-dose adjustment: 10.7
	Titration of opioid-dose for pain relief using the *for the individual* principle: 47.9	
	Escalation by treating adverse effects: 21.1	Eventual retention: 8.1
	Escalation as a simple approach: 19.7	Reduction or suspension: 1.3
	Seeking compromise to refractory toxicities: 0.7	
	Maximization of benefit and minimizing adverse effects using the *Attention to detail* principle: 66.3	
	Response to opioid-related adverse effects: 57.1	
	To constipation: 33.1	To delayed stomach emptying: 6.4
	To stimulated vomiting center: 27.7	To respiratory depression: 0.9
	To delirium: 8.2	To skin opioid toxicity: 0.9
	To stimulated vestibular nerve: 7.1	To drowsiness: 0.8
	Implementation of opioid rotation: 8.2	Switching administration route: 6.9
	Achieving accountability of the opioid regimen with other drug regimens: 39.0	
5	Response to opioid resistant pain: 34.5	
	Presumptive cause of resistant pain	
	Neuropathic pain: 20.6	Spastic pain: 3.7
	Ceiling effect of opioid: 5.6	Peritonitis carcinomatosa: 3.2
	Complex pain of bone metastasis: 4.3	Intracranial hypertension: 1.3
	Malignant mucositis or ulceration: 3.7	Inflammatory pain: 0.7
	Treatment for opioid resistance	
	Anticonvulsant: 10.1	Physical modality: 3.4
	Corticosteroid: 6.0	Antidepressant: 2.6
	Opioid rotation: 5.8	NSAIDs prescription: 1.5
	Antiarrhythmic agent: 5.4	Topical agent to mucosa or skin: 1.1
	Nerve block or ablation: 4.3	Anticholinergic agent: 0.4
	NMDA receptor antagonist: 4.3	
6	Psychological approach to manage pain: 11.0	
	Suspected etiology requiring psychological therapy	
	Anxiety: 8.2	Grief: 1.3
	Unexplainable insomnia: 2.6	Misunderstanding: 0.7
	Depression or adjustment disorder: 1.3	Anger: 0.6
	Specific psychological interventions	
	Active listening: 8.6	Communication facilitation: 4.3
	Psychologist consultation: 3.2	Sleeping medication: 2.1

Abbreviations: NSAID, nonsteroidal anti-inflammatory agent; NMDA, N-methyl D-aspartate.
[a]All data were collected during the first week of HPCT care (n = 534 patients).
[b]In each category, the sum of subcategory rates is greater than main category rates because of subcategory overlap.

Table 2. Demographics and Cancer-Related Information of All Enrolled Patients.[a]

Age, years (mean ± SD)	61.3 ± 14.7
Gender, male (% patients)	57.3
Primary site of cancer (% patients)	
Head and neck region	2.6
Alimentary tract	21.9
Hepatobiliary-pancreatic system	9.9
Respiratory system	16.9
Breast	7.9
Genitourinary system	24.5
Lymphatic-hematopoietic system	5.1
Skin, bones, connective tissue	3.9
Others or more than one	7.3
Performance status (PS[b] level, mean ± SD)	2.8 ± 1.0
PS 1	12.5
PS 2	28.7
PS 3	24.2
PS 4	34.6
Receiving antineoplastic therapy	37.8

Abbreviations: PS, performance status; SD, standard deviation.
[a]n = 534.
[b]Performance Status on the definition of Eastern Cooperative Oncology Group (ECOG).

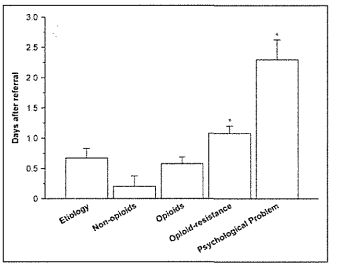

Figure 2. Priority of intervention of the hospital palliative care teams (HPCTs). Mean timing of HPCT interventions is displayed for each of the 5 Algorithm with Lists for Palliation Helped by Analgesia (ALPHA) categories (Figure 1). Error bars represent 1 standard error of the mean. * indicates $P < .0001$, as tested with the Kruskal-Wallis test. Etiology indicates etiology-oriented therapies; nonopioids, nonopioid interventions; opioids, opioid interventions; opioid resistance, interventions for opioid-resistant pain; psychological approach, psychological intervention to relieve pain.

Results

Patient Characteristics

A total of 534 patients (306 male and 228 female) were included in the study. The most common primary cancers observed were those of the digestive system, and approximately 60% of patients had a poor PS (Table 2).

Frequency of Interventions

In all enrolled patients, at least 1 intervention fell into one of the checklist items (Table 1). Re ALPHA symbol 1 (cause of pain), approximately 5% of the patients had pain caused by comorbid conditions (eg, disc herniation). Re ALPHA symbol 2 (etiology-oriented therapy), approximately 20% of the patients were treated with the relevant therapies (eg, decompression procedures). Re ALPHA symbol 3 (nonopioid analgesics), <5% of patients began a new regimen of nonopioid analgesics, whereas re ALPHA symbol 4 (interventions with opioid analgesics), 430 (80.5%) of the 534 patients in the study received some form of HPCT opioid analgesic intervention in accordance with the 5 principles of the WHO guidelines. Comparing the frequency of interventions of the 5 principles, "with attention to detail" (66.3%) and "for the individual" (52.1%) principles were the 2 most frequent, followed by "by the clock" (41.6%). Notably, the "with attention to detail" and "for the individual" principles were often applied concurrently. Of the 278 patients to whom the "for the individual" principle was applied, 225 (80.9%) concurrently received an "attention to detail" intervention. Of these 225 patients, 196 (87.1%) received an intervention based on "response to adverse effects of opioids," and 140 (62.2%) received an intervention based on "accountability of medicines." Re ALPHA symbol 5 (response to opioid-resistant pain), anticonvulsants were most often prescribed as adjuvant analgesic drugs. Interventions categorized as ALPHA symbol 6 (psychological approach) were used the least, in <10% of patients.

Priority of Interventions

The results of the study suggested that etiology-oriented therapy, nonopioid prescriptions, and opioid prescriptions were used before therapies for opioid-resistant pain and treatments for psychological problems (Figure 2). In addition, the rates of "early intervention" defined in this study suggested that the rationale of time frames of interventions corresponding to ALPHA symbols 4, 5, and/or 6 were as follows: 89.9% for symbol 4 (132 of 149 patients), 72.4% for symbol 5 (134 of 185 patients), and 48.3% for symbol 6 (28 of 58 patients).

Opioids and Adjuvant Analgesic Drugs for Pain Relief

The DOMED data are presented as the mean ± standard deviation (median) mg/d. Analysis of related data within groups was performed via the Wilcoxon sign-rank test. The HPCTs used opioids for pain relief in approximately 80% of the opioid-naive patients. On day 7, the DOMED had increased to 35.6 ± 29.0 (30.0) mg/d. Additionally, in the 380 patients (71.2% of all enrolled patients) who were opioid tolerant, the HPCTs' interventions increased the DOMED from 111.3 ± 143.9

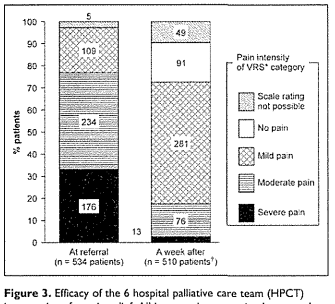

Figure 3. Efficacy of the 6 hospital palliative care team (HPCT) interventions for pain relief. All interventions examined occurred during the first week of HPCT intervention. The day of referral was defined as day 0. By day 7, patient pain intensity had significantly decreased ($P < .0001$, chi-square test). *indicates established 4-point verbal rating scale. † indicates 24 cases not included in day 7 data because of in-hospital death (n = 20 patients), hospital discharge (n = 3 patients), and HPCT round cessation at the patient's request (n = 1 patient).

(60.0) mg/d on day 0 to 143.9 ± 254.0 (84.0) mg/d on day 7 ($P = .0088$).

We divided the 380 opioid-tolerant patients into 3 subgroups based on the change rate of DOMED from days 0 to 7, increased, unchanged, or decreased. In the increased subgroup (n = 220, 57.9% of all opioid-tolerant patients), DOMED was increased significantly, from 84.4 ± 118.8 (59.0) mg/d to 147.1 ± 82.2 (105.0) mg/d ($P < .0001$). In the unchanged subgroup (n = 108, 28.4% of all opioid-tolerant patients), DOMED remained at 153.7 ± 387.7 (42.5) mg/d. In the decreased subgroup (n = 52, 13.7% of all opioid-tolerant patients), DOMED decreased significantly, from 137.0 ± 146.6 (90) mg/d to 68.6 ± 94.9 (30.0) mg/d ($P < .0001$). In the increased subgroup, the change rate was 1.6 ± 2.2 (2.0), and in the decreased subgroup it was 0.38 ± 0.34 (0.44). The number of patients prescribed adjuvant analgesics increased significantly, from 102 patients on day 0 (19.1% of the total 534 enrolled) to 178 (34.0%) on day 7 (chi-square test, $P = .025$).

Outcome of Pain Therapy Interventions

Average pain intensity, as determined via the VRS, decreased significantly during the first week of HPCT intervention (Figure 3). During this time, 68.9% of patients had their pain successfully reduced. Additionally, among all the enrolled patients, the prevalence of severe pain was reduced from 33.0% to 2.4%, and the prevalence of moderate pain was reduced from 33.9% to 15.1%. Finally, 410 patients (76.8% of the total enrolled) were suffering from pain and they rated moderate or greater on day 0, but on day 7, 68.0% of these patients reported that their pain had been reduced to mild or less than mild.

Discussion

The present study yielded 2 major findings. First, based on the WHO guidelines, we identified potential targets for improvements in cancer pain treatment by nonpalliative care physicians in Japan. The targets were clarified by our 1-year multicenter audit that analyzed day-to-day interventions used by the 6 experienced HPCTs in Japan to relieve cancer pain in their patients. The 1-year audit was based on an original protocol derived from the widely accepted WHO guidelines. We showed that interventions with opioids were used most frequently and that these tended to be given high priority because they were used early in the course of pain management. When used, the "for the individual" and "attention to detail" rationales were regarded as the most important 2 of the 5 principles in the WHO guidelines. In addition, the 2 were often used in combination. This suggests that major reasons for insufficient opioid dosage were inappropriate management of adverse effects (eg, opioid-induced constipation) and/or lack of adequate patient education on analgesics and other adjuvant medications (eg, disregard for patient anxiety on increased opioid doses).

The HPCT interventions for constipation were observed in approximately one-third of all the enrolled patients. Opioid-induced bowel dysfunction (OIBD) often limits opioid-dose escalation[21-23] and could result in insufficient pain relief.[21] Constipation is one of the most severe symptoms of OIBD and should be evaluated using objective measures (eg, abdominal radiography) rather than subjective patient symptoms.[21] It was suspected that the HPCTs acknowledged that constipation relief is one of the most important reasons why daily HPCT consultations successfully relieve patient pain.[21]

Patient/family education should be presented in clear writing,[10] and information on analgesic regimens is included under the "attention to detail" principle in the WHO guidelines.[11-13] Previous studies[2-5,24] validating the WHO guidelines have focused on the "by the ladder" principle. However, many Japanese patients having cancer with pain are most concerned about developing a psychological dependence on morphine, which results in patients taking inadequate opioid doses.[25] Therefore, we suggest that a trial in Japan examining the effects of "educational interventions"[1] is needed to determine whether following the WHO guidelines can improve the pain management ability of inexperienced HPCTs and nonpalliative care physicians.

This study suggested that the management of opioid-resistant pain and psychological interventions are utilized significantly later and less often than other types of HPCT interventions, at least by experienced HPCTs in Japan. Optimal opioid doses are not predictable,[26] and only approximately 20% of the cases with cancer-related pain are estimated to have

opioid resistance that could be relieved by means of opioid rotation.[26] Therefore, it is considered appropriate that HPCT interventions for managing opioid-resistant pain were administered significantly later than initial opioid therapy.

Psychological distress can be a sole cause of cancer pain,[12] and treatments aiming to improve mental health can improve treatment efficacy and reduce pain intensity.[27] However, we found that HPCT interventions of a psychological nature were administered significantly later than the physical treatments falling into the other 5 ALPHA symbol categories. We speculate that this occurred because HPCTs were aware of important clinical practice rules, as described subsequently. First, symptoms of disordered mood, thought, and behavior should be defined as nonspecific until a complete differential diagnosis can be obtained.[28] This is because more physically ill patients are more likely to have secondary psychological problems.[28] Second, HPCTs are often not able to effectively determine a patient's emotions and treat them via a psychological approach until they gain the patient's trust, which is often achieved through pain relief.[7] Third, if attending physicians requesting HPCT consultations did not request evaluation and resolution of a patient's mental or psychological issues and requested only the management of the patient's physical problems (eg, refractory pain), HPCT psychological interventions might be viewed as a violation of consultation etiquette.[29]

The second major finding of our study was confirmation that the HPCTs were successful in relieving difficult-to-manage pain, as assessed via a patient-rated pain scale. In Western countries, significant improvements in cancer pain, along with other symptoms, have been verified by systematic reviews.[30] In Japan, however, HPCT capabilities have only been certified in 2 single-center audits, neither of which used a patient-rated pain scale, but instead used a physician-rated one (Support Team Assessment Schedule-Japanese version).[7,31] To the best of our knowledge, the present 1-year audit is the first to report HPCT efficacy in Japan using a patient-rated pain scale across multiple centers. A randomized trial for verifying HPCT competence of pain relief is considered to be ethically questionable and thus infeasible.[32,33] Therefore, we propose that prospective, multi-centered, and before-and-after studies should be performed in Japan.

This study had some limitations. First, due to its retrospective nature we could not help omitting undocumented care, including informal psychosocial support. Second, the recognition of various symptoms besides pain is vital to properly implementing WHO guidelines[34] as has previously been shown in a group of Japanese patients.[7] However, our study did not evaluate physical symptoms other than pain. Third, we did not evaluate the potential underestimation of pain intensity by HPCT-referring physicians. Thus, the potential effects on the result of HPCT pain relief were not clear. Fourth, only ATC opioid doses were evaluated, and rescue opioid doses for breakthrough pain were not taken into account. This might be important in successful interventions, because breakthrough pain can severely reduce patient quality of life.[35] Fifth, some attending physicians in Japan are reluctant to refer their patients to HPCTs.[36] Therefore, our study population might not be representative of Japanese inpatients with pain. Future studies should explore the characteristics of all patients having cancer with substantial pain,[37] particularly those of patients not referred to an HPCT. Finally, our study only focused on pain intensity and did not review other aspects of pain, which is multifactorial (eg, perceived pain chronicity).[35]

In conclusion, our study indicates which parts of the WHO guidelines should be emphasized and prioritized in the management of cancer-related pain, at least in Japanese cancer center hospitals. Particularly, titrating opioid doses, responding to adverse effects, and patient education on analgesics were identified as the most important factors. In addition, we retrospectively verified the capabilities of 6 experienced HPCTs to relieve pain. Well-designed prospective clinical trials are needed to confirm the results of this audit, however, the present study will potentially help nonpalliative care physicians in Japan to effectively utilize the WHO guidelines.

Authors' Note

Ethical approval: The study protocol was approved by the institutional review board (#2015008 accepted on June 25 2015, Board Chief= Motohiro Shibata MD, PhD) of the Chukyo Hospital, where all the data analyses were conducted. According to the ethical guidelines for medical research in Japan, the hospitals that only submit already-existing data are not regarded as research facilities that require their own IRB approval.

Acknowledgments

We appreciate the respectful guidance of Takahiro Higashi and we are deeply grateful to Chika Ishikawa, Aya Takeda, Ayumi Ozeki, and Arata Uchida for their assistance with data collection.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by a Research Grant for Clinical Cancer Research from the Ministry of Health, Labour, and Welfare of Japan.

References

1. Cherny NI, Baselga J, de Conno F, Radbruch L. Formulary availability and regulatory barriers to accessibility of opioids for cancer pain in Europe: a report from the ESMO/EAPC Opioid Policy Initiative. *Ann Oncol*. 2010;21(3):615-626.
2. Grond S, Zech D, Schug SA, Lynch J, Lehmann KA. Validation of World Health Organization guidelines for cancer pain relief during the last days and hours of life. *J Pain Symptom Manage*. 1991;6(7):411-422.
3. Ripamonti C, Bandieri E. Pain therapy. *Crit Rev Oncol Hematol*. 2009;70(2):145-159.
4. Ventafridda V, Tamburini M, Caraceni A, De Conno F, Naldi F. A validation study of the WHO method for cancer pain relief. *Cancer*. 1987;59(4):850-856.

5. Zech DF, Grond S, Lynch J, Hertel D, Lehmann KA. Validation of World Health Organization Guidelines for cancer pain relief: a 10-year prospective study. *Pain*. 1995;63(1):65-76.
6. Ministry of Health, Labour, and Welfare (MHLW). Report of research and investigative commission about end-of-life care [In Japanese]. Web site. http://www.mhlw.go.jp/shingi/2004/07/s0723-8d9.html. Published July 16, 2004. Accessed September 20, 2015.
7. Morita T, Fujimoto K, Tei Y. Palliative care team: the first year audit in Japan. *J Pain Symptom Manage*. 2005;29(5):458-465.
8. Foley KM. How well is cancer pain treated? *Palliat Med*. 2011; 25(5):398-401.
9. Higashi T, Yoshimoto T, Matoba M. Prevalence of analgesic prescriptions among patients with cancer in Japan: an analysis of health insurance claims data. *Glob J Health Sci*. 2012;4(6): 197-203.
10. World Health Organization. *Cancer Pain Relief*. Geneva: WHO; 1986.
11. Twycross RG. *Pain Relief in Advanced Cancer*. Edinburgh: Churchill Livingstone; 1994.
12. Twycross R, Wilcock A, Toller CS. *Symptom Management in Advanced Cancer*. 4th ed. Nottingham: Palliativedrugs.com Ltd; 2009.
13. Hanks G, Cherny NI, Christakis NA, eds. *Oxford Textbook of Palliative Medicine*. 4th ed. Oxford: Oxford University Press; 2009.
14. Japan Clinical Oncology Group. *Additional Table of Performance Status* [In Japanese]. 1999. Web site. http://www.jcog.jp/doctor/tool/C_150_0050.pdf. Published April 30, 1999. Accessed September 20, 2015.
15. Blagden SP, Charman SC, Sharples LD, Magee LR, Gilligan D. Performance status score: do patients and their oncologists agree? *Br J Cancer*. 2003;89(6):1022-1027.
16. Kalso E, Vainio A. Morphine and oxycodone hydrochloride in the management of cancer pain. *Clin Pharmacol Ther*. 1990;47(5): 639-646.
17. Mercadante S, Ferrera P, Villari P, Casuccio A, Intravaia G, Mangione S. Frequency, indications, outcomes, and predictive factors of opioid switching in an acute palliative care unit. *J Pain Symptom Manage*. 2009;37(4):632-641.
18. Yoshimoto T, Hisada A, Yomiya K, et al. Efficacy and safety of compound oxycodone injection for cancer pain relief-a multicenter survey of prescriptions [In Japanese]. *Gan To Kagaku Ryoho*. 2010;37(5):871-878.
19. Swarm RA, Abernethy AP, Anghelescu DL, et al. Adult cancer pain. *J Natl Compr Canc Netw*. 2010;8(9):1046-1086.
20. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94(2):149-158.
21. Brock C, Olesen SS, Olesen AE, Frokjaer JB, Andresen T, Drewes AM. Opioid-induced bowel dysfunction: pathophysiology and management. *Drugs*. 2012;72(14):1847-1865.
22. Clemens KE, Mikus G. Combined oral prolonged-release oxycodone and naloxone in opioid-induced bowel dysfunction: review of efficacy and safety data in the treatment of patients experiencing chronic pain. *Expert Opin Pharmacother*. 2010; 11(2):297-310.
23. Kurz A, Sessler DI. Opioid-induced bowel dysfunction: pathophysiology and potential new therapies. *Drugs*. 2003;63(7): 649-671.
24. Grond S, Zech D, Lynch J, Diefenbach C, Schug SA, Lehmann KA. Validation of World Health Organization guidelines for pain relief in head and neck cancer. A prospective study. *Ann Otol Rhinol Laryngol*. 1993;102(5):342-348.
25. Yamaguchi T, Narita M, Morita T, Kizawa Y, Matoba M. Recent developments in the management of cancer pain in Japan: education, clinical guidelines and basic research. *Jpn J Clin Oncol*. 2012;42(12):1120-1127.
26. Khan MI, Walsh D, Brito-Dellan N. Opioid and adjuvant analgesics: compared and contrasted. *Am J Hosp Palliat Care*. 2011; 28(5):378-383.
27. Lovell MR, Forder PM, Stockler MR, et al. A randomized controlled trial of a standardized educational intervention for patients with cancer pain. *J Pain Symptom Manage*. 2010;40(1):49-59.
28. Goldberg RJ. *Practical Guide to the Care of the Psychiatric Patient*. 2nd ed. St. Louis, MO: Mosby; 1998.
29. Meier DE, Beresford L. Consultation etiquette challenges palliative care to be on its best behavior. *J Palliat Med*. 2007;10(1): 7-11.
30. Higginson IJ, Evans CJ. What is the evidence that palliative care teams improve outcomes for cancer patients and their families? *Cancer J*. 2010;16(5):423-435.
31. Iwase S, Murakami T, Saito Y, Nakagawa K. Preliminary statistical assessment of intervention by a palliative care team working in a Japanese general inpatient unit. *Am J Hosp Palliat Care*. 2007;24(1):29-35.
32. Gomez-Batiste X, Porta-Sales J, Espinosa-Rojas J, Pascual-Lopez A, Tuca A, Rodriguez J. Effectiveness of palliative care services in symptom control of patients with advanced terminal cancer: a spanish, multicenter, prospective, quasi-experimental, pre-post study. *J Pain Symptom Manage*. 2010;40(5):652-660.
33. Akashi M, Yano E, Aruga E. Under-diagnosis of pain by primary physicians and late referral to a palliative care team. *BMC Palliat Care*. 2012;11:7.
34. Meuser T, Pietruck C, Radbruch L, Stute P, Lehmann KA, Grond S. Symptoms during cancer pain treatment following WHO-guidelines: a longitudinal follow-up study of symptom prevalence, severity and etiology. *Pain*. 2001;93(3):247-257.
35. Rustoen T, Moum T, Padilla G, Paul S, Miaskowski C. Predictors of quality of life in oncology outpatients with pain from bone metastasis. *J Pain Symptom Manage*. 2005;30(3):234-242.
36. Tamiya N, Okuno M, Kashiwakgi M, Nishikitani M, Aruga E. Collaboration between physicians and a hospital-based palliative care team in a general acute-care hospital in Japan. *BMC Palliat Care*. 2010;9:13.
37. Melotti RM, Samolsky-Dekel BG, Ricchi E, et al. Pain prevalence and predictors among inpatients in a major Italian teaching hospital. A baseline survey towards a pain free hospital. *Eur J Pain*. 2005;9(5):485-495.

Japanese Journal of Clinical Oncology Advance Access published September 10, 2015

JJCO Japanese Journal of Clinical Oncology

Japanese Journal of Clinical Oncology, 2015, 1–6
doi: 10.1093/jjco/hyv130
Original Article

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Accuracy of using Diagnosis Procedure Combination administrative claims data for estimating the amount of opioid consumption among cancer patients in Japan

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Received 11 June 2015; Accepted 3 August 2015

Abstract

Objective: The state of opioid consumption among cancer patients has never been comprehensively investigated in Japan. The Diagnosis Procedure Combination claims data may be used to measure and monitor opioid consumption among cancer patients, but the accuracy of using the Diagnosis Procedure Combination data for this purpose has never been tested.

Methods: We aimed to ascertain the accuracy of using the Diagnosis Procedure Combination claims data for estimating total opioid analgesic consumption by cancer patients compared with electronic medical records at Aomori Prefectural Central Hospital. We calculated percent differences between estimates obtained from electronic medical records and Diagnosis Procedure Combination claims data by month and drug type (morphine, oxycodone, fentanyl, buprenorphine, codeine and tramadol) between 1 October 2012 and 30 September 2013, and further examined the causes of discrepancy by reviewing medical and administrative charts between April and July 2013.

Results: Percent differences varied by month for drug types with small prescription volumes, but less so for drugs with larger prescription volumes. Differences also tended to diminish when consumption was compared for a year instead of a month. Total percent difference between electronic medical records and Diagnosis Procedure Combination data during the study period was −0.1% (4721 mg per year per hospital), as electronic medical records as baseline. Half of the discrepancy was caused by errors in data entry.

Conclusion: Our study showed that Diagnosis Procedure Combination claims data can be used to accurately estimate opioid consumption among a population of cancer patients, although the same conclusion cannot be made for individual estimates or when making estimates for a group of patients over a short period of time.

Key words: palliative care, analgesics, opioid, pain

Introduction

Morphine-equivalent consumption of opioids in milligrams (mg) per capita is often used as an indicator of access to pain treatment and palliative care (1). Although this measure allows for a global comparison of drug accessibility, it does not tell us about the state of opioid consumption among cancer patients as it includes use by all patients for all purposes, including opioids prescribed against non-malignancy related pain. Similarly, the Ministry of Health, Labour and Welfare in Japan annually monitors and reports the state of nation-wide opioid consumption, but its use among cancer patients, in particular, is not known (2).

In order to fill this knowledge gap, many developed countries calculate the total amount of opioids prescribed to cancer patients by analyzing administrative claims data or prescription database (3–5). Claims data are useful for monitoring medical utilization and prescription patterns, but it requires that its accuracy, validity and reliability are tested, so that characteristics and limitations of the dataset is well understood by those who use the data for future research (6–9). However, these studies have not yet been adequately conducted in Japan, and it is not known whether estimates of opioid consumption could accurately be obtained from Diagnosis Procedure Combination (DPC) claims data.

The format of claims data was standardized in Japan in 2003, when the DPC system, similar to that of the Diagnosis-Related Group (DRG) classification system used in Medicare reimbursements in the USA, was introduced (10). Although the DPC system itself is a set of diagnosis groups, based on which the per diem reimbursements to hospitals are decided, the DPC claims database collects information on all prescriptions, procedures and administrative costs of patients from both inpatient and outpatient settings, in order to monitor the adequacy of the DPC groupings. As these data are being used more extensively to measure hospital activity and patterns of care, it is pertinent to test its accuracy compared with what is in the electronic medical records (EMR) so that the integrity of future studies that use the DPC database is ensured (11).

Therefore, we aimed to investigate the accuracy of total opioid consumption by cancer patients by using the DPC claims data compared with estimates obtained from EMR, and to examine the causes of discrepancies, if any exist.

Patients and methods

We identified all morphine, oxycodone, fentanyl, buprenorphine, codeine and tramadol prescriptions made between 1 October 2012 and 30 September 2013 at Aomori Prefectural Central Hospital using the DPC claims database (refer to Supplementary Table for a list of claims codes used). In order to abstract only the prescriptions that were made toward cancer patients, we linked DPC claims database with hospital-based cancer registry data, and excluded data of patients who have never been registered or those who were diagnosed with cancer after 30 September 2013. We also excluded prescriptions that were made on the day of any surgical procedures in order to exclude opioids used for surgical pain management.

Similarly, we obtained prescription data of all opioid analgesics prescribed for all patients between 1 October 2012 and 30 September 2013 using EMR's drug-dispensing data. By linking EMR data to hospital-based cancer registry data, we pulled prescriptions that were made for cancer patients who were diagnosed before 30 September 2013. Opioid prescriptions made on the day of surgical procedures were, again, omitted.

We calculated the amount of opioid analgesics prescribed for cancer patients by month in oral morphine equivalent dose (MED, mg), according to the type of opioids (morphine, oxycodone, fentanyl, buprenorphine, codeine and tramadol), drug form (injection, oral or suppository drugs) and patient setting (inpatient or outpatient). We compared the estimate of total opioid consumption obtained from DPC claims data and the estimate obtained from EMR, by calculating the percent difference between the two estimates for each month by drug type. Percent differences (%) were calculated by dividing the difference between the two estimates by the average of the two, with values obtained from EMR as the baseline. Lastly, we investigated the reasons and amount of dose discrepancy between EMR and DPC claims data by reviewing patients' medical charts and administrative data within the EMR for April, May, June and July 2013.

The study was approved by the Institutional Review Boards of the National Cancer Center and Aomori Prefectural Central Hospital.

Results

We identified 1158 cancer patients who received at least one prescription of an opioid analgesic at Aomori Prefectural Central Hospital between 1 October 2012 and 30 September 2013 (Table 1). The mean age (SD) of cancer patients was 64.9 (SD 10.7). The most common cancer sites were lung (30.4%), colorectal (12.8%) and stomach cancers (9.1%).

Figure 1 shows the total amount of opioid analgesic prescriptions calculated from EMR and DPC claims data by month. Percent differences between these two estimates were mostly between 0% and −3%, except for March 2013 (16.8%).

Variability in percent differences became evident when estimates of opioid consumption was compared for each drug type by month, but the range was larger for drugs that had smaller volumes of drugs prescribed, and smaller for drugs with larger prescription volumes (Table 2). Injection buprenorphines, which only had ~900 mg of MEDs prescribed, had percent differences that ranged from −43% (February 2013) to 66.7% (October 2012). Differences were much smaller for oral oxycodone, which had the largest prescription volume in MEDs of 2 million milligrams in total prescription volume, and ranged from −2.7% (June 2013) to 2.6% (May 2013). Estimate of total MEDs for the entire study period was 3 725 157 mg for EMR and 3 720 436 mg for DPC claims data, resulting in a total percent difference of −0.1% (4721 mg) between the two data sources.

Reasons for discrepancy between estimates obtained from EMR and DPC claims data were investigated for the months between April and July 2013, by reviewing administrative data and individual medical charts. We excluded March 2013 from this analysis, which had the greatest discrepancy (51 981 mg), due to an occurrence of an unusual error. There was a large volume of paper prescriptions that were accidentally not entered into the EMR, but the mistake was captured when DPC claims data were created. Table 3 shows the differences in total opioid consumption estimates obtained from EMR and DPC claims data in MED (mg), categorized by reasons for discrepancy.

We categorized the reasons for discrepancy into three major causes (Table 3). The first reason was due to the study design. We failed to fully exclude opioids used on the day of surgery from both EMR and DPC claims data, which resulted in differences in consumption estimates. Opioids for surgical pain management was excluded from DPC claims data by excluding all opioids flagged for opioids used during all surgical procedures (12). However, when surgical opioids were excluded from the analysis for EMRs, we only excluded opioids that were used from the operating room's drug inventory. This difference in how opioids for surgical use were excluded from the study accounted for about a third of the total discrepancy in our study.

The second cause was related to the nature of DPC claims data or how the data were created. Healthcare claims cannot be made for medical services that are self-pay, or are covered by worker's compensation insurance or patients on social welfare programs, and are not entered into DPC claims data. However, this reason accounted for only ~1% (484 mg) of the discrepancy in opioid estimates. Another reason that accounted for ~13% of the discrepancy in the estimates (5171 mg) was patient death. All prescriptions that were written before the date of patient's death, but cover for drugs beyond the date of death are included in the EMR database, but are excluded from DPC claims data as a coding rule. For instance, if a patient receives prescriptions for morphine on January 10th for 10 days, but dies on January 15th, DPC claims data will only include prescription data until January 15th, whereas EMR drug-dispensing data will include prescriptions for five more days. Furthermore, prescription orders that are made on the last day of the month are sometimes entered into the DPC data in the following month, resulting in differences in opioid consumption estimates. This occurs because DPC claims data are always created after all prescription orders are placed within the EMR, and orders placed on the last day of the month may not have had enough time to be entered on the same day. Lastly, prescriptions that cross over to the following month are sometimes divided into two DPC claims data. For instance, a prescription order for oral oxycodone for 30 days made on 20 May 2013 are divided into two data, one for 10 days prescription in May and another for 20 days in June, which was why there was 840 mg less opioids calculated from DPC claims data in April 2013, but an excess of 840 mg in May 2013. However, these differences in estimates tend to even out when opioid consumptions are followed over several months.

The third reason for discrepancy was caused by errors in data entry. Errors in data entry occurred when making DPC claims data, but also when prescription data were not entered accurately into the EMR. These accounted for over 50% of the discrepancy in the estimates (20 852 mg).

Table 1. Characteristics of cancer patients who received at least one prescription of opioid analgesic between 1 October 2012 and 30 September 2013 at Aomori Prefectural Central Hospital

Characteristics	*n*	%
Total patients, *n*	1158	
Age[a]	64.9	(10.7)
Sex, men	8067	(64.1)
Stage		
0	21	(1.8)
I	278	(24.0)
II	151	(13.0)
III	223	(19.3)
IV	345	(29.8)
Unknown	140	(12.1)
Tumor site, *n* (%)		
Head and neck	57	(4.9)
Lung	352	(30.4)
Esophagus	33	(2.8)
Stomach	105	(9.1)
Colorectal	148	(12.8)
Breast	51	(4.4)
Liver	31	(2.7)
Pancreas	54	(4.7)
Biliary track	38	(3.3)
Cervical	12	(1.0)
Uterus	12	(1.0)
Other	258	(22.3)
unknown	7	(0.6)

[a]Mean, (standard deviation).

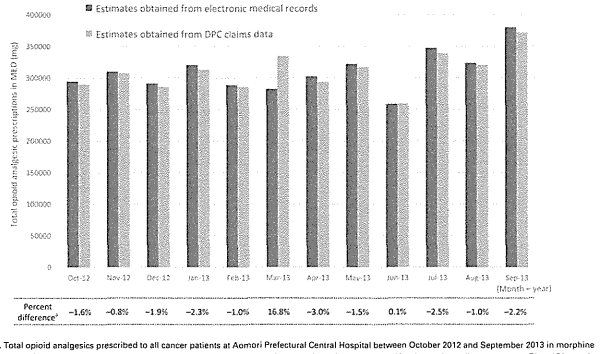

Figure 1. Total opioid analgesics prescribed to all cancer patients at Aomori Prefectural Central Hospital between October 2012 and September 2013 in morphine equivalent dose. *Percent differences were calculated by dividing the difference between the estimates obtained by electronic medical records (EMR) and Diagnosis Procedure Combination claims data by the average of the two, with values obtained from EMR as the baseline.

Table 2. Comparison of opioid analgesic prescriptions for all cancer patients (n = 1158) at Aomori Prefectural Central Hospital Between 1 October 2012 and 1 September 2013 in oral morphine equivalent dose (MED) using electronic medical records (EMR) and Diagnosis Procedure Combination (DPC) claims data

	Oct 12	Nov 12	Dec 12	Jan 13	Feb 13	Mar 13	Apr 13	May 13	Jun 13	Jul 13	Aug 13	Sep 13	Total
Amount of opioid analgesic prescription obtained from EMR in MED (mg)													
Oxycodone (PO)	152 798	160 849	134 490	156 870	151 313	175 001	171 454	173 209	132 859	200 175	172 894	230 314	2 012 224
Oxycodone (IV)	11 620	9600	31 220	49 680	33 580	4120	15 100	21 920	5080	12 000	6840	9420	210 180
Fentanyl (TD)	82 050	80 190	60 540	64 830	46 530	54 150	52 470	55 350	53 790	60 930	68 850	80 010	759 690
Fentanyl (IV)	3370	7050	770	640	2850	2310	4130	3980	8975	6030	15 830	17 380	78 535
Morphine (PO)	244 320	32 950	30	24 805	24 135	28 710	35 855	44 695	35 215	38 115	32 095	28 070	377 815
Morphine (supp)	885	30	330	1800	2290	750	450	165	300	1170	900	330	9400
Morphine (IV)	9200	14 550	24 610	21 210	9760	12 640	13 168	10 798	15 552	16 646	4933	4494	175 402
Codeine (PO)	2219	2372	3403	1171	2488	4550	4443	3975	7642	4223	4873	4308	50 217
Tramadol (PO)	3070	2500	5430	1695	3120	3600	5525	5040	5430	5540	4835	3900	49 685
Buprenorphine (supp)	200	200	200	100	0	60	600	840	0	0	10	0	2220
Buprenorphine (IV)	12	0	12	66	390	48	18	18	228	84	0	12	888
Total	294 764	310 320	291 265	320 869	289 215	282 759	302 785	322 363	258 896	347 468	323 837	380 616	3 725 157
Amount of opioid analgesic prescription obtained from DPC claims data in MED (mg)													
Oxycodone (PO)	150 863	159 810	132 431	154 526	149 100	176 839	167 565	168 821	136 474	197 119	175 136	228 398	1 997 081
Oxycodone (IV)	11 540	9320	30 240	48 720	33 320	3660	14 180	20 500	5060	11 560	6280	9720	204 100
Fentanyl (TD)	81 210	79 560	60 450	64 470	46 350	105 430	50 970	58 470	51 990	61 350	68 830	79 590	808 710
Fentanyl (IV)	9400	7070	770	710	2860	2200	3710	3870	8280	3610	13 420	12 260	67 160
Morphine (PO)	244 285	32 470	28 460	24 665	24 675	28 415	35 635	43 130	35 515	36 825	31 926	28 070	374 070
Morphine (supp)	705	30	330	1650	2290	750	450	165	300	1170	900	330	8970
Morphine (IV)	7440	14 660	24 330	17 709	9760	12 640	10 020	12 460	9960	13 280	14 530	5720	157 508
Codeine (PO)	2219	2235	3380	3079	2488	4550	5003	3978	5922	7198	4873	4308	49 633
Tramadol (PO)	3070	2500	5430	1695	3120	3600	5525	5040	5430	6660	4835	3900	50 805
Buprenorphine (supp)	200	200	200	10	0	60	600	1120	0	10	10	0	2410
Buprenorphine (IV)	24	0	24	132	252	96	36	36	252	72	0	12	936
Total	289 956	307 835	285 895	313 437	286 235	334 740	293 694	317 571	259 162	338 854	320 750	372 307	3 720 436
Percent difference[a] between EMR and DPC claims data (%)													
Oxycodone (PO)	−1.3%	−0.6%	−1.5%	−1.5%	−1.5%	1.0%	−2.3%	−2.6%	2.7%	−1.5%	1.3%	−0.8%	−0.8%
Oxycodone (IV)	−0.7%	−3.0%	−3.2%	−2.0%	−0.8%	−11.8%	−6.3%	−6.7%	−0.4%	−3.7%	−8.5%	3.1%	−2.9%
Fentanyl (TD)	−1.0%	−0.8%	−0.1%	−0.6%	−0.4%	64.3%	−2.9%	5.5%	−3.4%	0.7%	0.0%	−0.5%	6.3%
Fentanyl (IV)	0.4%	0.3%	0%	10.4%	0.4%	−4.9%	−10.7%	−2.8%	−8.1%	−50.5%	−16.3%	−33.7%	−15.6%
Morphine (PO)	−0.1%	−1.5%	−1.4%	−0.6%	2.2%	−1.0%	−0.6%	−3.6%	0.8%	−3.4%	−0.5%	0%	−1.0%
Morphine (supp)	−22.6%	0.0%	−2.7%	−8.7%	0%	−3.8%	0%	−23.9%	−5.7%	−5.7%	0%	0%	−7.7%
Morphine (IV)	−21.4%	−8.3%	−1.2%	−19.7%	−0.3%	0%	−3.8%	0%	0%	−17.7%	−9.3%	−12.6%	−10.7%
Codeine (PO)	−0.1%	−5.9%	−0.7%	−3.0%	0%	0%	0%	11.9%	−4.9%	−4.7%	−1.2%	−4.2%	−1.2%
Tramadol (PO)	0%	0%	0%	0%	0%	0%	0%	0%	0%	18.4%	0%	0%	2.2%
Buprenorphine (supp)	0%	0%	0%	−163.6%	N/A	0%	0%	0%	28.6%	0%	0%	N/A	8.2%
Buprenorphine (IV)	66.7%	N/A	66.7%	66.7%	−43.0%	66.7%	66.7%	66.7%	10.0%	−15.4%	N/A	0%	5.3%
Total	−1.6%	−0.8%	−1.9%	−2.3%	−1.0%	16.8%	−3.0%	−1.5%	0.1%	−2.5%	−1.0%	−2.2%	−0.1%

PO, per oral; IV, intravenous and other injection drugs; TD, transdermal; supp: suppository.
[a]Percent differences were calculated by dividing the difference between the estimate obtained from EMR and DPC claims data by the average of the two numbers as EMR as the baseline.

Table 3. Difference in oral MED calculated from EMR and DPC claims data between 1 April 2013 and 31 July 2013

Reasons for discrepancy between EMR and DPC claims data	Differences in oral MED (mg)				Total	(%)
	Apr 13	May 13	Jun 13	Jul 13		
Discrepancy caused by study design						
Failure to exclude surgical use from EMR	140	0	230	20	390	(1)
Failure to exclude surgical use from claims data	−4200	−1720	−1850	−6012	−13 782	(34)
Discrepancy related to the nature of claims data						
Workers compensation	−64	−420	0	0	−484	(1)
Self-pay	0	0	0	0	0	(0)
Death or discharge	−455	−1325	−683	−2708	−5171	(13)
Claims made in the following month	0	−4650	4650	0	0	(0)
Divided claims	−840	840	0	0	0	(0)
Discrepancy caused by errors in data entry						
Different doses administered than what was claimed	6	12	83	128	229	(1)
Failure to enter prescription data into claims data	−5060	−1182	−2835	−2941	−12 018	(30)
Failure to enter prescription data into EMR	1382	3653	670	2900	8605	(20)
Total	−5031	−3072	1885	−2621	−8839	(100)

[a]Differences in oral MED (mg) were calculated by subtracting estimates obtained from EMR from the estimates obtained from DPC claims data.

Discussion

The accuracy of using DPC claims data for calculating opioid consumption among cancer patients has never been tested since the launch of the DPC system in 2002. Findings in our study showed that DPC claims data has over 99% accuracy compared with EMR data in estimating the total amount of opioid analgesics prescribed to all cancer patients, but only so, when prescriptions estimates are calculated for large volumes of prescriptions across a group of patients over some length of time that is longer than several months.

Total discrepancy between opioid consumption estimates obtained from EMR and DPC claims data was only 0.1% (4721 mg in MEDs for 12 months). Investigation of data discrepancy revealed that discrepancies tend to arise when total opioid consumption is compared by drug type on a month-to-month basis. This is due to the nature of DPC claims data, where data are created and submitted on a monthly basis, whereas EMR data depicts actual drugs dispensed on a daily basis. Prescription orders that are made at the end of the month are not always, but sometimes, entered into the DPC claims data for the following month. In addition, DPC claims data are only created until the date of patient's death, although EMR's drug-dispensing data will include prescriptions that were made before the patient's death and lasts beyond the patient's death. DPC claims data also do not include data for self-pay patients and patients on worker's compensation insurance. Although these differences in characteristics exist, both data are prone to human error, which accounted for roughly half of the discrepancy in our study. However, the amount of this error was very small in relation to the total amount of opioid prescription and can be disregarded if the purpose is to measure total consumption for a large number of patients. Future studies that aim to estimate the amount of opioid consumption among cancer patients using DPC claims data should take these data characteristics into consideration.

One of the major limitations of our study is that this was a single-center study. There may be variability in the accuracy of DPC claims data across various hospitals that use different EMR systems. Another limitation is sample size. Although we had ~1158 cancer patients with opioid prescriptions during the study period, we do not know how accurate opioid consumption estimates will be when data for much larger population of cancer patients are estimated. We also did not investigate the accuracy of prescription volumes for individual patients, but rather a group of patients.

However, there are major advantages of using the DPC claims database. First is the format of the data, which is standardized across a wide number of cancer treatment hospitals in Japan. Secondly, although self-pay patients and patients on workers compensation insurance or social welfare programs are excluded, DPC claims data include data of all other patients regardless of the type of health insurance they have. Therefore, it is relatively easy to collect DPC claims data of cancer patients treated at various hospitals throughout the country. Future analysis of DPC claims data should be expanded to assess for opioid consumption among a larger population of cancer patients in Japan.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

Funding

This study was funded by grant-in-aid from the Ministry of Health, Labor and Welfare, Japan.

Conflict of interest statement

None declared.

References

1. The World Medicines Situation Report, 2011 3rd edition—Access to Controlled Medicines. http://www.who.int/medicines/areas/policy/world_medicines_situation/en/index.html (13 January 2015, date last accessed).
2. Ministry of Health, Labour and Welfare. Pharmaceutical and Food Safety Bureau. Compliance and Narcotics Division. Guidelines for appropriate use of medical opioids. Medical opioid consumption in Japan. https://web.cn.edu/kwheeler/documents/Lit_Citation_Problems.pdf (10 February 2015, date last accessed).
3. Jarlbaek L, Andersen M, Kragstrup J, Hallas J. Cancer patients' share in a population's use of opioids. A linkage study between a prescription database and the Danish Cancer Registry. *J Pain Symptom Manage* 2004;27:36–43.

4. Pan HH, Ho ST, Lu CC, et al. Trends in the consumption of opioid analgesics in Taiwan from 2002 to 2007: a population-based study. *J Pain Symptom Manage* 2013;45:272–8.
5. Fisher J, Urquhart R, Johnston G. Use of opioid analgesics among older persons with colorectal cancer in two health districts with palliative care programs. *J Pain Symptom Manage* 2013;46:20–9.
6. Du XL, Key CR, Dickie L, et al. External validation of medicare claims for breast cancer chemotherapy compared with medical chart reviews. *Med Care* 2006;44:124–31.
7. Lund JL, Stürmer T, Harlan LC, Sanoff HK, Sandler RS, Brookhart MA, Warren JL. Identifying specific chemotherapeutic agents in Medicare data: a validation study. *Med Care* 2013;51:e27–34. doi: 10.1097/MLR.0b013e31823ab60f.
8. Miller DC, Saigal CS, Warren JL, et al. External validation of a claims-based algorithm for classifying kidney-cancer surgeries. *BMC Health Serv Res* 2009;9:92. doi: 10.1186/1472-6963-9-92.
9. Lamont EB, Lauderdale DS, Schilsky RL, Christakis NA. Construct validity of medicare chemotherapy claims: the case of 5FU. *Med Care* 2002;40:201–11.
10. Matsuda S, Ishikawa KB, Kuwabara K, et al. Development and use of the Japanese case-mix system. *Eurohealth* 2008;14:25–30.
11. Higashi T, Nakamura F, Saruki N, Sobue T. Establishing a quality measurement system for cancer care in Japan. *Jpn J Clin Oncol* 2013;43:225–32. doi: 10.1093/jjco/hys001.
12. Guidelines for submitting DPC survey data. Ministry of Health, Labour and Welfare. 1 April 2013. http://www.mhlw.go.jp/seisakunitsuite/bunya/kenkou_iryou/iryouhoken/dl/h26_dpc_1.pdf (10 February 2015, date last accessed).

Tramadol and Its Metabolite M1 Selectively Suppress Transient Receptor Potential Ankyrin 1 Activity, but Not Transient Receptor Potential Vanilloid 1 Activity

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BACKGROUND: The transient receptor potential vanilloid 1 (TRPV1) and the transient receptor potential ankyrin 1 (TRPA1), which are expressed in sensory neurons, are polymodal nonselective cation channels that sense noxious stimuli. Recent reports showed that these channels play important roles in inflammatory, neuropathic, or cancer pain, suggesting that they may serve as attractive analgesic pharmacological targets. Tramadol is an effective analgesic that is widely used in clinical practice. Reportedly, tramadol and its metabolite (M1) bind to μ-opioid receptors and/or inhibit reuptake of monoamines in the central nervous system, resulting in the activation of the descending inhibitory system. However, the fundamental mechanisms of tramadol in pain control remain unclear. TRPV1 and TRPA1 may be targets of tramadol; however, they have not been studied extensively.

METHODS: We examined whether and how tramadol and M1 act on human embryonic kidney 293 (HEK293) cells expressing human *TRPV1* (*hTRPV1*) or *hTRPA1* by using a Ca^{2+} imaging assay and whole-cell patch-clamp recording.

RESULTS: Tramadol and M1 (0.01–10 μM) alone did not increase in intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) in HEK293 cells expressing hTRPV1 or hTRPA1 compared with capsaicin (a TRPV1 agonist) or the allyl isothiocyanate (AITC, a TRPA1 agonist), respectively. Furthermore, in HEK293 cells expressing hTRPV1, pretreatment with tramadol or M1 for 5 minutes did not change the increase in $[Ca^{2+}]_i$ induced by capsaicin. Conversely, pretreatment with tramadol (0.1–10 μM) and M1 (1–10 μM) significantly suppressed the AITC-induced $[Ca^{2+}]_i$ increases in HEK293 cells expressing hTRPA1. In addition, the patch-clamp study showed that pretreatment with tramadol and M1 (10 μM) decreased the inward currents induced by AITC.

CONCLUSIONS: These data indicate that tramadol and M1 selectively inhibit the function of hTRPA1, but not that of hTRPV1, and that hTRPA1 may play a role in the analgesic effects of these compounds. (Anesth Analg 2015;120:790–8)

Among the transient receptor potential (TRP) family, the TRP vanilloid 1 (TRPV1) and TRP ankyrin 1 (TRPA1) are important detectors of pain sensation in sensory afferent neurons.[1,2] These nonselective cation channels are activated by numerous stimuli. TRPV1, which is stimulated by capsaicin, heat (>45°C), proton, and lipid peroxidation products,[3–5] is distributed in sensory afferent neurons expressing pain transmitters, such as substance P (SP).[5,6] Conversely, TRPA1, which is activated by allyl isothiocyanate (AITC), formaldehyde, and reactive oxygen species,[7–10] colocalizes mainly with TRPV1 in sensory afferent neurons.[11] We previously showed that these agonists induced SP release from sensory afferent neurons,[12–15] indicating that pain information activated by these channels is transmitted to spinal dorsal horn via SP.[16] Many studies using pain models, including knockout mice lacking the channels and their selective inhibitors, demonstrated that both TRPV1 and TRPA1 contribute to severe pain, such as allodynia or hyperalgesia. Thus, these channels are evidently involved in pain transmission in primary sensory neurons and are potential targets for analgesic development.

Tramadol has commonly been used as an analgesic in clinical practice to moderate cancer or postoperative pain.[17–19] Currently, 2 actions of tramadol are believed to contribute to its analgesic effects by activating the descending inhibitory system: (1) tramadol binds to μ-opioid receptors (the affinity of tramadol for the receptors is approximately 6000 times weaker than that of morphine) and (2) tramadol inhibits the reuptake of monoamines, such as norepinephrine and serotonin, in the central nervous system.[20,21] Compared with the typical opioid agonist morphine, tramadol rarely causes adverse effects, such as respiratory depression and

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Accepted for publication November 6, 2014.

Funding: This work was supported by a Grant-in-Aid for the Third-term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare, Japan; the National Cancer Center Research and Development Fund (23-A-29 and 23-A-30); Grants-in-Aid for Scientific Research (C) No. 23592318 and No. 24590740 from the Ministry of Education, Culture, Sports, Science and Technology of Japan and a Grant-in-Aid for Young Scientists (B) No. 23790315 and No. 25860199 from the Ministry of Education, Culture, Sports, Science and Technology of Japan.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

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DOI: 10.1213/ANE.0000000000000625

physical dependence[22,23] although it possesses 1/30 of the analgesic efficacy of morphine.[24] Tramadol undergoes biotransformation in the liver via 2 metabolic pathways to form 5 *N*-desmethyl or *O*-desmethyl metabolites (M1-5),[25] among which, only *O*-desmethyl tramadol (M1) has analgesic activity in mice and rats.[26] Despite extensive investigation into tramadol, the mechanisms underlying its (and M1's) therapeutic actions remain unclear. Previous studies suggest that the analgesic mechanisms of tramadol are complex; our previous studies revealed that both tramadol and M1 suppress the activation of receptors related to pain transmission, such as the γ-aminobutyric acid receptor, *N*-methyl-D-aspartate receptors, and some G protein–coupled receptors, such as 5-hydroxytryptamine type 2C (5-HT_{2C}) receptors or the type-1 muscarinic (M1) receptor.[27–30] Moreover, TRPV1 is also involved in postoperative and cancer pain.[31–38] Marincsák et al.[39] reported that tramadol increased intracellular Ca^{2+} concentration ($[Ca^{2+}]_i$) via the activation of TRPV1; this could be rapidly followed by the rapid desensitization of the sensory afferent neurons and then produce analgesic effects. However, the effects of M1 on TRPV1 have not been studied in detail. In addition, little is known about the involvement of tramadol in the functions of TRPA1, even though it is an attractive analgesic pharmacological target. We investigated the effects of tramadol and M1 on the function of TRPV1 and TRPA1 in human embryonic kidney (HEK293) cells expressing human TRPV1 (hTRPV1) and hTRPA1, respectively, by using an electrophysiology method and a Ca^{2+} imaging system.

METHODS

All experiments were approved and performed in accordance with the Guide for Genetic Modification Safety Committee, National Cancer Center, Japan.

Materials

The following reagents were used in the present study: fura-2 acetoxymethyl ester (Dojindo Laboratories, Kumamoto, Japan); fetal bovine serum and 0.25% trypsin-EDTA (Gibco, Carlsbad, CA); blasticidin S and zeocin (Invitrogen, Carlsbad, CA); AITC and Dulbecco's modified Eagle medium (Nacalai Tesque, Kyoto, Japan); capsaicin, penicillin/streptomycin, and poly-D-lysine (Sigma-Aldrich, St. Louis, MO); and tetracycline (Wako Pure Chemical Industries, Osaka, Japan). Tramadol and M1 were kindly provided by Nippon Shinyaku (Kyoto, Japan). All other reagents were of the highest purity available from commercial sources.

Cell Culture

All experiments were performed using HEK293 cells stably expressing hTRPV1 or hTRPA1, which were prepared using the tetracycline-inducible T-Rex™ expression system (Invitrogen). The cDNAs for hTRPV1 and hTRPA1 were amplified by reverse-transcriptase polymerase chain reaction using mRNAs obtained from OriGene Technologies (Rockville, MD; NM_018727 for hTRPV1 and NM_007332 for hTRPA1). The cDNAs were subcloned into pcDNA4/TO (Invitrogen) and then transfected into HEK-T-Rex cells using Lipofectamine 2000 (Invitrogen). HEK T-Rex cells that stably maintained the hTRPV1 or hTRPA1 gene were selected using zeocin (100 μg/mL) and blasticidin S (10 μg/mL) and were grown in Dulbecco's modified Eagle medium supplemented with 10% fetal bovine serum, penicillin (100 U/mL), and streptomycin (100 mg/mL) at 37°C in a humidified atmosphere of 95% air and 5% CO_2. The cells were treated with tetracycline (1 μg/mL) the day before experiments to induce the expression of hTRPV1 and hTPRA1, which was confirmed by Western blot analysis using an anti-TRPV1 rabbit antibody (Abcam, Cambridge, UK) and an anti-TRPA1 mouse antibody (Abgent, San Diego, CA).

Measurement of $[Ca^{2+}]_i$ in hTRPV1 or hTRPA1-Expressing HEK293 Cells

The measurement of $[Ca^{2+}]_i$ was performed using a method described previously.[40] The cells were plated into glass-bottom dishes (diameter, 35 mm; Greiner Bio-One, Frickenhausen, Germany) precoated with poly-D-lysine (50 μg/mL) at a density of 1.6×10^5 cells/dish the day before the assay. To obtain hTRPV1-expressing or hTRPA1-expressing HEK293 cells, 1 μg/mL of tetracycline was added to the growth medium to induce the expression of either the hTRPV1 or hTRPA1 protein. All experiments were performed in Hanks balanced salt solution (1.3 mM $CaCl_2{\cdot}2H_2O$, 0.81 mM $MgSO_4$, 5.4 mM KCl, 0.44 mM KH_2PO_4, 4.2 mM $NaHCO_3$, 136.9 mM NaCl, 0.34 mM Na_2HPO_4, and 5.6 mM D-glucose) at room temperature. The cells were loaded with 5 μM of fura-2 acetoxymethyl ester for 20 minutes at 37°C. After washing, the cells were pretreated with tramadol or M1 for 5 minutes at room temperature. Subsequently, these cells were continuously treated with a TRPV1 or TRPA1 agonist, respectively. The fluorescence intensity was measured at excitation wavelengths of 340 and 380 nm and at an emission wavelength of 510 nm. The video image output was digitized using AquaCosmos 2.5 (Hamamatsu Photonics, Shizuoka, Japan). The extent of increase in the fura-2 fluorescence ratio (340/380), which was considered as relative and qualitative change of $[Ca^{2+}]_i$, was estimated using the peak value of the fura-2 fluorescence ratio (340/380) after treatment with each reagent.

Electrophysiological Recordings in hTRPV1-Expressing or hTRPA1-Expressing HEK293 Cells

The cells were plated on coverslips precoated with poly-L-lysine (Iwaki, Tokyo, Japan). The coverslips were transferred to the recording chamber[41] and kept in a perfusion solution (140 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 2 mM $MgCl_2{\cdot}6H_2O$, 10 mM glucose, and 10 mM HEPES; pH 7.4 with NaOH). The volume of the recording chamber was 1 mL, and the perfusion rate was 1.4 mL/min. Recording electrodes were triple-pulled using a Flaming/Brown micropipette puller (P-97; Sutter Instrument Co., Novato, CA) from glass capillaries. Patch electrodes were filled with the pipette solution (140 mM K-gluconate, 1 mM $MgCl_2$, 1 mM $CaCl_2$, 10 mM EGTA, and 2 mM adenosine triphosphate-Mg; pH 7.3 with Tris base). Their tip resistance was 5 to 9 MΩ. Patch-clamp experiments were conducted in the tight-seal whole-cell configuration using a MultiClamp 700B apparatus (Axon Instruments, Forster City, CA). Voltage-clamp experiments were performed at a holding potential of −60 mV, and recordings were sampled at 10 kHz and filtered at 2 kHz. Currents were recorded and analyzed using the pCLAMP software (Axon Instruments). The current magnitude was quantified using peak current amplitude in all experiments and normalized to the currents evoked initially by the agonist. Current density (pA/pF) was also measured. In some experiments, reagents were contained in perfusion solution. All patch experiments were performed at room temperature.

Statistical Analysis

The data are presented as the means ± SEM. All data were analyzed using a statistical analysis software SAS v. 9.3. (SAS Institute Inc., Cary, NC). The statistical analysis of all data was performed using the Dunnet method adjusted for unequal variances and unequal sample sizes which is used for multiple comparison tests with the control groups and the simultaneous confidence intervals (CIs). We used SAS Proc Mixed ADJUST=DUNNETT option in LSMEANS statement and the LS-means are correlated; PROC MIXED uses the factor-analytic covariance approximation described in the study by Hsu.[42] In this study, $P < 0.05$ was considered statistically significant.

RESULTS

Neither Tramadol nor Its Metabolite M1 Changed the Capsaicin-Induced Increase in $[Ca^{2+}]_i$ in HEK293 Cells Expressing hTRPV1

Anesthetic modulation of receptor functions often depends on the degree of activation of the receptor.[43] Therefore, we first examined the relation between a TRPV1 agonist capsaicin concentration and Ca^{2+}-mobilizing effects under our experimental conditions (Fig. 1, A and B). In hTRPV1-expressing HEK293 cells, capsaicin rapidly evoked an increase in $[Ca^{2+}]_i$, which gradually decreased (Fig. 1A). As shown in Figure 1B, significant increases in $[Ca^{2+}]_i$ were observed after treatment with capsaicin at 0.1 to 10 μM (vehicle [n = 25] versus capsaicin; 0.01 μM [n = 25]: mean difference, 0.0153 [adjusted 95% CI, −0.039 to 0.1415; P = 0.4470], 0.1 μM [n = 25]: 5.450 [2.516–8.384; P = 0.0001], 1 μM [n = 18]: 18.14 [10.62–25.66; P < 0.0001], 10 μM [n = 21]: 10.99 [5.679–16.30; P < 0.0001]). Conversely, capsaicin at 0.1 μM did not change the level of $[Ca^{2+}]_i$ in HEK293 cells not expressing hTRPV1 (Fig. 1A), suggesting that capsaicin specifically elicited an increase in $[Ca^{2+}]_i$ via hTRPV1. Based on these results, 0.1 μM capsaicin was used for the activation of hTRPV1 in further investigations examining the effects of tramadol and of its metabolite M1.

In such experimental conditions, we investigated the effects of tramadol and M1 (both at 0.01–10 μM) on hTRPV1 activity. As shown in Figure 2, A–E, treatment with tramadol or M1 alone did not induce an increase in $[Ca^{2+}]_i$ in HEK293 cells expressing hTRPV1, when compared with the capsaicin-induced increase in $[Ca^{2+}]_i$ (vehicle [n = 35] versus tramadol; 0.01 μM [n = 21]: mean difference, −0.04432 [adjusted 95% CI, −0.07746 to −0.01119; P = 0.0061], 0.1 μM [n = 44]: −0.01345 [−0.05059 to 0.02369; P = 0.7522], 1 μM [n = 13]: −0.05069 [−0.09150 to −0.00989; P = 0.0114], 10 μM [n = 13]: −0.05175 [−0.08693 to −0.1656; P = 0.0025]), and (vehicle [n = 35] versus M1; 0.01 μM [n = 33]: mean difference, −0.02915 [adjusted 95% CI, −0.06308 to 0.004738; P = 0.1133], 0.1 μM [n = 30]: −0.02334 [−0.06230 to 0.01562; P = 0.3857], 1 μM [n = 40]: −0.03536 [−0.07150 to 0.000783; P = 0.0571], 10 μM [n = 42]: 0.03407 [−0.02830 to 0.09644; P = 0.4694]). After pretreatment with tramadol or M1 for 5 minutes, the cells were subsequently stimulated with capsaicin; tramadol and M1 did not significantly change the capsaicin-induced increase in $[Ca^{2+}]_i$ (capsaicin [n = 35] versus tramadol + capsaicin; 0.01 μM [n = 21]: 0.5269 [adjusted 95% CI, −0.5226 to 1.5764; P = 0.7519], 0.1 μM [n = 44]: 0.7414 [−0.05685 to 1.5398; P = 0.2408], 1 μM [n = 13]: 0.03142 [−0.8325 to 0.8953; P = 1.0000], 10 μM [n = 41]: 0.9992 [−0.8554 to 1.0535; P = 0.9992]) and (capsaicin [n = 35] versus M1 + capsaicin; 0.01 μM [n = 31]: mean difference, 0.4116 [adjusted 95% CI, −0.1511 to 0.9742; P = 0.4114], 0.1 μM [n = 24]: 0.4756 [−0.03394 to 0.9852, P = 0.2059], 1 μM [n = 40]: 0.07118 [−0.4801 to 0.6225; P = 0.9971], 10 μM [n = 42]: −0.07219 [−1.1282 to 0.9839; P = 0.9998]). We also examined the pretreatment time of tramadol (Fig. 2F); however, regardless of the treatment time, tramadol did not change the capsaicin-induced increase in $[Ca^{2+}]_i$ (capsaicin [n = 35] versus tramadol + capsaicin; 30 seconds [n = 6]: mean difference, 1.6852 [adjusted 95% CI, −1.2125 to 4.5830; P = 0.2942], 5 minutes [n = 40]: 0.08914 [−1.1504 to 1.3287; P = 0.9788]).

A previous study reported that tramadol activates TRPV1 and causes an increase in $[Ca^{2+}]_i$ in Chinese hamster ovary (CHO) cells expressing rat TRPV1 (rTRPV1).[39] Therefore, we investigated the effects of tramadol (1 μM) on the activity of rTRPV1 in HEK293 cells expressing rTRPV1. As shown in Figure 3, tramadol changed neither the basal $[Ca^{2+}]_i$ level (vehicle [n = 42] versus tramadol; 0.1 μM [n = 95]: mean difference, 0.004123 [adjusted 95% CI, −0.00378 to 0.01203; P = 0.4404], 1 μM [n = 57]: 0.007512 [−0.00258 to 0.01761; P = 0.1841], 10 μM [n = 52]: −0.00081 [−0.00843 to 0.006817; P = 0.9866]) nor the capsaicin-induced increase in $[Ca^{2+}]_i$ (capsaicin [n = 42] versus tramadol + capsaicin; 0.1 μM [n = 95]: mean difference, 0.2889 [adjusted 95% CI, −0.9173 to 1.4952; P = 0.8801], 1 μM [n = 57]: 0.09926 [−1.7421 to 1.9406; P = 0.9982], 10 μM [n = 52]: −0.3479 [−1.4030 to 0.7072; P = 0.7518]) in rTRPV1-expressing HEK293 cells. These data were similar to those obtained with HEK293 cells expressing hTRPV1.

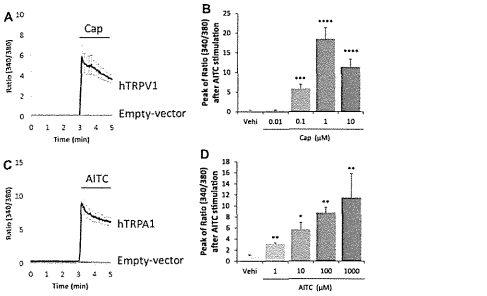

Figure 1. Changes of the fura-2 fluorescence ratio in human transient receptor potential vanilloid 1 (hTRPV1)-expressing or human transient receptor potential ankyrin 1 (hTRPA1)-expressing human embryonic kidney 293 (HEK293) cells stimulated with each agonist. A, Changes of the fura-2 fluorescence ratio (340/380) by treatment with capsaicin in HEK293 cells expressing hTRPV1 or empty-vector, respectively. The fura-2-loaded cells expressing empty-vector or hTRPV1 were treated with 0.1 μM capsaicin (Cap, A) in Hank's balanced salt solution, respectively. B, Concentration-response relationship for the increase in the fura-2 fluorescence ratio (340/380) induced by Cap. C, Changes of the fura-2 fluorescence ratio (340/380) by treatment with 100 μM allyl isothiocyanate (AITC) in HEK293 cells expressing hTRPA1 or empty-vector, respectively. D, Concentration-response relationship for the increase in the fura-2 fluorescence ratio (340/380) induced by AITC. The extent of increase in the fura-2 fluorescence ratio (340/380) induced by capsaicin (B) or AITC (C) was estimated using the peak value of the fura-2 fluorescence ratio (340/380) after treatment with each agonist. The data are expressed as the means ± SEM (bars). *P < 0.05, **P < 0.01, ***P < 0.001, and ****P < 0.0001 compared with the value observed in cells treated with vehicle alone.

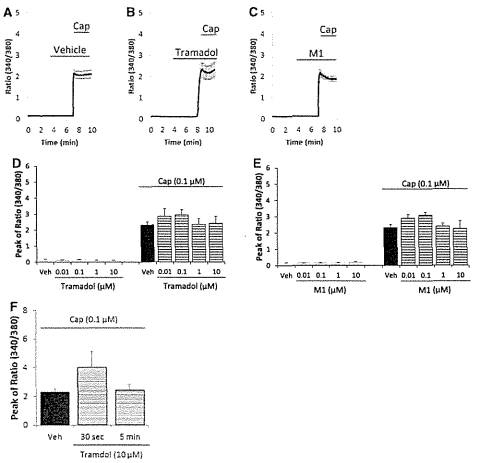

Figure 2. Effects of tramadol and M1 on the human transient receptor potential vanilloid 1 (hTRPV1) channels. A–C, Changes of the fura-2 fluorescence ratio (340/380) in hTRPV1-expressing cells. The fura-2-loaded cells were treated with vehicle (A), 1 μM tramadol (B), or 1 μM M1 (C) and were then stimulated with 0.1 μM capsaicin (Cap). D and E, Effects of tramadol (D) or M1 (E) at a concentration range of 0.01–10 μM on the Cap-induced increase in the fura-2 fluorescence ratio (340/380). F, Effects of pretreatment duration of 10 μM tramadol on the Cap-induced increase in the fura-2 fluorescence ratio (340/380). The extent of increase in the fura-2 fluorescence ratio (340/380) was estimated using the peak value of the fura-2 fluorescence ratio (340/380) after treatment with each reagent. The data are expressed as the means ± SEM (bars).

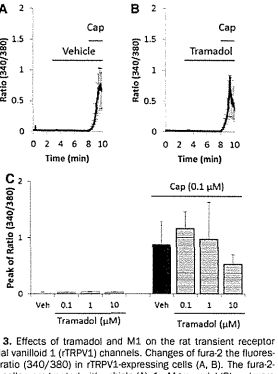

Figure 3. Effects of tramadol and M1 on the rat transient receptor potential vanilloid 1 (rTRPV1) channels. Changes of fura-2 the fluorescence ratio (340/380) in rTRPV1-expressing cells (A, B). The fura-2-loaded cells were treated with vehicle (A), 1 μM tramadol (B) and were then stimulated with 0.1 μM capsaicin (Cap). C, Effects of tramadol at a concentration range of 0.1–10 μM on the Cap-induced increase in the fura-2 fluorescence ratio (340/380). The extent of increase in the fura-2 fluorescence ratio (340/380) was estimated using the peak value of the fura-2 fluorescence ratio (340/380) after treatment with each reagent. The data are expressed as the means ± SEM (bars).

Both Tramadol and M1 Suppressed the AITC-Induced hTRPA1 Activation in hTRPA1-Expressing HEK293 Cells

The effects of AITC (a TRPA1 agonist) on intracellular Ca^{2+} mobilization were examined in hTRPA1-expressing HEK293 cells. As shown in Figure 1C, AITC at 100 μM significantly evoked an increase in $[Ca^{2+}]_i$ in hTRPA1-expressing cells, but not induce any significant change in cells that did not express hTRPA1. In addition, AITC at 1 to 1000 μM concentrations induced an increase in $[Ca^{2+}]_i$ in a dose-dependent manner (vehicle [n = 4] versus AITC; 1 μM [n = 7]: mean difference, 2.3044 [adjusted 95% CI, 1.1436–3.4652; P = 0.0024], 10 μM [n = 3]: 4.8832 [0.4631–9.3033; P = 0.0338], 100 μM [n = 49]: 7.9164 [4.4159–11.4168; P = 0.0012], 1000 μM [n = 19]: 10.6265 [4.0445–17.2084; P = 0.0064]) (Fig. 1D). These data suggest that AITC stimulates TRPA1 to elicit increases in $[Ca^{2+}]_i$. Based on these results, AITC at 100 μM was used for further investigation of the effects of tramadol and M1 on hTRPA1 activation.

Compared with the AITC-induced increase in $[Ca^{2+}]_i$, treatment with tramadol and M1 alone did not induce a dose-dependent and large change of $[Ca^{2+}]_i$, although some doses of tramadol (0.01 and 0.1 μM) and M1 (0.1 and 10 μM) induced a slight increase in $[Ca^{2+}]_i$ (Fig. 4, A–E) (vehicle [n = 39] versus tramadol; 0.01 μM [n = 26]: mean difference, 0.07868 [adjusted 95% CI, 0.005530–0.1518; P = 0.0321], 0.1 μM [n = 9]: 0.1084 [0.01248–0.2044; P = 0.0231], 1 μM [n = 34]: 0.06218 [−0.00328 to 0.1276; P = 0.0665], 10 μM [n = 22]: 0.1162 [−0.01781 to 0.2502; P = 0.1048]) and (vehicle [n = 39] versus M1; 0.01 μM [n = 18]: mean difference, 0.06010 [adjusted 95% CI, −0.01300 to 0.1332; P = 0.1266], 0.1 μM [n = 17]: 0.06638 [0.005024–0.1277; P = 0.0317], 1 μM [n = 60]: 0.05474 [−0.00065 to 0.1547; P = 0.0533], 10 μM [n = 7]: 0.08693 [0.01911–0.1547; P = 0.0099]). In contrast, pretreatment with tramadol for 5 minutes dose dependently suppressed the AITC-induced increase in $[Ca^{2+}]_i$ (AITC [n = 39] versus tramadol + AITC; 0.01 μM [n = 26]: mean difference, −1.3038 [adjusted 95% CI, −3.1056 to 0.4980; P = 0.1942], 0.1 μM [n = 9]: −2.9075 [−5.0443 to −0.7707; P = 0.0055], 1 μM [n = 34]: −2.2820 [−3.9133 to −0.6508; P = 0.0043], 10 μM [n = 22]: −2.8138 [−4.5441 to −1.0835; P = 0.0009]) (Fig. 4D). M1 also inhibited the increase in $[Ca^{2+}]_i$ evoked by AITC in a dose-dependent manner (Fig. 4E); at concentrations of 1 and 10 μM, M1 significantly attenuated the AITC-induced $[Ca^{2+}]_i$ increase, respectively (AITC [n = 39] versus M1 + AITC; 0.01 μM [n = 18]: mean difference, −0.6108 [−2.7631 to 1.5415; P = 0.7912], 0.1 μM [n = 18]: −1.4498 [−3.1421 to 0.2425; P = 0.1032], 1 μM [n = 27]: −2.1736 [−3.7670 to −0.5802; P = 0.0059], 10 μM [n = 7]: −2.7950 [adjusted 95% CI, −4.4650 to −1.1249; P = 0.0007]). However, pretreatment with tramadol for 30 seconds did not change the capsaicin-induced increase in $[Ca^{2+}]_i$ (Fig. 4F), suggesting tramadol pretreatment was necessary for at least 5 minutes to inhibit the hTRPA1 activation (AITC [n = 39] versus tramadol + AITC; 30 seconds [n = 15]: mean difference, −0.3107 [adjusted 95% CI, −5.5114 to 4.8901; P = 0.9867], 5 minutes [n = 21]: −2.8138 [adjusted 95% CI, −4.5227 to −1.1049; P = 0.0014]).

To further elucidate the influence of tramadol and M1 on AITC-induced hTRPA1 activation, we measured the AITC-evoked inward currents using a whole-cell patch-clamp technique. Treatment with AITC at 100 μM for 20 seconds elicited rapid inward currents (−1.0 ± 0.39 nA), which returned toward the basal level within 2 to 3 minutes. After a 20 minutes washing interval, it was confirmed that the response to AITC was recovered (data not shown). Therefore, the inward currents initially elicited by AITC were regarded as a control response. Subsequently, we elucidated the effects of tramadol and M1 at 20 minutes after first stimulation. Treatment with tramadol and M1 alone did not change the basal current in HEK293 cells expressing hTRPA1 (Fig. 5, A and B). Conversely, as shown in Figure 5, C and D, pretreatment with tramadol and the M1 metabolite for 5 minutes inhibited the AITC-induced inward currents (AITC [n = 5] versus tramadol + AITC [n = 3]; mean difference, −91.9667 [adjusted 95% CI, −172.83 to −11.1056; P = 0.0339], AITC [n = 5] versus M1 + AITC [n = 3]; −88.3184 [−168.89 to −7.7515; P = 0.0378]). The AITC-induced current density was also decreased by tramadol treatment (AITC [n = 7] versus tramadol + AITC [n = 3]; mean difference, 52.6905 [4.7303–100.65; P = 0.0361]) and M1 (AITC [n = 7] versus M1+AITC [n = 3]; mean difference, 48.3381 [adjusted 95% CI, 0.1604–96.5158; P = 0.0494]) (Fig. 5, E and F).

DISCUSSION

In clinical practice, tramadol has analgesic effects on various types of pain, such as cancer pain or postoperative pain.[17–19] Many studies using animal models have shown that some of these types of pain are associated with TRP channel activation.[31–38] The results of the present study showed that

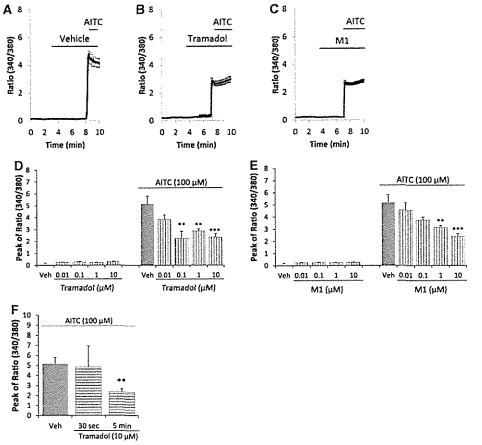

Figure 4. Effects of tramadol and M1 on the human transient receptor potential ankyrin 1 (hTRPA1) channels. A–C, Changes of the fura-2 fluorescence ratio (340/380) in hTRPA1-expressing cells. The fura-2-loaded cells were treated with vehicle (A), 1 μM tramadol (B), or 1 μM M1 (C) and then were stimulated with 100 μM allyl isothiocyanate (AITC). D and E, Effects of tramadol (D) or M1 (E) at a concentration range of 0.01–10 μM on the AITC-induced increase in the fura-2 fluorescence ratio (340/380). The results of Shapiro-Wilk test for each group (vehicle, Tramadol: 0.01, 0.1, 1, and 10 μM) are $P = 0.0548$, 0.1682, 0.2208, 0.2566, and 0.2689, respectively. F, Effects of pretreatment duration of 10 μM tramadol on the AITC-induced increase in the fura-2 fluorescence ratio (340/380). The data are expressed as the means ± SEM (bars). The extent of increase in the fura-2 fluorescence ratio (340/380) was estimated using the peak value of the fura-2 fluorescence ratio (340/380) after treatment with each reagent. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ compared with the value observed cells treated with AITC alone.

tramadol and its metabolite M1 inhibited the function of hTRPA1, but not that of hTRPV1, at a concentration of 0.1 to 10 μM. According to Lintz et al.,[25] the concentration of tramadol in human serum reaches 612.7 ± 221 ng/mL (approximately 2 μM) after IV injection of 100 mg, which could be used for a clinical dosage. Accordingly, the concentrations of tramadol and M1 (up to 10 μM) used in the present study may reflect concentrations that can be used in human clinical practice. These data suggest that both tramadol and M1 act as inhibitors of TRPA1 in patients taking tramadol clinically.

One difference between TRPV1 and TRPA1 regarding their activation is temperature. TRPV1 is activated by heat (>43°C), whereas TRPA1 is activated by cold (<17°C). Ta et al.[41] have demonstrated that TRPV1 is involved in heat hyperalgesia, but not in cold hyperalgesia, induced by the anticancer drug cisplatin. Nassini et al.[45] also have shown that the TRPA1 antagonist HC-030031 decreases cold hyperalgesia induced by the anticancer drug oxaliplatin, indicating that cold and heat hyperalgesia may be regulated by TRPA1 and TRPV1, respectively. Conversely, tramadol was effective against cold hyperalgesia but did not produce antihyperalgesic effects on capsaicin-induced nociceptive responses in a mouse model of post-traumatic trigeminal neuropathic pain.[46] In healthy volunteers, tramadol at 100 mg significantly reduced menthol (an agonist of TRPA1 and TRPM8)-evoked cold hyperalgesia although the effects of the nonsteroidal anti-inflammatory drug ibuprofen (600 mg) and the anticonvulsant/analgesic adjuvant pregabalin (100 mg) were not as significant.[47] These data are in accordance with our data: the antinociceptive effects of tramadol and M1 on cold hyperalgesia may depend on inhibition of TRPA1 activity.

The presence of a methyl group ($-CH_3$) or hydroxyl group (-OH) constitutes the differences in chemical structure between tramadol and M1. Grond et al.[48] showed that the therapeutic (minimal effective) serum concentration of tramadol (2.0 ± 1.4 μM) is 7 times greater than that of its metabolite M1 (0.29 ± 0.12 μM). In this study, significant inhibition by tramadol was observed at 0.1 to 10 μM, whereas that exerted by M1 was observed at 1 to 10 μM (Fig. 4, D and E), suggesting that tramadol rather than M1 is important for the regulation of TRPA1 functions. In addition, we showed previously that tramadol inhibits the function of muscarinic M3 receptors, which are central nervous system targets of analgesic drugs, whereas M1 had little effect on the function of M3 receptors.[49] Conversely, Gillen et al.[50] showed that M1 had 300 to 400 times greater affinity for opioid receptors than did the parent compound tramadol. Collectively, these data suggest that this small structural difference between tramadol and M1 might play an important role in regulating pain-related receptors or channels. In the pain produced by TRPA1 activation, such as cancer pain and neuropathic pain, the inhibitory effect of tramadol on TRPA1 activation might be at least one of the mechanisms underlying tramadol-induced analgesic actions.

In our present study, we investigated the pretreatment time of tramadol on the activation of both TRPV1 and TRPA1. Interestingly, pretreatment with tramadol for 5 minutes significantly suppressed the AITC-induced increase in $[Ca^{2+}]_i$, but not that for 30 seconds in hTRPA1-expressing HEK293 cells (Fig. 4F). These data indicated that at least 5-minute pretreatment was required for the inhibition of TRPA1 activation, suggesting that it would be unlikely that tramadol had direct antagonistic effects on TRPA1. In other words, the mechanism of these inhibitory effects seems to be involved in some metabolic changes, such as changes in intracellular signaling. Some reports revealed that the activation of TRPA1 was regulated by changing the intracellular signaling, such as protein kinase A.[51,52] It might be possible that tramadol inhibits the activation of TRPA1 by regulating intracellular signaling, such as protein kinase A, although further study is needed to reveal the inhibitory mechanisms.

In contrast, Marincsák et al.[39] have shown that tramadol directly activated TRPV1 and led to an increase in $[Ca^{2+}]_i$, which was not consistent with our present results. The present study was performed in HEK293 cells expressing hTRPV1, whereas the study reported by Marincsák et al.[39] was performed in CHO cells expressing rTRPV1. Therefore, we examined the effects of tramadol on the activity of rTRPV1 using rTRPV1-expressing HEK293 cells. However, tramadol alone did not cause any increase in $[Ca^{2+}]_i$ (Fig. 3). In addition, tramadol did not affect the capsaicin-induced increase in $[Ca^{2+}]_i$ (Fig. 3) as well as hTRPV1-expressing HEK293 cells. These data suggest a possibility that the reason for this discrepancy between the study reported by Marincsák et al.[39] and our study might have been the differences of cell line expressing TRPV1 (CHO versus HEK293), rather than different species. Several reports have indicated that differences of cell lines had effects on the function of TRP channels. For example, Veldhuis et al.[53] reported that *N*-glycosylation regulated inactivation and ion selectivity of TRPV1. Go et al.[54] showed that there were specific glycosylation profiles between CHO and HEK293T cells. These data suggest that differences of glycosylation between CHO and HEK293 cells might be one of the keys demonstrating the conflict between previous reports and ours. However, further experiments could be required to settle this issue.

In conclusion, our results indicate that tramadol and its metabolite M1 inhibit the functions of TRPA1, but not those of TRPV1. These observations provide valuable new insights regarding the explanation of one of the pharmacological properties of tramadol.

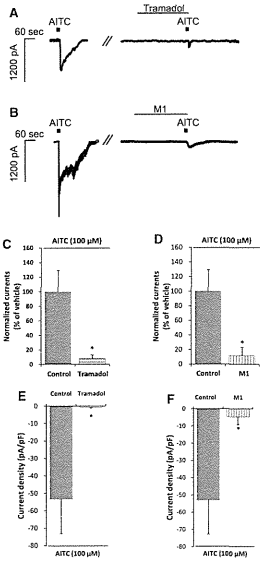

Figure 5. Effects of tramadol and M1 on the inward currents induced by allyl isothiocyanate (AITC). A and B, Representative tracings of the currents in human transient receptor potential ankyrin 1 (hTRPA1)-expressing human embryonic kidney 293 (HEK293) cells that was voltage-clamped at −60 mV. The cells were stimulated with 100 μM AITC for 20 seconds. After a 20-minute washing interval, the inward currents induced by AITC were completely recovered to the basal level. Tramadol (10 μM, A) and M1 (10 μM, B) were preapplied for 5 minutes before and during AITC application for 20 seconds. Currents were normalized to the currents evoked by AITC alone as a control (C, D). C, AITC ($n = 5$) versus Tramadol + AITC ($n = 3$); $P = 0.0339$. The results of Shapiro-Wilk test for each group are $P = 0.3609$ and 0.6286. D, AITC ($n = 5$) versus M1 + AITC ($n = 3$); $P = 0.0378$. The results of Shapiro-Wilk test for each group are $P = 0.3604$ and 0.7664. Current density (pA/pF) was also measured (E, F). E, AITC ($n = 7$) versus Tramadol + AITC ($n = 3$); $P = 0.0361$. The results of Shapiro-Wilk test for each group are $P = 0.1058$ and 0.3914. F, AITC ($n = 7$) versus M1 + AITC ($n = 3$); $P = 0.0494$. The results of Shapiro-Wilk test for each group are $P = 0.0911$ and 0.0629. The data are expressed as the means ± SEM (bars). *$P < 0.05$ compared with the value observed in cells treated with AITC alone.

DISCLOSURES

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Attestation: Kanako Miyano approved the final manuscript. She attests to the integrity of the original data and the analysis reported in this manuscript. She is also the archival author.
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Contribution: This author helped prepare the manuscript and conduct the study.
Attestation: Yasuhito Uezono approved the final manuscript. He attests to the integrity of the original data and the analysis reported in this manuscript.
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REFERENCES

1. García-Añoveros J, Nagata K. TRPA1. Handb Exp Pharmacol 2007;179:347–62
2. Spicarová D, Palecek J. The role of spinal cord vanilloid (TRPV1) receptors in pain modulation. Physiol Res 2008;57 Suppl 3:S69–77
3. Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997;389:816–24
4. Tominaga M, Caterina MJ, Malmberg AB, Rosen TA, Gilbert H, Skinner K, Raumann BE, Basbaum AI, Julius D. The cloned capsaicin receptor integrates multiple pain-producing stimuli. Neuron 1998;21:531–43
5. Hwang SW, Cho H, Kwak J, Lee SY, Kang CJ, Jung J, Cho S, Min KH, Suh YG, Kim D, Oh U. Direct activation of capsaicin receptors by products of lipoxygenases: endogenous capsaicin-like substances. Proc Natl Acad Sci U S A 2000;97:6155–60
6. Kobayashi K, Fukuoka T, Obata K, Yamanaka H, Dai Y, Tokunaga A, Noguchi K. Distinct expression of TRPM8, TRPA1, and TRPV1 mRNAs in rat primary afferent neurons with adelta/c-fibers and colocalization with trk receptors. J Comp Neurol 2005;493:596–606
7. Jordt SE, Bautista DM, Chuang HH, McKemy DD, Zygmunt PM, Högestätt ED, Meng ID, Julius D. Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. Nature 2004;427:260–5
8. McNamara CR, Mandel-Brehm J, Bautista DM, Siemens J, Deranian KL, Zhao M, Hayward NJ, Chong JA, Julius D, Moran MM, Fanger CM. TRPA1 mediates formalin-induced pain. Proc Natl Acad Sci U S A 2007;104:13525–30
9. Bessac BF, Sivula M, von Hehn CA, Escalera J, Cohn L, Jordt SE. TRPA1 is a major oxidant sensor in murine airway sensory neurons. J Clin Invest 2008;118:1899–910
10. Sawada Y, Hosokawa H, Matsumura K, Kobayashi S. Activation of transient receptor potential ankyrin 1 by hydrogen peroxide. Eur J Neurosci 2008;27:1131–42
11. Bautista DM, Jordt SE, Nikai T, Tsuruda PR, Read AJ, Poblete J, Yamoah EN, Basbaum AI, Julius D. TRPA1 mediates the inflammatory actions of environmental irritants and proalgesic agents. Cell 2006;124:1269–82
12. Oshita K, Inoue A, Tang HB, Nakata Y, Kawamoto M, Yuge O. CB(1) cannabinoid receptor stimulation modulates transient receptor potential vanilloid receptor 1 activities in calcium influx and substance P release in cultured rat dorsal root ganglion cells. J Pharmacol Sci 2005;97:377–85
13. Tang HB, Nakata Y. Olopatadine attenuates the enhancement of capsaicin-evoked substance P release by bradykinin from cultured dorsal root ganglion neurons. Eur J Pharmacol 2006;552:78–82
14. Tang HB, Li YS, Miyano K, Nakata Y. Phosphorylation of TRPV1 by neurokinin-1 receptor agonist exaggerates the capsaicin-mediated substance P release from cultured rat dorsal root ganglion neurons. Neuropharmacology 2008;55:1405–11
15. Tang HB, Nakata Y. The activation of transient receptor potential vanilloid receptor subtype 1 by capsaicin without extracellular Ca^{2+} is involved in the mechanism of distinct substance P release in cultured rat dorsal root ganglion neurons. Naunyn Schmiedebergs Arch Pharmacol 2008;377:325–32
16. Nakamura Y, Une Y, Miyano K, Abe H, Hisaoka K, Morioka N, Nakata Y. Activation of transient receptor potential ankyrin 1 evokes nociception through substance P release from primary sensory neurons. J Neurochem 2012;120:1036–47
17. Husslein P, Kubista E, Egarter C. [Obstetrical analgesia with tramadol—results of a prospective randomized comparative study with pethidine]. Z Geburtshilfe Perinatol 1987;191:234–7
18. Kupers R, Callebaut V, Debois V, Camu F, Verborgh C, Coppejans H, Adriaensen H. Efficacy and safety of oral tramadol and pentazocine for postoperative pain following prolapsed intervertebral disc repair. Acta Anaesthesiol Belg 1995;46:31–7
19. Leppert W, Luczak J. The role of tramadol in cancer pain treatment—a review. Support Care Cancer 2005;13:5–17
20. Raffa RB, Friderichs E, Reimann W, Shank RP, Codd EE, Vaught JL. Opioid and nonopioid components independently contribute to the mechanism of action of tramadol, an 'atypical' opioid analgesic. J Pharmacol Exp Ther 1992;260:275–85
21. Driessen B, Reimann W, Giertz H. Effects of the central analgesic tramadol on the uptake and release of noradrenaline and dopamine in vitro. Br J Pharmacol 1993;108:806–11
22. Houmes RJ, Voets MA, Verkaaik A, Erdmann W, Lachmann B. Efficacy and safety of tramadol versus morphine for moderate and severe postoperative pain with special regard to respiratory depression. Anesth Analg 1992;74:510–4
23. Vickers MD, O'Flaherty D, Szekely SM, Read M, Yoshizumi J. Tramadol: pain relief by an opioid without depression of respiration. Anaesthesia 1992;47:291–6
24. Preston KL, Jasinski DR, Testa R. Abuse potential and pharmacological comparison of tramadol and morphine. Drug Alcohol Depend 1991;27:7–17
25. Lintz W, Erlaçin S, Frankus E, Uragg H. Biotransformation of tramadol in man and animal. Arzneimittelforschung 1981;31:1932–43
26. Hennies HH, Friderichs E, Schneider J. Receptor-binding, analgesic and antitussive potency of tramadol and other selected opioids. Arzneimittelforschung 1988;38-2:877–80
27. Shiga Y, Minami K, Shiraishi M, Uezono Y, Murasaki O, Kaibara M, Shigematsu A. The inhibitory effects of tramadol on muscarinic receptor-induced responses in Xenopus oocytes expressing cloned M-3 receptors. Anesth Analg 2002;95:1269–73
28. Ogata J, Minami K, Uezono Y, Okamoto T, Shiraishi M, Shigematsu A, Ueta Y. The inhibitory effects of tramadol on 5-hydroxytryptamine type 2C receptors expressed in Xenopus oocytes. Anesth Analg 2004;98:1401–6
29. Hara K, Minami K, Sata T. The effects of tramadol and its metabolite on glycine, gamma-aminobutyric acid A, and *N*-methyl-D-aspartate receptors expressed in Xenopus oocytes. Anesth Analg 2005;100:1400–5
30. Horishita T, Minami K, Uezono Y, Shiraishi M, Ogata J, Okamoto T, Shigematsu A. The tramadol metabolite, O-desmethyl tramadol, inhibits 5-hydroxytryptamine type 2C receptors expressed in *Xenopus* Oocytes. Pharmacology 2006;77:93–9
31. Ghilardi JR, Röhrich H, Lindsay TH, Sevcik MA, Schwei MJ, Kubota K, Halvorson KG, Poblete J, Chaplan SR, Dubin AE, Carruthers NI, Swanson D, Kuskowski M, Flores CM, Julius D, Maniyth PW. Selective blockade of the capsaicin receptor TRPV1 attenuates bone cancer pain. J Neurosci 2005;25:3126–31
32. Kissin I, Davison N, Bradley EL Jr. Perineural resiniferatoxin prevents hyperalgesia in a rat model of postoperative pain. Anesth Analg 2005;100:774–80
33. Pospisilova E, Palecek J. Post-operative pain behavior in rats is reduced after single high-concentration capsaicin application. Pain 2006;125:233–43
34. Shinoda M, Ogino A, Ozaki N, Urano H, Hironaka K, Yasui M, Sugiura Y. Involvement of TRPV1 in nociceptive behavior in a rat model of cancer pain. J Pain 2008;9:687–99
35. Wu C, Gavva NR, Brennan TJ. Effect of AMG0347, a transient receptor potential type V1 receptor antagonist, and morphine on pain behavior after plantar incision. Anesthesiology 2008;108:1100–8
36. Chen Y, Yang C, Wang ZJ. Proteinase-activated receptor 2 sensitizes transient receptor potential vanilloid 1, transient receptor potential vanilloid 4, and transient receptor potential ankyrin 1 in paclitaxel-induced neuropathic pain. Neuroscience 2011;193:440–51
37. Barrière DA, Rieusset J, Chanteranne D, Busserolles J, Chauvin MA, Chapuis L, Salles J, Dubray C, Morio B. Paclitaxel therapy potentiates cold hyperalgesia in streptozotocin-induced diabetic rats through enhanced mitochondrial reactive oxygen species production and TRPA1 sensitization. Pain 2012;153:553–61
38. Wei H, Karimaa M, Korjamo T, Koivisto A, Pertovaara A. Transient receptor potential ankyrin 1 ion channel contributes to guarding pain and mechanical hypersensitivity in a rat model of postoperative pain. Anesthesiology 2012;117:137–48
39. Marincsák R, Tóth BI, Czifra G, Szabó T, Kovács L, Bíró T. The analgesic drug, tramadol, acts as an agonist of the transient receptor potential vanilloid-1. Anesth Analg 2008;106:1890–6
40. Miyano K, Tang HB, Nakamura Y, Morioka N, Inoue A, Nakata Y. Paclitaxel and vinorelbine, evoked the release of substance P from cultured rat dorsal root ganglion cells through different PKC isoform-sensitive ion channels. Neuropharmacology 2009;57:25–32
41. Kabashima N, Shibuya I, Ibrahim N, Ueta Y, Yamashita H. Inhibition of spontaneous EPSCs and IPSCs by presynaptic GABAB receptors on rat supraoptic magnocellular neurons. J Physiol 1997;504 (Pt 1):113–26
42. Hsu JC. The factor analytic approach to simultaneous inference in the general linear model. J Comput Graph Stat 1992;1:151–68
43. Harris RA, Mihic SJ, Dildy-Mayfield JE, Machu TK. Actions of anesthetics on ligand-gated ion channels: role of receptor subunit composition. FASEB J 1995;9:1454–62
44. Ta LE, Bieber AJ, Carlton SM, Loprinzi CL, Low PA, Windebank AJ. Transient Receptor potential vanilloid 1 is essential for cisplatin-induced heat hyperalgesia in mice. Mol Pain 2010;6:15
45. Nassini R, Gees M, Harrison S, De Siena G, Materazzi S, Moretto N, Failli P, Preti D, Marchetti N, Cavazzini A, Mancini F, Pedretti P, Nilius B, Patacchini R, Geppetti P. Oxaliplatin elicits mechanical and cold allodynia in rodents via TRPA1 receptor stimulation. Pain 2011;152:1621–31
46. Alvarez P, Brun A, Labertrandie A, Lopez J, Correa A, Constandil L, Hernández A, Pelissier T. Antihyperalgesic effects of clomipramine and tramadol in a model of posttraumatic trigeminal neuropathic pain in mice. J Orofac Pain 2011;25:354–63
47. Altis K, Schmidtko A, Angioni C, Kuczka K, Schmidt H, Geisslinger G, Lötsch J, Tegeder I. Analgesic efficacy of tramadol, pregabalin and ibuprofen in menthol-evoked cold hyperalgesia. Pain 2009;147:116–21
48. Grond S, Meuser T, Stagg H, Stahlberg HJ, Lehmann KA. Serum concentrations of tramadol enantiomers during patient-controlled analgesia. Br J Clin Pharmacol 1999;48:254–7
49. Nakamura M, Minami K, Uezono Y, Horishita T, Ogata J, Shiraishi M, Okamoto T, Terada T, Sata T. The effects of the tramadol metabolite O-desmethyl tramadol on muscarinic receptor-induced responses in Xenopus oocytes expressing cloned M1 or M3 receptors. Anesth Analg 2005;101:180–6
50. Gillen C, Haurand M, Kobelt DJ, Wnendt S. Affinity, potency and efficacy of tramadol and its metabolites at the cloned human mu-opioid receptor. Naunyn Schmiedebergs Arch Pharmacol 2000;362:116–21
51. Wang S, Dai Y, Fukuoka T, Yamanaka H, Kobayashi K, Obata K, Cui X, Tominaga M, Noguchi K. Phospholipase C and protein kinase A mediate bradykinin sensitization of TRPA1: a molecular mechanism of inflammatory pain. Brain 2008;131:1241–51
52. Chen Y, Yang C, Wang ZJ. Proteinase-activated receptor 2 sensitizes transient receptor potential vanilloid 1, transient receptor potential vanilloid 4, and transient receptor potential ankyrin 1 in paclitaxel-induced neuropathic pain. Neuroscience 2011;193:440–51
53. Veldhuis NA, Lew MJ, Abogadie FC, Poole DP, Jennings EA, Ivanusic JJ, Eilers H, Bunnett NW, McIntyre P. N-glycosylation determines ionic permeability and desensitization of the TRPV1 capsaicin receptor. J Biol Chem 2012;287:21765–72
54. Go EP, Liao HX, Alam SM, Hua D, Haynes BF, Desaire H. Characterization of host-cell line specific glycosylation profiles of early transmitted/founder HIV-1 gp120 envelope proteins. J Proteome Res 2013;12:1223–34

Journal of Neuroscience Methods 239 (2015) 162–169

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

Basic Neuroscience

Novel methods of applying direct chemical and mechanical stimulation to the oral mucosa for traditional behavioral pain assays in conscious rats

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HIGHLIGHTS

- We developed two new methods to apply direct stimulations to the oral mucosa for traditional behavioral pain assays in conscious rats.
- Measurements of facial grooming behavior following application of pungent solutions via the intraoral dropping method enable evaluation of chemically induced nociception in the oral mucosa.
- Measurements of head withdrawal threshold to mechanical stimulations using the stable intraoral opening method enable evaluation of mechanical nociception in the oral mucosa.
- Oral ulcers induced hypersensitivity to pain associated with chemical and mechanical stimulations.

ARTICLE INFO

Article history:
Received 13 August 2014
Received in revised form 17 October 2014
Accepted 18 October 2014
Available online 29 October 2014

Keywords:
Intraoral evoked pain
Oral ulcer
Facial grooming
Head withdrawal threshold to von Frey stimulation
Conscious rats

ABSTRACT

Background: Stomatitis induces severe and painful hypersensitivity to pungency and physical contact during meals. Many studies have used anesthetized animals to examine evoked nociception in the oral mucosa, but no reports have used traditional behavioral assays to evaluate nociception in conscious animals.
New methods: We developed two new methods of applying chemical or mechanical stimulation directly to the oral mucosa of the mandibular vestibule of conscious rats. Nociceptive evaluations were performed by measuring facial grooming time and the head withdrawal threshold to von Frey stimulations. (1) For the intraoral dropping method, rat mucosa was transiently exposed by hand, and a drop of a pungent solution was applied. (2) For the stable intraoral opening method, rat mucosa was long-term exposed following piercing surgery of the mental skin after habitual training for 2–3 weeks.
Results: In the intraoral dropping method, the application of 100 μM capsaicin or 100 mM allyl isothiocyanate prolonged mouth-rubbing time. Capsaicin-induced mouth-rubbing time was further enhanced following the development of an acetic acid-induced ulcer. The stable intraoral opening method enabled stable measurements of the mechanical withdrawal threshold in the oral mucosa of conscious rats. Ulcer development decreased the mechanical threshold, whereas topical lidocaine treatment increased the threshold.
Comparison with existing methods: These new methods enable the evaluations of motivational nocifensive behaviors in response to intraoral stimulations without any anesthetic effects.
Conclusions: The intraoral dropping and stable intraoral opening methods can be used in combination with traditional behavioral assays to evaluate nociception in the oral mucosa of conscious rats.

Abbreviations: SIO, stable intraoral opening; OU, oral ulcer; *i.p.*, intraperitoneally; AITC, allyl isothiocyanate; DMSO, dimethyl sulfoxide; TRP, transient receptor potential; V1, vanilloid 1; A1, ankyrin 1.

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http://dx.doi.org/10.1016/j.jneumeth.2014.10.013
0165-0270/

1. Introduction

In pain research, a variety of behavioral assays have been employed to qualify and quantify nociceptive sensations in experimental animals. Nocifensive behaviors, including grooming-like and withdrawal behaviors, have traditionally been measured as signs of spontaneous and/or evoked nociception in the hind paw and orofacial regions, such as the whisker pad skin (Krzyzanowska and Avendano, 2012). Most facial grooming behaviors, including mouth rubbing (licking) and wiping by the forelimbs, have been used as signs of orofacial pain in models of inflammatory, neuropathic and cancer pain (Chidiac et al., 2002; Clavelou et al., 1989; Harano et al., 2010; Hidaka et al., 2011; Hitomi et al., 2012; Ono et al., 2009; Pelissier et al., 2002; Sago et al., 2012; Shimada and LaMotte, 2008). However, facial scratching by the hind paw is considered to reflect an itch sensation rather than pain (Shimada and LaMotte, 2008). The head withdrawal threshold/latency in the orofacial regions has been used as a measure of evoked pain sensations to mechanical or thermal stimulation in orofacial pain models (Krzyzanowska and Avendano, 2012).

Stomatitis and oral cancer induce severe pain (Lam and Schmidt, 2011; Leao et al., 2007). Oral mucosal pain is triggered by pungent food and physical contact during eating and swallowing (Donnelly et al., 2003; Trotti et al., 2003). Therefore, it is important to understand the mechanisms that underlie chemically or mechanically induced pain in the oral mucosa. Because of the technical difficulties associated with the application of these types of stimulations to the oral mucosa of conscious animals, most intraoral pain studies have used anesthetized rats and electromyograms to measure the head withdrawal reflex following mechanical and/or thermal stimulations (Katagiri et al., 2012; Ohara et al., 2013). Because general anesthetic agents have been reported to affect peripheral nociception and central pain perception (Cornett et al., 2008; Devor and Zalkind, 2001), the results obtained from anesthetized animals are complicated by the potential effects of anesthesia. Recently, several new pain assays have been developed to evaluate intraoral nociception in conscious animals, including measurements of gnawing time, sucrose intake and grimacing (Dolan et al., 2010; Gibbs et al., 2013; Liao et al., 2014). These novel assays have great potential in the evaluation of oral mucosal pain in conscious animals, but special equipment is required to perform these assays. In addition, the results obtained from these assays cannot be directly compared to previously reported results from extra-oral regions using traditional pain assays.

Therefore, in this study, we developed two new methods to directly stimulate the oral mucosa in conscious rats prior to the assessment of traditional behavioral pain assays. One previous study that examined pungency-induced pain in the incisors of rats reported that facial grooming is enhanced following the application of a capsaicin solution into the oral cavity (Chidiac et al., 2002). Based on the results of this study, we first established a new method to directly apply pungent solutions to the oral mucosa of the mandibular vestibule in conscious rats using a plastic dropper (termed the 'intraoral dropping method') and then measured facial grooming behaviors. Because it was impossible to apply mechanical stimulation with von Frey filaments while performing the intraoral dropping method, we subsequently developed a second method to expose the mucosa more stably (termed the 'stable intraoral opening (SIO) method'). Furthermore, to examine whether these methods are available to evaluate pain hypersensitivity in oral mucosal disease, we performed traditional pain assays in an experimental model of oral ulcers (OUs).

2. Materials and methods

2.1. Animals

Male Wistar rats (150–350 g, $n = 100$, Kyudo, Saga, Japan) were used in the present study. The rats were maintained on a light-dark cycle (L:D, 12:12-h) and housed in pairs in a temperature- and humidity-controlled room (22–25 °C and 40–60%) with food and water provided ad libitum. All experiments were conducted in accordance with the National Research Council of the National Academies Guide for the Care and Use of Laboratory Animals (8th edition) and were approved by the Animal Experiment Committee of Kyushu Dental University. All efforts were made to minimize animal suffering. Rats were randomly selected for each experiment.

2.2. Histology

All samples of lower lip tissue, including the oral mucosa and mental skin, were collected from rats that were deeply anesthetized with sodium pentobarbital (100 mg/kg, intraperitoneally (*i.p.*)) following aortic perfusion with 4% paraformaldehyde in 0.1 M phosphate buffer (pH 7.4). The tissues were post-fixed in the same fixative for 1 day at 4 °C. The fixed tissues were subsequently embedded in paraffin, and 5-μm-thick sagittal sections were cut and stained with hematoxylin and eosin.

2.3. Intraoral dropping method

To expose the labial fornix region of the inferior incisors for several seconds, each rat was briefly held in the left hand of the operator, as shown in Fig. 1A. First, both forelimbs of each rat were held between the second and third fingers. The rat's head was then extended to the back using the thumb, and the lower lip was pulled down using the forefinger. A drop of stimulant was administered using a plastic dropper (VECTASTAIN ABC kit; Vector Lab, CA, USA). All rats were acclimated to this procedure by administering drops of distilled water at least three times prior to the behavioral measurements. The method was termed the "intraoral dropping method" in this study. Capsaicin (Wako, Osaka, Japan) and allyl isothiocyanate (AITC; Wako, Osaka, Japan) were used as painful stimulants because they are reliable nociceptive substances. Capsaicin was diluted with dimethyl sulfoxide (DMSO) to make a stock solution and was further diluted to 0.1% with water (10 and 100 μM) just prior to the behavioral assessments. AITC was diluted to 10 or 100 mM with mineral oil (Sigma, MO, USA). The effects of vehicle treatment (0.1% DMSO for capsaicin and 100% mineral oil for AITC) were observed 20 min prior to the application of the pungent solutions. To determine the effects of repetitive application of the pungent solutions on grooming behavior, the rats were observed following the administration of 100 μM capsaicin or 100 mM AITC twice at 20 min intervals in the control rats.

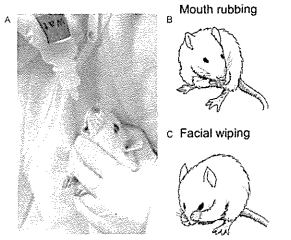

Fig. 1. Intraoral dropping method. (A) A rat was held tightly in the experimenter's left hand, and the forelimbs of the rat were held between the second and third fingers. The rat's head was extended by the experimenter's thumb, and the lower lip was pulled down by the forefinger. The stimuli were placed on the labial fornix region of the inferior incisors using a plastic dropper. (B) Mouth rubbing behavior. (C) Facial wiping behavior.

2.4. Measurements of facial grooming behaviors

In the present study, facial grooming behaviors were divided into two different parameters: (1) mouth rubbing by both forelimbs with licking (Fig. 1B) and (2) facial wiping with one or both forelimbs (Fig. 1C). Animal observations were performed for 3 min to evaluate pungent-evoked nociception and for 10 min to evaluate spontaneous nociception. All studies were conducted between 1:00 and 5:00 pm. All rats were acclimated to the plastic cage (30 cm × 30 cm × 30 cm) that was used for the observations over a period of 3 days (one time per day) prior to the measurements. To examine whether prolonged facial grooming is a nocifensive behavior, one cohort of rats were administered morphine *i.p.* (either 4 or 10 mg/kg dissolved in saline at a final volume of 0.5 ml) 40 min before capsaicin application. As a control for morphine administration, another group of rats received an equivalent volume of saline (saline group). The morphine concentration used and the subsequent timing of the behavioral observations were chosen based on previously published studies (Shimada et al., 2008). The morphine experiment was performed blindly with respect to the drug administration.

2.5. SIO method

To stably expose the oral mucosa in the labial fornix region of the inferior incisors, the mental skin of 5-week-old rat was pierced with a magnetized ring (Fig. 2A); the rats were then trained in the necessary experimental procedures prior to von Frey filament tests (Fig. 2B). The SIO method was carefully developed with considerable trial and error. First, the rats were anesthetized with sodium pentobarbital (50 mg/kg, *i.p.*), and additional local anesthesia was applied to the mental skin (8% lidocaine, Astra Zeneca, Osaka, Japan). A magnetized needle (22-gauge-like size, Daiso Sangyo, Hiroshima, Japan) was used to pierce the mental skin below the rat's lower lip. The needle was then bent into a ring, and the tip of the needle was cut off. One week after the piercing, the rats were trained for 10 min per day to stably protrude their perioral regions through a hole in a hand-made black box (*W*: 6 cm, *L*: 6 cm, *H*: 13 cm), made from plastic rectangular bottle, the so-called restrainer, as previously described (Kobayashi et al., 2011). Importantly, the rats were free to avoid the stimulations if they felt pain. After demonstrating stable behavior in the restrainer (approximately 3–4 days from the initiation of training), the rats were further trained to expose the oral mucosa. A small neodymium magnet, which was attached to a weight by a string (3, 4 and 5 g weights were tried, but 4 g was ultimately used), was attached to the ring that was inserted in the rat's lip, which resulted in a constant vertical pressure on the ring (Fig. 2C). When the rats flicked away and backed away, the magnet was released from the ring without damage to the pierced region. The following intraoral behavioral test was performed after confirming that each rat had adapted to the experimental conditions (approximately 2–3 weeks after the piercing).

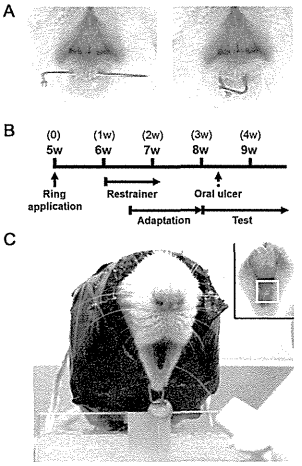

Fig. 2. Stable intraoral opening (SIO) method. (A) Ring application. A magnetized needle (22-gauge-like size) was used to pierce the mental skin below the rat's lower lip (left). The needle was bent into a ring, and the tip of the needle was cut off (right). (B) The method consists of three steps: (1) ring application in 5-week-old rats, (2) training to attain stable behavior in the restrainer and (3) adaptation to stimulation with von Frey filaments 1–2 weeks after ring application. (C) Performing the pain test. The oral mucosa of rats is stably exposed by pulling the lower lip with the magnetic ring, and the exposed oral mucosa is stimulated using von Frey filaments in a black restrainer. The white square in the inset shows the stimulated oral mucosal region.

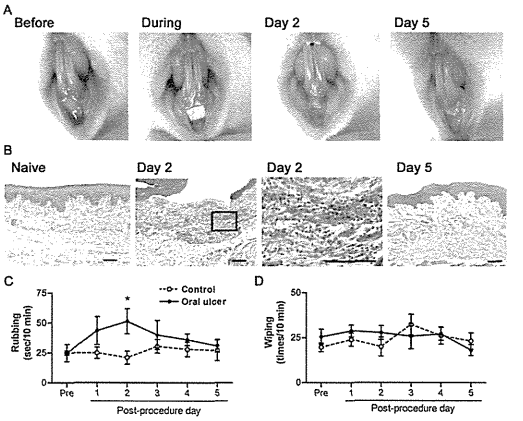

Fig. 3. Oral ulcer (OU) model. (A) Typical images of the oral mucosa in the labial fornix region before, on day 2 and day 5 after 50% acetic acid treatment. (B) Histology of the mucosal region in naive and OU model rats on day 2 and day 5 after acetic acid treatment. Scale bars, 100 μm. Spontaneous rubbing time (C) and the number of wiping (D) during a 10 min period in control and OU model rats. *$P < 0.05$ versus control. Error bars indicate the SEM.

2.6. Measurements of the head withdrawal threshold to mechanical stimulation

In the SIO method, head withdrawal threshold to mechanical stimulation was measured in the oral mucosa using a set of von Frey filaments (0.02, 0.04, 0.07, 0.16, 0.4, 0.6, 1, 2, 4 and 6 g, North Coast Medical, Morgan Hill, CA, USA) to evaluate the mechanical pain threshold. We prepared two hand-made filaments as follows: 0.2 g filament was made by cutting to 3.4 cm from 3.7 cm of a 0.16 g von Frey filament and 0.3 g filament was made by using 4.1 cm of nylon fiber (#3, TOHO, Hiroshima, Japan). The filaments were applied to the labial fornix region of the inferior incisors (Fig. 2C inset). For stimulations of the mucosa, a cut-off of 6 g was established to prevent tissue damage. These measurements were also performed in the whisker pad skin and mental skin. The head withdrawal threshold was defined as the minimum pressure required to evoke an escape attempt in at least 3 of the 5 tests at that pressure. To examine the effects of topical anesthesia on the withdrawal threshold, a small swab soaked with 20 μl lidocaine (8%) was applied to the exposed oral mucosa for 5 min. The thresholds were measured prior to and after the topical anesthetic treatment.

2.7. OU model

OUs were induced in rats using previously described methods (Vilela-Goulart et al., 2008). Eight-week-old rats were anesthetized with sodium pentobarbital (50 mg/kg, *i.p.*). A 9 mm^2 piece of filter paper (3 mm × 3 mm, Whatman, Maidstone, UK) was soaked in 50% acetic acid diluted with water and placed in the labial fornix region of the inferior incisors for 30 s (Fig. 3A). Chemical and mechanical stimulations were applied to acetic acid-induced leukoderma (white area, indicated in Fig. 3A, day 2) in OU model. Behavioral observations were performed before and after the induction of OUs. The control rats received only *i.p.* anesthesia without any treatment. OU rats were housed alone or mixed housed with control rats.

2.8. Analysis

The data are expressed as the mean ± SEM, and *n* represents the number of rats. To analyze spontaneous grooming behavior, a two-way analysis of variance followed by Bonferroni post hoc tests was used to compare the control and the OU model. Student's *t*-tests were used to compare the pungency-evoked grooming behaviors and the grooming behaviors observed following vehicle application in the same animal group (paired) or between different animal groups (unpaired). To evaluate the effects of morphine on capsaicin-evoked grooming behaviors, Dunnett's post hoc tests were used following one-way analysis of variance. To analyze the head withdrawal threshold to von Frey stimulations, Dun's multiple post hoc tests were used following Friedman tests for time course changes in the mental skin after piercing, among examined different pulling weights or different facial regions. Wilcoxon signed rank tests were used to evaluate OU development and the effects of lidocaine. Differences were considered significant at *P* values <0.05.

3. Results

3.1. Characteristics of experimental OUs

To determine the availability of new methods to evaluate intraoral nociception, we prepared an experimental OU model. Fig. 3A shows the typical images of the oral mucosa before, during and after

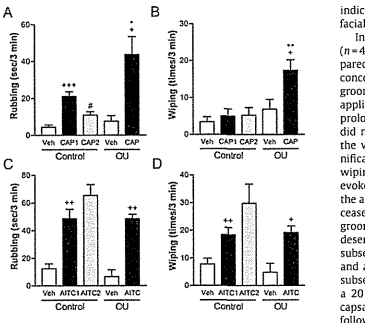

Fig. 4. Evaluation of oral mucosal pain by facial grooming behavior following the intraoral dropping method. The rubbing time (A) and the number of wiping (B) during a 3 min period following the application of vehicle (0.1% DMSO) or 100 μM capsaicin to the labial fornix region of the inferior incisors in control rats and on day 2 of the rat ulcer model. The rubbing time (C) and the number of wiping (D) during a 3 min period following the application of vehicle (mineral oil) or 100 mM AITC to the labial fornix region of the inferior incisors in the control rats and on day 2 of the rat ulcer model. OU: oral ulcer; Veh: vehicle; CAP: capsaicin; CAP1: first application of capsaicin; CAP2: second application of capsaicin; AITC1: first application of allyl isothiocyanate (AITC); AITC2: second application of AITC. $^{+}P<0.05$, $^{++}P<0.01$ and $^{+++}P<0.001$ versus vehicle application. $^{*}P<0.05$ and $^{**}P<0.01$ versus control. $^{\#}P<0.05$ versus CAP1. Error bars indicate the SEM.

treatment with acetic acid in the same rat. On days 2–3 after the treatment, the appearance of the mucosa had clearly changed from pink to white, which indicates the development of leukoderma. In addition, the white mucosal membrane was occasionally peeled and the dermis was exposed. On day 5, the acetic acid-treated region was visibly cured. Histology revealed a significant infiltration of inflammatory cells into the dermis of the treated mucosa on day 2, but this pathological aspect had disappeared by day 5 (Fig. 3B). To examine spontaneous nociception in the OU model, mouth rubbing (Fig. 3C) and facial wiping (Fig. 3D) were observed for 10 min in the non-treated control rats and in the rats exposed to the OU model (each $n=6$). Compared with the control rats, the spontaneous rubbing time was significantly prolonged in the OU model rats on day 2 ($P<0.05$, Fig. 3C). No significant differences were observed in the amount of wiping between the two groups of animals (Fig. 3D). From these results, we performed the pain tests prior to treatment (day 0) and day 2 after treatment with acetic acid.

3.2. Intraoral dropping method and facial grooming behaviors

To evaluate evoked nociception in the oral mucosal region, pungent solutions were directly applied to rats using the intraoral dropping method, as shown in Fig. 1A, and facial grooming behaviors were subsequently measured in the plastic cage. To avoid the potential involvement of spontaneous facial grooming effects on the measurements, we observed the behaviors for the first 3 min immediately after the application. Vehicle application (0.1% *DMSO in water and 100% mineral oil*) led to no significant differences between the non-treated control and OU model groups with respect to mouth rubbing and facial wiping (Fig. 4A and B), which indicates spontaneous nociception has no effects on short-time facial grooming behavior following drug application.

In the control rats, capsaicin at 10 μM ($n=5$) and AITC at 10 mM ($n=4$) had no significant effects on facial grooming behaviors compared with vehicle (data not shown). However, tenfold higher concentration of these drugs induced significant changes in facial grooming behavior (Fig. 4A, C and D). Compared with the vehicle application (0.1% DMSO in water), capsaicin at 100 μM significantly prolonged rubbing time for 3 min ($P<0.001$, $n=10$, Fig. 4A), but it did not change the number of wiping (Fig. 4B). Compared with the vehicle application (100% mineral oil), AITC at 100 mM significantly prolonged rubbing time and increased the number of wiping for 3 min ($P<0.01$, $n=5$, Fig. 4C and D). These pungency-evoked facial grooming behaviors were observed immediately after the application. Capsaicin-induced facial grooming had essentially ceased by the end of the observation time, but AITC-induced facial grooming continued past the observation time. To examine the desensitization of pungency-evoked facial grooming behaviors, a subset of control rats that received 100 μM capsaicin ($n=4$ of 10) and all control rats that received 100 mM AITC ($n=5$ of 5) were subsequently administered the same pungent solution following a 20 min interval. Rubbing behavior in response to the second capsaicin application was significantly shorter than that observed following the first application ($P<0.05$, Fig. 4A). In contrast, the second AITC application tended to prolong rubbing time and increase facial wiping compared with the behaviors observed following the first application, although this effect was not significant (Fig. 4C and D). These results suggest that capsaicin and AITC have the potential to induce desensitization and sensitization, respectively, of facial grooming behaviors in the second application. Hence, in the following experiments, pungent solutions were applied only once to each rat to avoid repetitive effects. Furthermore, to confirm whether pungency-evoked facial grooming behavior is caused by nociceptive sensation, we investigated the effects of morphine administration on the capsaicin-induced prolongation of rubbing time. Compared with the saline group (31.0 ± 3.5 s, $n=6$), morphine pre-treatment led to a significant, dose-dependent reduction in the capsaicin-induced prolongation of rubbing time (4 mg/kg: 16.7 ± 4.3 s, $n=6$, $P<0.05$ and 10 mg/kg: 5.6 ± 3.3 s, $n=5$, $P<0.01$). No motor defects were observed in the morphine-administered rats.

In the OU model, the rubbing time observed following capsaicin administration was significantly longer compared with the control rats ($P<0.05$, Fig. 4A) or the OU model animals following vehicle administration ($P<0.05$, $n=6$, Fig. 4A). Interestingly, the number of wiping observed in the model animals was significantly increased by capsaicin ($P<0.05$ compared with vehicle, Fig. 4B) despite the fact that no changes in this behavior were observed following capsaicin administration in the control rats ($P<0.01$ compared with the OU model). In contrast, AITC significantly prolonged rubbing time and increased the number of wiping compared with the vehicle ($P<0.01$ and 0.05, respectively, $n=5$, Fig. 4C and D). Unlike capsaicin, the AITC-evoked facial grooming behaviors in the OU model animals were similar compared with the control rats (Fig. 4C and D).

3.3. SIO method and head withdrawal threshold to mechanical stimulation

To apply mechanical stimulation and longer drug treatments, we developed the 'SIO method', which consists of surgically piercing the mental skin (Fig. 2A) and subsequently training and habituating rats prior to the performance of pain tests (Fig. 2B). *To examine the effects of piercing on nociception in the mental* skin, the head withdrawal threshold to von Frey stimulation in the pierced region was measured on days 3, 7, 14 and 21 after the ring

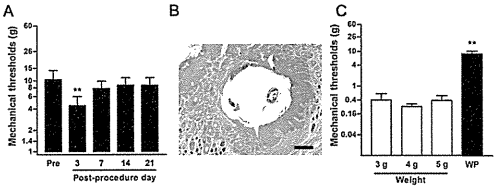

Fig. 5. Effect of ring application on the mental skin and intraoral mechanical pain threshold. (A) Withdrawal thresholds in response to mechanical stimulation of the pierced regions in the mental skin before and after ring implantation. $^{**}P<0.01$ versus pre-ring implantation. (B) Histological appearance of the pierced regions 3 weeks after ring implantation. Scale bar, 100 μm. (C) Withdrawal threshold in response to the stimulation of the oral mucosa and the whisker pad skin. WP: whisker pad skin. $^{**}P<0.01$ versus 4 g weight. Error bars indicate the SEM.

application ($n=6$). The mechanical threshold in the mental skin was significantly decreased on day 3 after the piercing, but it recovered to pre-surgery levels from days 7 to 21 (Fig. 5A). Histological analyses revealed that the pierced region exhibited epithelialization without inflammatory cell infiltration on day 21 after the piercing (Fig. 5B). The behavioral and histological results indicate that complete healing of the pierced mental skin had occurred, and no pain hypersensitivity was observed when we measured the head withdrawal threshold in the oral mucosa on our experimental schedule. As shown in Fig. 2C, the rats with pierced mental skin were trained to stably expose the labial fornix region of the inferior incisors in a black restrainer for 2 weeks. We subsequently determined the appropriate pulling force for the lower lip. No significant differences in the head withdrawal thresholds were observed among the three pulling weights examined (3, 4 and 5 g, $n=6$, Fig. 5C). Finally, the 4 g weight was selected as the most appropriate pulling force because it exposed the largest mucosal area. In the final experimental condition of the SIO method, the mechanical threshold of the oral mucosa that was vertically pulled by 4 g was significantly lower (0.25 ± 0.05 g, $n=13$, $P<0.01$) compared with the whisker pad skin (8.58 ± 1.66 g, $n=15$, Fig. 5C) and the mental skin (10.38 ± 3.67 g, $n=6$, Fig. 5A pre).

Compared with the pre-treatment with acetic acid, the head withdrawal threshold to von Frey stimulation in the oral mucosa was significantly decreased from its peak on day 2 ($n=5$, $P<0.05$, Fig. 6A), which is similar to the time course observed for spontaneous rubbing time (Fig. 3C). Our previous study reported heterotopic pain in the whisker pad skin associated with inflammation of the lower lip (Shinoda et al., 2011). However, no significant differences in the threshold of the whisker pad skin were observed in the OU model (Pre: 7.21 ± 1.79 g and day 2: 8.12 ± 3.11 g, $n=6$). We next investigated the effects of topical anesthesia with lidocaine on the mechanical pain threshold of the oral mucosa. In all control rats ($n=6$), topical anesthesia permitted the stimulation to reach the cut-off value (6 g) (Fig. 6B). On day 2 following acetic acid treatment in the same rats, the mechanical threshold was significantly decreased ($P<0.05$ compared with the pre-level prior to OU development). The mechanical threshold of the OU was also significantly increased by the administration of topical anesthesia ($P<0.05$ compared with the pre-level after OU development), but it did not reach the cut-off value (Fig. 6B).

4. Discussion

The present study demonstrated that the intraoral dropping method enables relatively easy evaluations of pungency-evoked nociception in the oral mucosa using traditional pain assays for facial grooming behaviors. A similar application technique of capsaicin- and formalin-containing solutions to the oral cavity has been previously demonstrated in a preliminary experiment (Chidiac et al., 2002). Compared with the previous study, our-developed intraoral dropping method has an advantage in stimulation to a more limited oral mucosal region, in which ulcer

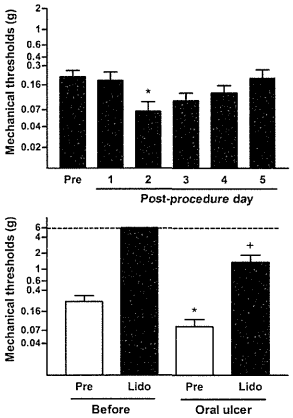

Fig. 6. Mechanical pain hypersensitivity in the oral mucosal region after oral ulcer (OU) development. (A) The mechanical pain threshold was assessed based on changes in the head withdrawal threshold to von Frey stimulation of the oral mucosa in the OU model. $^{*}P<0.05$ versus pre-ulcer development (Pre). (B) The mechanical pain thresholds in the oral mucosa following lidocaine application to the mucosa before and during the OU model. Pre: pre-application of lidocaine; Lido: lidocaine. $^{*}P<0.05$ versus Pre before the OU. $^{+}P<0.05$ versus Pre in OU model. Error bars indicate the SEM.

was developed, without any special restrainers. Capsaicin and AITC were used as painful stimulants because these chemicals are widely known to be the pungent compounds in red hot chili pepper and wasabi, respectively (Bautista et al., 2005; Jancso et al., 1967). Capsaicin and AITC activate transient receptor potential (TRP), vanilloid 1 (V1) and TRP ankyrin 1 (A1) channels, respectively, in primary sensory neurons (Caterina et al., 1997; Jordt et al., 2004). In the present study, prolonged rubbing time was observed following 100 μM capsaicin and 100 mM AITC, but not following ten times lower concentrations. These results suggest that the prolongation of rubbing time induced by pungent stimulation is dose-dependent. In addition, because the increment in rubbing time induced by 100 μM capsaicin could be inhibited by morphine, we conclude that this prolongation of rubbing time is a nocifensive behavioral response in the oral cavity, which has been suggested by previous studies (Chidiac et al., 2002). AITC also increased wiping behavior in the control rats, which suggests that facial wiping is also a sign of intraoral nociception, as reported for facial nociception (Pelissier et al., 2002). Compared with mouth rubbing, facial wiping behavior appears to be less sensitive to nociception because no changes in spontaneous wiping were observed in the OU model and wiping did not increase following capsaicin administration in the control rats.

This study is the first report to show a stable method (SIO method) of direct mechanical stimulation to the oral mucosa in conscious rats. The baseline mechanical pain threshold observed in the oral mucosa was considerably lower compared with the facial skin, which is consistent with previous reports in humans (Jacobs et al., 2002; Rath and Essick, 1990). This difference in pain threshold is most likely caused by differences in tissue toughness and/or mechanical sensor expression. Because most published pain-related animal studies of inflammatory and neuropathic pain have measured thresholds regarding mechanical/thermal stimulation (Mogil and Crager, 2004), the mechanical thresholds in the oral mucosa in conscious animals can be compared with many published results from extra-oral regions. In anesthetized animals, it is possible that a specific nociceptive threshold involves both peripheral and central anesthetic effects (Cornett et al., 2008; Dever and Zalkind, 2001). A previous human study reported that the pain threshold was increased by anesthesia (Siker et al., 1967). Thus, there are significant advantages to observing mechanical nociception in the oral cavity of conscious animals.

In the OU model, capsaicin application induced a further pro*longation of rubbing time and a significant increment of wiping* behavior compared with the control rats. These results suggest that OU induces pain hypersensitivity to capsaicin. The destruction of the epidermal layer that was observed in OUs is thought to increase the accessibility of chemicals to free-nerve endings in the oral mucosa. Therefore, the capsaicin solution that is applied via the intraoral dropping method may activate more peripheral nerves in animals with OUs compared with rats characterized by healthy mucosa. Because inflammation has been reported to elicit pain hypersensitivity as a result of the up-regulation of TRPV1 expression in sensory nerves and/or TRPV1 phosphorylation in peripheral tissues (Caterina et al., 2000; Kwon et al., 2014), it is possible that these TRPV1 modulations are related, in part, to the capsaicin hypersensitivity in OU regions characterized by inflammation in histological analyses. Unexpectedly, AITC application did not change rubbing time or wiping behavior after OU development despite the fact that TRPA1 sensitization has been implicated in pain hypersensitivity following inflammation and nerve injury (Bonet et al., 2013; Staaf et al., 2009). The lack of changes in AITC-evoked facial grooming behavior in animal models of OUs may result from an insufficient observation time to detect nociceptive hypersensitivity to AITC. *In the present experiments, AITC-evoked* facial grooming behaviors were observed continuously over the observation time, which is different from the time course observed for capsaicin-evoked mouth rubbing. The difference in AITC- and capsaicin-evoked facial grooming time appears to depend on sensitization and desensitization, respectively, in the second application. Similarly, a previous study (Raisinghani et al., 2011) reported longer nocifensive licking behavior after an AITC injection in the hind paw, compared with a capsaicin injection. However, the amount of spontaneous mouth rubbing measured over 10 min was prolonged in the OU model; thus, the longer observation times required to measure pungent-evoked facial grooming were unsuitable for the evaluation of hypersensitivity to pungency in the OU model because of its involvement in spontaneous behavior. Therefore, further research is required to determine whether TRPA1 sensitization is involved in OU-induced nociception.

OU development significantly reduced the mechanical pain threshold, which suggests OUs lead to mechanical pain hypersensitivity. The mechano-sensitive channels TRPA1, TRPV4 and Piezo2 have all been associated with mechanical hypersensitivity under conditions of inflammation and nerve injury (Alessandri-Haber et al., 2008; Bonet et al., 2013; Dubin et al., 2012). Therefore, these channels may be involved in the mechanical hypersensitivity induced by OUs. Clinically, topical anesthesia is often insufficient to suppress the pain in pulpitis and apical periodontitis (Boronat Lopez and Penarrocha Diago, 2006; Ueno et al., 2008). In the present study, the topical treatment of lidocaine in rats with OUs significantly increased the mechanical pain threshold, but the anesthetic effect was considerably less compared with the healthy oral mucosa. The following two hypotheses may explain the anesthetic failure in inflammation: (1) a decrease in the active non-ionized drug molecules in inflamed tissues because of inflammation-induced metabolic acidosis (Pamnia-Moorthy, 1987); (2) an increase in the number of inflammatory cells that produce peroxynitrite, which is known to antagonize anesthetic effects (Ueno et al., 2008).

Using both the intraoral dropping and SIO methods complements the individual methodological limitations of each method. Although the intraoral dropping method is relatively easy, it provides less spatial specificity in the stimulation because stimulants applied in this manner gradually diffuse throughout the entire mouth through the saliva during licking and movement of the mandible. The SIO method provides advantages in spatial specificity and in the variety of stimulation modes it allows (e.g., mechanical, thermal and chemical stimuli), but the SIO method *requires substantially longer preparation periods (i.e., more than* 3 weeks) to heal after piercing surgery and the habituation of animals to the experimental handling conditions compared with the intraoral dropping method. As a common limitation in both the methods, it is arisen the subjectivity of experimenters in measuring facial grooming and head withdrawal behaviors. Measurements of gnawing time using a "Dolognawmeter" (Dolan et al., 2010), sucrose consumption (Gibbs et al., 2013) and thermal operant behavior based on a reward-conflict paradigm using Orofacial Pain Assessment Device (Anderson et al., 2013; Neubert et al., 2005), which represent three recently developed methods for orofacial pain assessments in conscious rodents, enable the assessment of nociception that does not depend on the subjectivity of the experimenters.

The intraoral dropping and SIO methods are applicable for use not only in the oral mucosa but also in other intraoral regions. For example, stimulations of the inferior periodontal membrane/tissue are enabled using the intraoral dropping method by spreading a stimulant solution in the mouth. The SIO method also enables stimulations of the inferior gingiva and incisor teeth for investigations of pain sensation in experimental periodontal disease, pulpitis or *tooth movement. Clinically, oral pain is the primary complaint* in the field of dentistry. Pain during orthodontic therapy is a major problem that can lead to poor appetite. Patients with head and neck cancer treated with chemo-radiotherapy frequently exhibit oral mucositis, which causes oral hypersensitivity that can result in difficulties in eating, talking and swallowing (Donnelly et al., 2003). Our newly developed methods will contribute to future investigations of these unsolved problems of oral pain and may facilitate the development of drug therapies to prevent oral pain.

5. Conclusion

The two new methods of intraoral dropping and SIO allow for the evaluation of motivational pain-related behaviors in response to intraoral nociception in the absence of potentially confounding anesthetic effects. Our data reveal that OUs lead to pain hypersensitivity to both direct chemical and mechanical stimulations. We believe that the assessment of behavioral pain assays with our new methods will provide novel clues to explore new pain therapies for patients with severe oral mucosal pain in the future.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

Acknowledgements

This work was supported by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science and Technology of Japan (JSPS KAKENHI 25861760, 24592810 and 24792247), a Grant-in-Aid for the Third-Term Comprehensive 10-year Strategy for Cancer Control from the Ministry of Health, Labor and Welfare, Japan (148936) and the National Cancer Center Research and Development Fund (23-A-29 and 23-A-30).

References

Alessandri-Haber N, Dina OA, Joseph EK, Reichling DB, Levine JD. Interaction of transient receptor potential vanilloid 4, integrin, and SNC tyrosine kinase in mechanical hyperalgesia. J Neurosci 2008;28:1046–57.
Anderson EM, Mills R, Nolan TA, Jenkins AC, Mustafa G, Lloyd C, et al. Use of the Operant Orofacial Pain Assessment Device (OPAD) to measure changes in nociceptive behavior. J Vis Exp 2013 e50336.
Bautista DM, Movahed P, Hinman A, Axelsson HE, Sterner O, Hogestatt ED, et al. Pungent products from garlic activate the sensory ion channel TRPA1. Proc Natl Acad Sci U S A 2005;102:12248–52.
Bonet IJ, Fischer L, Parada CA, Tambeli CH. The role of transient receptor potential A 1 (TRPA1) in the development and maintenance of carrageenin-induced hyperalgesia. Neuropharmacology 2013;85:200–12.
Boronat Lopez A, Penarrocha Diago M. Failure of locoregional anesthesia in dental practice. Review of the literature. Med Oral Patol Oral Cir Bucal 2006;11:E510–3.
Caterina MJ, Leffler A, Malmberg AB, Martin WJ, Trafton J, Petersen-Zeitz KR, et al. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. Science 2000;288:306–13.
Caterina MJ, Schumacher MA, Tominaga M, Rosen TA, Levine JD, Julius D. The capsaicin receptor: a heat-activated ion channel in the pain pathway. Nature 1997;389:816–24.
Chidiac JJ, Rifai K, Hawwa NN, Massaad CA, Jurjus AR, Jabbur SJ, et al. Nociceptive behaviour induced by dental application of irritants to rat incisors: a new model for tooth inflammatory pain. Eur J Pain 2002;6:55–67.
Clavelou P, Pajot J, Dallel R, Raboisson P. Application of the formalin test to the study of orofacial pain in the rat. Neurosci Lett 1989;103:349–55.
Cornett PM, Matta JA, Ahern GP. General anesthetics sensitize the capsaicin receptor transient receptor potential V1. Mol Pharmacol 2008;74:1261–8.
Devor M, Zalkind V. Reversible analgesia, atonia, and loss of consciousness on bilateral intracerebral microinjection of pontobulbar local anesthetic. Pain 2001;94:101–12.
Dolan JC, Lam DK, Achdjian SH, Schmidt BL. The dolognawmeter: a novel instrument and assay to quantify nociception in rodent models of orofacial pain. J Neurosci Methods 2010;187:207–15.
Donnelly JP, Blijlevens NM, Verhagen CA. Can anything be done about oral mucositis? Ann Oncol 2003;14:505–7.
Dubin AE, Schmidt M, Mathur J, Petrus MJ, Xiao B, Coste B, et al. Inflammatory signals enhance piezo2-mediated mechanosensitive currents. Cell Rep 2012;2:511–7.
Gibbs JL, Urban R, Basbaum AI. Paradoxical surrogate markers of dental injury-induced pain in the mouse. Pain 2013;154:1358–67.
Harano N, Ono K, Hidaka K, Kai A, Nakanishi O, Inenaga K. Differences between orofacial inflammation and cancer pain. J Dent Res 2010;89:615–20.
Hidaka K, Ono K, Harano N, Sago T, Nunomaki M, Shiiba S, et al. Central glial activation mediates cancer-induced pain in a rat facial cancer model. Neuroscience 2011;180:334–45.
Hitomi S, Shinoda M, Suzuki I, Iwata K. Involvement of transient receptor potential vanilloid 1 in ectopic pain following inferior alveolar nerve transection in rats. Neurosci Lett 2012;528:315–9.
Jacobs R, Wu CH, Goossens K, Van Loven K, Van Hees J, Van Steenberghe D. Oral mucosal versus cutaneous sensory testing: a review of the literature. J Oral Rehabil 2002;29:923–50.
Jancso N, Jancso-Gabor A, Szolcsanyi J. Direct evidence for neurogenic inflammation and its prevention by denervation and by pretreatment with capsaicin. Br J Pharmacol Chemother 1967;31:138–51.
Jordt SE, Bautista DM, Chuang HH, McKemy DD, Zygmunt PM, Hogestatt ED, et al. Mustard oils and cannabinoids excite sensory nerve fibres through the TRP channel ANKTM1. Nature 2004;427:260–5.
Katagiri A, Shinoda M, Honda K, Toyofuku A, Sessle BJ, Iwata K. Satellite glial cell P2Y12 receptor in the trigeminal ganglion is involved in lingual neuropathic pain mechanisms in rats. Mol Pain 2012;8:32.
Kobayashi A, Shinoda M, Sessle BJ, Honda K, Imamura Y, Hitomi S, et al. Mechanisms involved in extraterritorial facial pain following cervical spinal nerve injury in rats. Mol Pain 2011;7:12.
Krzyzanowska A, Avendano C. Behavioral testing in rodent models of orofacial neuropathic and inflammatory pain. Brain Behav 2012;2:678–97.
Kwon SG, Roh DH, Yoon SY, Moon JY, Choi SR, Choi HS, et al. Acid evoked thermal hyperalgesia involves peripheral P2Y1 receptor mediated TRPV1 phosphorylation in a rodent model of thrombus induced ischemic pain. Mol Pain 2014;10:2.
Lam DK, Schmidt BL. Orofacial pain onset predicts transition to head and neck cancer. Pain 2011;152:1298–9.
Leao JC, Gomes VB, Porter S. Ulcerative lesions of the mouth: an update for the general medical practitioner. Clinics (Sao Paulo) 2007;62:769–80.
Liao L, Long H, Zhang L, Chen H, Zhou Y, Ye N, et al. Evaluation of pain in rats through facial expression following experimental tooth movement. Eur J Oral Sci 2014;122:121–4.
Mogil JS, Crager SE. What should we be measuring in behavioral studies of chronic pain in animals? Pain 2004;112:12–5.
Neubert JK, Widmer CG, Malphurs W, Rossi HL, Vierck CJ Jr, Caudle RM. Use of a novel thermal operant behavioral assay for characterization of orofacial pain sensitivity. Pain 2005;117:386–96.
Ohara K, Shimizu K, Matsuura S, Ogiso B, Omagari D, Asano M, et al. Toll-like receptor 4 signaling in trigeminal ganglion neurons contributes tongue-referred pain associated with tooth pulp inflammation. J Neuroinflammn 2013;10:139.
Ono K, Harano N, Nagahata S, Seta Y, Tsujisawa T, Inenaga K, et al. Behavioral characteristics and c-Fos expression in the medullary dorsal horn in a rat model for orofacial cancer pain. Eur J Pain 2009;13:473–9.
Pelissier T, Pajot J, Dallel R. The orofacial capsaicin test in rats: effects of different capsaicin concentrations and morphine. Pain 2002;98:63–7.
Punnia-Moorthy A. Evaluation of pH changes in inflammation of the subcutaneous air pouch lining in the rat, induced by carrageenan, dextran and *Staphylococcus aureus*. J Oral Pathol 1987;16:36–44.
Raisinghani M, Zhong L, Jeffry JA, Bishnoi M, Pabbidi RM, Pimentel F, et al. Activation characteristics of transient receptor potential ankyrin 1 and its role in nociception. Am J Physiol Cell Physiol 2011;301:C927–C600.
Rath EM, Essick GK. Perioral somesthetic sensibility: do the skin of the lower face and the midface exhibit comparable sensitivity? J Oral Maxillofac Surg 1990;48:1181–90.
Sago T, Ono K, Harano N, Furuta-Hidaka K, Hitomi S, Nunomaki M, et al. Distinct time courses of microglial and astrocytic hypertrophy and the glial contribution to pain hypersensitivity in a facial cancer model. Brain Res 2012;1457:70–80.
Shimada SG, LaMotte RH. Behavioral differentiation between itch and pain in mouse. Pain 2008;139:681–7.
Shinoda M, Asano M, Omagari D, Honda K, Hitomi S, Katagiri A, et al. Nerve growth factor contribution via transient receptor potential vanilloid 1 to ectopic orofacial pain. J Neurosci 2011;31:7145–55.
Shinoda M, Ogino A, Ozaki N, Urano H, Hironaka K, Yasui M, et al. Involvement of TRPV1 in nociceptive behavior in a rat model of cancer pain. J Pain 2008;9:687–99.
Siker ES, Wolfson B, Ciccarelli HE, Telan RA. Effect of subanesthetic concentrations of halothane and methoxyflurane on pain elicited in conscious volunteers. Anesthesiology 1967;28:337–42.
Staaf S, Oerther S, Lucas G, Mattsson JP, Ernfors P. Differential regulation of TRP channels in a rat model of neuropathic pain. Pain 2009;144:187–99.
Trotti A, Bellm LA, Epstein JB, Frame D, Fuchs HJ, Gwede CK, et al. Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review. Radiother Oncol 2003;66:253–62.
Ueno T, Tsuchiya H, Mizogami M, Takakura K. Local anesthetic failure associated with inflammation: verification of the acidosis mechanism and the hypothetic participation of inflammatory polymorphs. J Inflamm Res 2008;1:41–8.
Vilela-Goulart MG, Teixeira RT, Rangel DC, Niccoli-Filho W, Gomes MF. Homogenous amniotic membrane as a biological dressing for oral mucosine in rats: histomorphometric analysis. Arch Oral Biol 2008;53:1165–71.

10. 外来通院中のがん疼痛患者の除痛率を含めた緩和ケア提供体制の評価に関する研究

がん診療センター
○的場　元弘

1．目的

青森県立中央病院がん診療センターにおいて提供されている緩和ケアの質の一層の向上を図るため，外来部門における除痛率の継続的評価や改善すべき点を明らかにし，現場に改善を促すフィードバックシステムを構築することを目的とする．今年度は，(1)予備調査として2か月間麻薬処方量が同一患者の疼痛評価の現状を診療録から後方視的に情報収集し調査した，(2) 遺族を対象にインタビュー調査を行い，痛みの評価と疼痛治療における患者・家族の教育について検討する，(3) 外来における痛みとつらさのスクリーニングの実施方法の検討及びシステムの開発をしたので報告する．

(1) 予備調査として2か月間麻薬処方量が同一患者の疼痛評価の現状を診療録から後方視的に情報収集し調査した

1) 対象患者

がん診療センターに来院したがん患者の内，2014年2月1日から2014年4月30日に麻薬処方量が同一の患者

2) 研究方法

がん総合データーベース（DPC）EFファイル）を基に2014年2月1日から2014年4月30日に麻薬処方量が同一の患者を抽出した．抽出した患者リストを下記の手順に従って，集計した．

①がん疼痛緩和指導管理料算定書類（資料1参照）の使用の有無を確認する

・ありの場合

痛みの強さ，指導内容の項目のチェック項目または数値を確認し集計する

期間内に複数ある場合は，複数分集計する

・なしの場合

期間内の診療録から疼痛の状態を把握し，□疼痛管理良好　□疼痛不良　□評価なしの3つに区分し集計する

・集計された結果から，がん性疼痛指導管理料算定書類の活用率，がん性疼痛指導管理料の指導内容の内訳（延べ），文書がない場合は疼痛の評価状況の内訳を集計する．

3) 結果

がん総合データーベースを基に対象期間に麻薬処方量が同一量であった患者は85名であった．診療録を基に後方視的に調査した結果，がん性疼痛指導管理料活用率は19%であった．図1に示すようにテンプレート活用患者の「痛みがない」または「弱い痛み」の患者が全体の8割を占めていた．一方，図2に示すようにテンプレート未使用患者の半数が「痛み不良」または「痛みの状態が評価されていない」ことが明らかになった．

4) 考察

2013年度の外来の除痛率の結果を基に，2014年度から痛みの看護外来やホットラインを開設し痛みの訴えに応じた体制を外来と緩和ケアチームで連携し取り組んでいる．しかし，今回の予備調査の結果から痛みの看護外来などに紹介する以前の課題として，痛みの評価が適切になされていないことが明らかになった．痛みの訴えに応じた体制のシステムの活用と併用し，痛みに気がつく医師や外来看護師の意識づけについてもさらに検討する必要があると考える．

5) 結論

がん性疼痛指導管理料算定書類の活用率は19%と低く，テンプレート未使用患者の半数が「痛み不良」または「痛みの状態が評価されていない」であった．

(2) 遺族を対象にインタビュー調査を行い，痛みの評価と疼痛治療における患者・家族の教育について検討

遺族2名を対象に痛みを訴えること，及び痛みの治療を受けている時に感じていたこと，緩和ケアに対するイメージについて半構造化面接を行った．【医療者への気兼ね】【他患者への気兼ね】【麻薬＝怖い】といった要因から外来で医療者に痛みを訴えることが難しいことが明らかになり，この結果を基に患者・家族教育用のDVDを作成した．来年度，患者・家族へ外来待ち時間等に閲覧できるよう検討していく予定である．

(3) 外来における痛みとつらさのスクリーニングの実施方法の検討及びシステムの開発

外来におけるスクリーニングをするためのツールとしてiPodによるシステム厚生労働がん政策研究「緩和ケアセンターを軸としたがん疼痛の評価と治療改善の統合に関する多施設研究」（的場班）と共同企画・開発し，3月中に知的財産の申請をする予定である．

11. 内分泌療法施行した乳癌患者におけるKi67の変化，病理学的奏効および臨床的有用性

外科
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(目的) 術前化学療法では患者の予後を示す代替マーカーとしてpCR率を用いることが可能であり広く使用されているが，ホルモン受容体陽性患者ではpCRを示した患者と全生存率および無病生存率との間に有意な相関がみられなかったと報告されている．このためホルモン受容体陽性乳癌患者では，pCRは有効性，予後を評価するマーカーとして有用でないと思われる．術前内分泌療法の代替マーカーとして期待できるのは腫瘍細胞における Ki67であるが，その有用性は未だ十分に検討されていない．今回，術前内分泌療法施行した乳癌患者における Ki67の変化，病理学的奏効および臨床的有用性などにつき検討した．

(方法) 2010年4月より2014年12月までに当科で術前内分泌療法に対し同意が得られた10例を対象とした．ホルモン感受性の十分ある症例に対して，閉経前症例31例は tamoxifen or anastrozole + LH-RH agonist，閉経後症例74例は letrozole，男性乳癌症例1例は tamoxifen による内分泌療法を行い，6ヵ月後に手術を行った．Ki67は，治療前は針生検標本で，治療後は手術標本にて測定した．奏効判定は，臨床的には CT，US を用い，組織学的評価は手術標本にて行った．

(結果) 臨床学的効果判定では，CR が1例（1%），PR が56例（53%）で奏効率は54%であった．乳房温存率は88%であった．組織学的効果判定では，grade 3(pCR) が2例（2%），grade 2 が21例（21%），grade 1b が45例（45%）で histopathological response rate は68%であった．治療前の Ki67は17.8+14.4%，治療後の Ki67は10.3+13.6%と有意に低下がみられた（p<0.001）．閉経前，閉経後症例でそれぞれ検討したところ，閉経後症例で有意な低下がみられた（17.2+12.7 vs. 9.7+12.8% p<0.001）．一方，閉経前症例で検討したところ，低下傾向にあったが有意差はなかった（19.5+19 vs. 12.4+15.7%, *ns*）．術前内分泌療法において予後予測因子として有用と考えられている PEPI（preoperative endocrine prognostic index）を用いて，低リスク群（score 0），中リスク群（score 1-3），高リスク群（score >4）に分類し検討したところ，低リスク群で Ki67の著明な低下がみられた（14+11 vs. 1+0%, p<0.001）．一方，中リスク群で検討したところ，低下傾向にあったが有意差はなかった（18+16 vs. 13+16%, *ns*）．また高リスク群で検討したところ，Ki67の有意な低下がみられた（21+14 vs. 14+12%, p=0.03）

院内キーステーションとしての緩和ケアチームとがん疼痛治療

Palliative care team functioning as a key station within the hospital and treatment for cancer pain

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Key Words

緩和ケアチーム（palliative care team）　がん疼痛（cancer pain）
コンサルテーション（consultation）　医療用麻薬消費量（consumption of medications）
がん対策推進基本計画（basic plan to promote cancer management programs）

Summary

2014（平成26）年1月に「がん診療連携拠点病院等の整備について」と題する通知が出され，「週1回以上の病棟ラウンドとカンファレンスの開催」「がん疼痛治療薬の緩和ケアチームによる初回処方」といった具体的な対応を求めている．また，これに先立って策定された「がん対策推進基本計画（平成24年6月）」では，過去5年間の総括として，がん疼痛治療に用いられる医療用麻薬消費量は依然として少なく，がん患者の除痛がいまだ十分に行われていないとしている．これまでの緩和ケアチームの推奨一辺倒のあり方をやめ，実際に処方を含めて痛みの治療を行い，がん治療を担う担当医に対して疼痛治療のプロセスをみせる教育も重要であろう．

専門的緩和ケアとは何か．痛みの治療のプロフェッショナルとして，技術を一層高める必要がある．症例数が少なかったり，緩和ケアの臨床経験の少ないチームが多施設でフィールド体験しながら経験を重ねる仕組みの構築も重要である．

In January, 2014, the notice on "Maintenance of Designated Regional Cancer Centers and Hospitals in Japan" was issued. The notice included details on requirements for concrete measures, including "making rounds in the ward and holding conferences at least once weekly," as well as "having the palliative care team prescribe initial cancer pain therapeutic drugs." The Basic Plan to Promote Cancer Management Programs (June 2012), which was revised prior to the notice, summarized results over the past 5 years and included findings showing that medications for the treatment of cancer are used infrequently, indicating that pain relief for cancer patients remains insufficient. This emphasizes the importance of physician education by showing the physicians the entire pain treatment process, including the actual prescription of medications, thereby necessitating a deviation from the palliative care team's conventional approach of exclusively recommending pain treatment.

In order to provide answers to the question of what professional palliative care is, further enhancement of the skills of professional in pain treatment is necessary, as well as establishing a system that allows even a team with a small number of patients or little clinical experience in palliative care to accumulate experience through practice in the field in many facilities.

はじめに

2014年1月10日に各都道府県知事宛てに厚生労働省健康局長名で「がん診療連携拠点病院等の整備について」と題する通知が出された．この通知では基幹がん診療連携拠点病院が整備するべき診療体制について，集学的治療，手術療法，放射線治療，化学療法，緩和ケア，他の医療機関との連携，セカンドオピニオンの7項目について要点が述べられている．

このなかで，緩和ケアに関連する内容は半分以上を占め，詳細な内容となっている．「週1回以上の病棟ラウンドとカンファレンスの開催」「がん疼痛治療薬の緩和ケアチームによる初回処方」といった，他の項目ではみられないような具体的な指示の記載もある．よみかえれば，週1回程度の病棟ラウンドもしない緩和ケアチームがあり，痛みで辛い思いをしている患者を診察してもカルテに"拝見（コメント）"だけを記載している緩和ケアチームがあるということではないだろうか？

緩和ケアチームがん疼痛や症状緩和治療において院内ニーズに応えるためには，担当医や病棟スタッフとのディスカッションと同時に，苦痛緩和のための治療の目途がつく段階まで緩和ケアチームによる直接的な初期対応が必須である．

オピオイドが患者に届いていない

日本の医療用麻薬消費量は増加傾向にあるが，欧米先進諸国と比較すると依然として少ない．（平成24年6月 がん対策推進基本計画）

がん対策推進基本計画は，がん対策基本法に基づき，長期的視点に立って第1期は平成19（2007）～23（2011）年度の5年間を，第2期は平成24（2012）～28（2016）年度の5年間を対象として策定されており，緩和ケアについては「がんと診断された時からの緩和ケアの推進」を掲げ，以下のように問題点が整理されている．

日本では，欧米先進諸国に比べ，がん性疼痛の緩和等に用いられる医療用麻薬の消費量は少なく，がん性疼痛の緩和が十分でないと指摘されること，がん医療に携わる医師の緩和ケアの重要性に対する認識もまだ十分でないこと，国民に対しても未だ緩和ケアに対する正しい理解や周知が進んでいないこと，身体的苦痛のみならず精神心理的苦痛への対応も求められていること等から，緩和ケアはまだ一分にがん医療に浸透していないと考えられる．

これに対して，2012年に5年間の現状分析が行われ，緩和ケアについては以下のように述べられている．

日本の医療用麻薬消費量は増加傾向にあるが，欧米先進諸国と比較すると依然として少なく，がん性疼痛に苦しむがん患者の除痛がまだ十分に行われていないことが推測される他，がんと診断された時から，身体的苦痛だけでなく，不安や抑うつなどの精神心理的苦痛，就業や経済負担などの社会的苦痛など，患者とその家族が抱える様々な苦痛に対して，迅速かつ適切な緩和ケアががん診療の中でまだ十分に提供されていない．

厚生労働省医薬食品局監視指導・麻薬対策課が毎年刊行している「麻薬・覚醒剤行政の概況（2013）2014年1月」によると，がん対策推進基本計画の当初計画の5年間にあたる2007～2012年の間にモルヒネ錠費量は毎年減少し，2012年には264kgと，対2007年比で116kg減少している．オキシコドンは227kg増加，フェンタニルは9.82kg増加している．

これらの増減を経口モルヒネに換算したものを図1に示す．がん疼痛治療薬のうち強い痛みに用

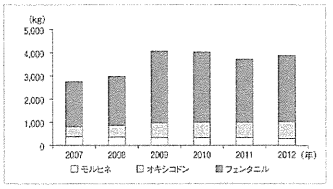

図1．モルヒネ，オキシコドン，フェンタニルの消費量の推移
モルヒネ，オキシコドン，フェンタニルをすべて経口モルヒネ量に換算して推移（モルヒネ1，オキシコドン1.5，フェンタニル100として算出）。
［厚生労働省医薬食品局監視指導・麻薬対策課：麻薬・覚醒剤行政の概況（2013）2014年1月．より作成］

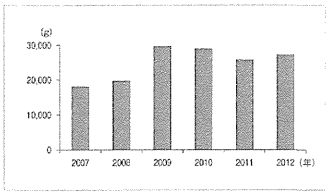

図2．フェンタニルの消費量の推移

いられるオピオイドは2009年をピークに減少傾向が認められ，強い痛みに用いられる経口製剤のモルヒネやオキシコドンの消費量はほぼ横ばいであり，増減の変化はフェンタニルの消費量に依存しているのがわかる（図2）。日本国内での医療用麻薬消費量は増えていない，というのが本当のところであろう。

ここ数年の間にメサドン，タペンタドールなどの強い痛みに用いられる新しいオピオイドの導入が進められており，患者の病状や鎮痛効果，副作用などにあわせて選択肢が広がりつつある。しかし，最近に至るまでがん疼痛治療の状況が改善していないのではないかという評価に謙虚に耳を傾ければ，高度の痛みに対する初期治療薬として用いられる基本的なオピオイド製剤がここ数年頭打ちの状況にある以上，基本的なオピオイドの初期導入が改善していないと考えるべきである。

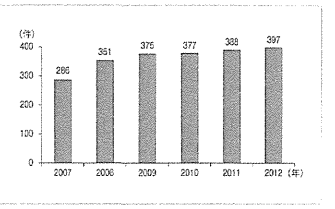

図3．がん診療連携拠点病院の指定件数の推移
制度上は，すべての拠点病院に緩和ケアチームが設置されていることが前提となっている。

速やかな鎮痛のためには緩和ケアチームの踏み込んだ対応が求められる

拠点病院に設置されている専門的緩和ケアを提供すべき緩和ケアチームの実績や体制等に質の格差が見られる。（平成24年6月 がん対策推進基本計画）

2006年より，都道府県および地域がん診療連携拠点病院（以下，両者を指す場合は“拠点病院”と略すの）の指定が開始され，すべての拠点病院に緩和ケアチームの設置が必須となった（図3）。

この後，2008年に「がん診療連携拠点病院の整備について」（平成20年3月1日付け 健発第0301001号 厚生労働省健康局長通知）によって改訂され，現在の制度上の基礎が整備された（表1）。

制度に従った緩和ケアチームなどの整備が進められる一方，緩和ケアを担う現場の医師の不足は深刻な問題であった。これに対して国立がん研究センターなどを中心に緩和ケアチームを対象にした研修会などの開催が進められてきたが，コンサルテーションチームの構築に主眼が置かれており，現場で求められている苦痛症状に対応するための問診，診察，画像所見や検査所見を適した病態の診断や治療の考え方など，実臨床で症状緩和治療を行っていくために必要な実務型の研修は行われていない。

緩和ケアチームが院内においてがん疼痛治療の中心的な核となるためには，まず“問診→診察→診断→治療”というコンサルテーション型の形式にこだわることなく，“問診→診察→診断→治療（処方）→改善状況の評価”といった対応を行い，痛みに対して速やかな対応を取る必要がある。

緩和ケアチームには具体的な処方行動が求められている

がん疼痛をはじめとするがん患者の苦痛に対して，必要に応じて初回処方を緩和ケアチームで実施する等，院内の診療従事者と連携し迅速かつ適切に緩和する体制を整備すること。（平成26年1月10日 がん診療連携拠点病院等の整備について）

表1．がん診療連携拠点病院における緩和ケアの提供体制

1）専任の身体症状の緩和に携わる医師，専従の看護師，精神症状の緩和に携わる医師を構成員とする緩和ケアチームを整備。当該緩和ケアチームを組織上明確に位置づけ，がん患者に対し適切な緩和ケアを提供すること
2）外来において専門的な緩和ケアを提供できる体制を整備すること
3）緩和ケアチームならびに必要に応じて主治医および看護師などが参加する症状緩和に係るカンファレンスを週1回程度開催すること
4）院内のみやすい場所に緩和ケアチームによる診察が受けられる旨の掲示をするなど，がん患者に対し必要な情報提供を行うこと
5）かかりつけ医の協力・連携を得て，主治医および看護師が緩和ケアチームとともに，退院後の居宅における緩和ケアに関する療養上必要な説明および指導を行うこと
6）緩和ケアに関する要請および相談に関する受付窓口を設けるなど，地域の医療機関および在宅療養支援診療所などとの連携協力体制を整備すること
7）当該2次医療圏においてがん医療に携わる医師を対象とした緩和ケアに関する研修を毎年定期的に実施すること

オピオイドの開始やオピオイド開始時の悪心への対応などの基本的な対応についてはコンサルテーション屋の対応も教育と並行して実施することは可能であるが，基本的なオピオイド開始後などにも残存する痛みや神経障害性疼痛などが疑われる場合には，緩和ケアチームが積極的に処方を手掛け，治療の足がかりを示す必要がある。

“緩和ケアチームが処方までを担当することは担当医の痛みの治療の丸投げにつながり，緩和ケアの普及にマイナス”という議論が過去にあった。現状はどうだろうか？　緩和ケアが普及しないのは全国で丸投げのコンサルテーションが広がっているからなのだろうか？

緩和ケアチームへの依頼後の対応について，「問診や診察後に，カルテに主治医へ薬剤などの開始や増量などの指示を記載するだけで，処方もしない」という批判もしばしば聞かれる。現場にとって，速やかに痛みを緩和してほしいという思いは，丸投げ云々という理屈とは別次元の問題である。

この問題を検討するには，痛みのある患者のどの程度が緩和ケアチームに依頼されているかを知る必要がある。

具体的な例を挙げよう。青森県立中央病院では，2012年4月よりすべての入院がん患者を対象に痛みの問診（スクリーニング）を毎日実施している。2012年5月22日～10月26日の間に入院したがん患者は1,171名であった。このうち，弱い痛み～強い痛みの何らかの痛みがある患者は501名（42.8%）であった。このうち，“痛みでできないことや困っていることがある”と回答したのは何らかの痛みがあると回答した患者の約半数の252名であり，全入院がん患者の2割に相当した（図4）。

青森県立中央病院の年間がん患者数は2,800名程度であり，“痛みでできないことや困っていることがある”入院がん患者数は500～600名程度と推測され，緩和ケアチームに依頼された患者数はこの5分の1程度に止まった。

専門的緩和ケアを担うべき緩和ケアチームが5人に1人の痛みのある患者の治療を実施し，がん治療を担う外科医や内科医ががんの痛みの治療などのプロセスをみることが，緩和ケアの普及を阻

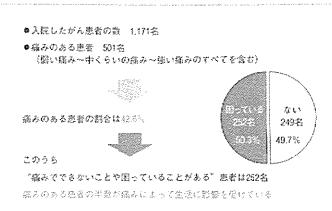

図4　青森県立中央病院の全入院患者における痛みや生活に支障を与えている割合
2012年5月22日～10月26日　青森県立中央病院入院患者

害する“丸投げ”という悪しき習慣を助長するとは考えられない。むしろ，現場におけるOJT（on-the-job training）と位置づけられるべきである。

2014年1月10日に各都道府県知事宛てに出された「がん診療連携拠点病院等の整備について」の通知は，もっぱらコンサルテーションに終始してきた緩和ケアチームのなかには大きな負担と感じるチームもあるかもしれない。しかし，臨床現場での治療体験が少ないままでは，新たな鎮痛薬などを含む治療の発展や発展を期待することはできない。

緩和ケアチームへの依頼を看護師や薬剤師などが行うことが業務上の役割として守られる必要がある

緩和ケアチームへがん患者の診療を依頼する手順には，医師だけではなく，看護師や薬剤師など他の診療従事者からも依頼できる体制を確保すること。緩和ケアチームへがん患者の診療を依頼する手順など，評価された苦痛に対する対応を明確化し，院内の全ての診療従事者に周知するとともに，患者とその家族に緩和ケアに関する診療方針を提示すること。（平成26年1月10日　がん診療連携拠点病院等の整備について）

多くの主治医は，担当している患者の痛みなどの苦痛が明らかになれば経験に基づいて対応しようとするであろう。主治医自身が速やかに対応することで，痛みの改善が得られることは間違いない。

青森県立中央病院においても，入院時のスクリーニングで“痛みでできないことや困っていることがある”と回答した患者において，スクリーニングから1週間以内に行われる緩和ケアチーム看護師のヒアリングまでに，4分の1の患者の痛みは改善が認められている。これは，主治医による初期対応が一定の効果をあげていることを示している。

一方，担当する看護師や薬剤師あるいは看護師などから相談を受けた緩和ケアチームなどが主治医に対して患者の痛みや苦痛があることを伝え，速やかな対応の必要性を指摘したとしても，一切

対応しようとしない主治医がいることも多くの病院において事実であろう。

しかし，対応しようとしない主治医を飛び越えて緩和ケアチームに依頼することは，現場の看護師や薬剤師にとってその後の主治医との業務遂行が困難になる可能性が著しく高くなることを意味するであろう。話し合いに応じ，ともに対応を検討しようとする主治医であれば，相談なく緩和ケアチームに依頼がくることはありえない。

「がん診療連携拠点病院等の整備について」のこの一文は，このような状況を改善し，すべての苦痛のあるがん患者に緩和ケアを届けるために重要なメッセージであるといえる。

しかし，この重要性は，がん患者の主治医ばかりでなく病院の管理者や管理者に理解していただかない限り，活かすことができない。苦痛緩和に目を向けようとしない問題に対して，看護師や薬剤師などが緩和ケアチームに相談したとき，そのことで受ける“パワハラ”を小さな問題として捉えるべきではない。

この通知が，すべての拠点病院において確実に運用されることが求められる。

おわりに

緩和ケアチームに依頼を出そうとしない主治医にも，それぞれ意見はあると思う。筆者も何人かのがん治療医からこれらの問題についての意見を聞いている。「意識状態の悪化など，かえって問題が大きくなった」「緩和ケアチームに依頼すると入院期間が長くなる」「痛みの治療の依頼をしたら，病状説明の不足や頼んでいないような問題ばかり指摘された」「アドバイスばかりで，夜間など本当に困ったときには現場にいたことがない」「痛みの治療がうまくいかないことが多い」。これは，緩和ケアチームを担っている医師やチームにとって辛い話である。

緩和ケアを担う側の思いとしては，病状の進行の著しい患者への対応は常に難しい。悪重になりすぎれば痛みの遷延を招き，思い切った処方では副作用が前面に出てしまうこともある。しかし，それでもなお主治医が苦痛の緩和の必要性を認め緩和ケアチームと話し合っていくことは，困難な痛みの改善につながっていく。経験を重ねることで主治医の思いを理解でき，苦痛を緩和するノウハウも知識でなく技術として蓄積されていく。

緩和ケアチームの側も，“丸投げ”ばかりを恐れて「コンサルテーション歴一辺倒」にしがみつくべきではなく，主治医とともに「やってみる，やり方をみてもらう，ともに悩む」という姿勢をみせることも必要である。

参考

1）厚生労働省：がん対策推進基本計画．(www.mhlw.go.jp/bunya/kenkou/dl/gan_keikaku02.pdf)（2015年8月閲覧）
2）厚生労働省：がん診療連携拠点病院等の整備について．(www.pref.miyagi.jp/uploaded/attachment/266559.pdf)（2015年8月閲覧）
3）国立研究開発法人国立がん研究センターがん対策情報センター：がん情報サービス（http://ganjoho.jp/public/index.html）（2015年8月閲覧）
4）日本緩和医療学会緩和ケアチーム検討委員会：緩和ケアチーム活動の手引き．2013
5）がん性疼痛治療の施設成績を評価する指標の妥当性を検証する研究（班長　的場元弘）：総合研究報告書．2013
6）緩和ケアセンターを軸としたがん疼痛の評価と治療改善の統合に関する多施設研究（班長　的場元弘）：平成26年度総括・分担研究報告書．2015

原著

がん患者の疼痛の実態と課題
—外来/入院の比較と高齢者に焦点をあてて—

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受付日 2014 年 11 月 10 日／改訂日 2015 年 3 月 26 日／受理日 2015 年 4 月 1 日

【背景】高齢がん患者の疼痛の実態は十分に明らかとなっていないことが多い．ケアの質向上のためにも，こうした実態を含めた課題の把握が必要である．【目的】がん患者の疼痛と対処状況の特徴，および，課題を把握する．【方法】都道府県がん診療連携拠点病院である青森県立中央病院の全がん患者で同意が得られた者を対象に疼痛の状況や QOL，治療歴等を収集し，入院/外来，および，高齢者（≧65 歳）/非高齢者（＜65 歳）を比較した．【結果】回答率は 57.0%であり，入院より外来で疼痛患者のうち除痛不十分な頻度は高く（除痛率: 外来 28.9% vs 入院: 52.6%，NRS: 外来 3.9 vs 入院 2.1，P<0.001），外来で特に高齢者の除痛率が低かった（高齢者: 24.7% vs 非高齢者: 35.8%，P<0.01）．【結論】一般に外来での疼痛の評価・介入の工夫が必要であると考えられるが，特に高齢者への介入の優先度が高いことがうかがえた．
Palliat Care Res 2015; 10(2): 135-41

Key words: 緩和ケア，高齢者，がん，疼痛，除痛

緒　言

WHO の緩和ケアの定義では疾患の早期から疼痛をはじめとした心身の苦痛の評価と予防・対処の重要性が謳われており[1]，わが国の施策においても緩和ケアは重点課題として位置づけられ，早期からの緩和ケアや症状のスクリーニングの重要性が強調されている[2]．しかしながら，わが国では，患者の疼痛が十分に対処されていない実態が国際比較研究で推定されるが[3]，国内調査は進行がん，終末期患者を対象とした報告に限られている[4~6]．緩和ケアは，がんと診断された時から提供されるとともにさまざまな場面で切れ目なく実施される必要があるが，より早期からのがん患者全体の疼痛の状況，および，入院や外来などの場によるこれらの特徴も明らかになっていない．同様に，がん患者のどの程度の人が疼痛への対処を必要とし，どの程度の割合で対処されているのかという，需要と供給のデータも十分ではない．

また，年齢にかかわらず，多くのがん患者が疼痛を抱えながら生活している実態がある中で[4~6]，高齢がん患者は世界的に増加している[7]．高齢者は疼痛を我慢しがちであり[8]，高齢者への疼痛の対処が不十分である可能性がある．一般に高齢者は調査や研究から除外されることが多く，研究数も限られている[9~11]．それは，がん領域においても同様であり[12~14]，わが国においても高齢者人口は急増しているが[15]，高齢がん患者の疼痛の実態は，十分に明らかにされていない．

以上のことから，全病期および高齢者という 2 つの観点からの検証は緩和ケア推進のため必要であると考えられる．本研究の目的は，都道府県がん診療連携拠点病院である青森県立中央病院における初診時からの全病期，全がん患者を対象に，疼痛の頻度や程度，疼痛の対処における実態，および，課題の把握である．さらに，疼痛への対処を行うにあたり，より優先度の高い介入の場や対象を検討する基礎とするため，入院/外来，および，高齢者（≧65 歳）/非高齢者（＜65 歳）を比較した．

方　法

2013 年 4 月 16 日～8 月 16 日の間に，青森県立中央病院にて行った．期間中にがん関連の診療科を受診した全患者（外来/入院）を対象候補とした．そのうち，担当医が調査協力に可能な状態であると判断した者，および，認知機能に問題がなく日本語の読解および会話能力がある者，研究参加の承諾を得た者を対象とした．対象者に自己記入式質問紙票を用いて，①対象者の特性，②日本語版 EORTC QOL C15-PAL（the European Organization for Research and Treatment of Cancer quality of life core 15 palliative questionnaire），③簡易疼痛調査用紙 Brief Pain Inventory（BPI），④有症者数および除痛率，について情報を収集した．

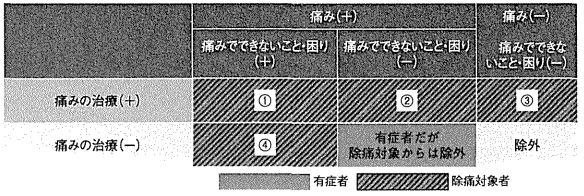
本研究では，疼痛の「有症者」を，聴取時に「痛みがある」と答えた，あるいは「鎮痛薬を服用している」と答えた患者と定義した．このうち，「鎮痛薬を服用している」と答えた者と「痛みでできないことや困っていることがありますか」の質問に「ある」と答えた者を除痛対象者とした．除痛対象者数を分母として，同質問に対し「ない」と答えた患者の割合を「除痛率」と定義した（図 1）．また，本研究における疼痛とは，がん患者における痛みの原因として挙げられている以下のすべてを含む[16]．①がん自体が原因となった痛み，②がんに関連した痛み（筋の攣縮，リンパ浮腫，便秘，褥瘡などによる痛み），③がん治療に関連して起こる痛み（手術瘢痕の慢性的な痛み，化学療法に起因した口内炎の痛みなど），④がん患者に併発したがん以外の疾患による痛み（変形性脊椎症，骨関節炎の痛みなど）．

痛みの情報収集に関しては，入院中は担当看護師が検温などの通常業務と同時に聴取したデータを二次解析し，外来においては対象施設職員でもあり，研究に従事している医師事務補助職が自己記入式質問紙を配布・回収した．さらにカルテから収集したデータを加え，①疼痛の有症率，②除痛率，③痛みの程度，④除痛の有無に関連する要因の検討，⑤QOL の解析を行った．記述解析に加え，外来/入院，および，高齢者（≧65 歳）/非高齢者（＜65 歳）に層別化し，χ^2検定，t 検定，ロジスティック回帰分析を行った．なお，複数回答した者に関しては各患者初回のデータを使用した．ロジスティック回帰分析は「痛みでできないこと・困っていること」が生じることをアウトカムとした危険因子の探索を検証した．独立変数として，性別，年齢，活動性〔外来: 移動手段（徒歩，それ以外），入院: performance status（PS）〕，診療科を投入した．年齢に関しては，サンプル数の関係もあり，50 歳未満とそこから 10 歳おきに 5 層化した．入院においては 70 歳以上でサンプル数が少なくなったため，ひとまとめとして解析した．

本研究は国立がん研究センター，および調査施設の倫理審査委員会の承認を得て実施した．

結　果

期間中のがん患者（対象候補）は，外来で延べ 14,233 名であった．そのうち，基準外の患者（認知・精神的問題のある患者，重症患者など）を除き，延べ 7,265 名からの回答（回答数＝同意数）を得た（51.0%）．入院では，対象候補者は延べ 1,632 名で基準外を除いた 1,023 名から回答を得た（62.7%）．複数回答を除いた各患者初回の分析対象は，外来 3,333 名，入院 701 名，合計 4,034 名であった．有症者数は外来 1,001 名（30.0%），入院 297 名（42.4%），合計 1,298 名（32.2%）であった．有症者から除痛対象外の患者，および，質問欠損を除いた 821 名（63.3%）で，主解析（除痛率，痛みの程度，除痛の有無に関連する要因の検討）を行った．QOL の解析は，主解析で用いたデータから QOL の質問の欠損を除いた 634 名（77.2%）で解析した．本研究の主解析で用いたデータの患者属性を表 1 に示す．



除痛率＝②＋③／①＋②＋③＋④

図 1　有症者と除痛対象者，除痛率の定義

1 有症者の割合

全体の疼痛有症者の割合は 32.2%（1,298/4,034）であった．外来では 30.0%で（1,001/3,333），高齢者よりも非高齢者における割合が多かった〔28.8%（592/2,059）vs 32.1%（409/1,274），P=0.04〕．入院では 42.4%（297/701）で，高齢者と非高齢者に差はほとんどなかった〔42.1%（168/399）vs 42.7%（129/302），P=0.87〕．

本研究における有症者の割合は，（疼痛の有無にかかわらず）疼痛の治療中の者と未治療で疼痛がある者の 2 つに分かれるが，その内訳を見ると，有症者の中で疼痛が取り切れている患者（「疼痛なし・治療あり」）の割合は 9.2%（120/1,298）であった〔外来 7.9%（79/1,001），入院 13.8%（41/297）〕．「疼痛あり・治療なし」の患者〔外来 52.3%（524/1,001），入院 39.7%（118/297）〕と「疼痛あり・治療あり」の患者〔外来 39.8%（398/1,001），入院 46.5%（138/297）〕の割合が有症者の大半を占め，治療をしていても疼痛が残っているケースや，疼痛があっても未治療であることが多い現状が明らかとなった．なお，10 歳おきの年齢層で区切った有症者の割合に，外来および入院でそれぞれ，外来 28.1～38.0%，入院 27.3～47.3%と幅はみられたが，一貫した傾向はなく，統計検定上これらの差は有意水準には到達しなかった（P=0.19，P=0.58）（図 2）．

2 除痛率

外来と入院では外来の除痛率が低く〔28.9%（177/612）vs 52.6%（110/209），P<0.001〕，外来の高齢者は非高齢者に比べて除痛率が低かった〔24.7%（94/380）vs 35.8%（83/232），P=0.003〕．入院の高齢者および非高齢者の除痛率は，46.8%（51/109），59.0%（59/100）であった（P=0.08）（表 2）．10

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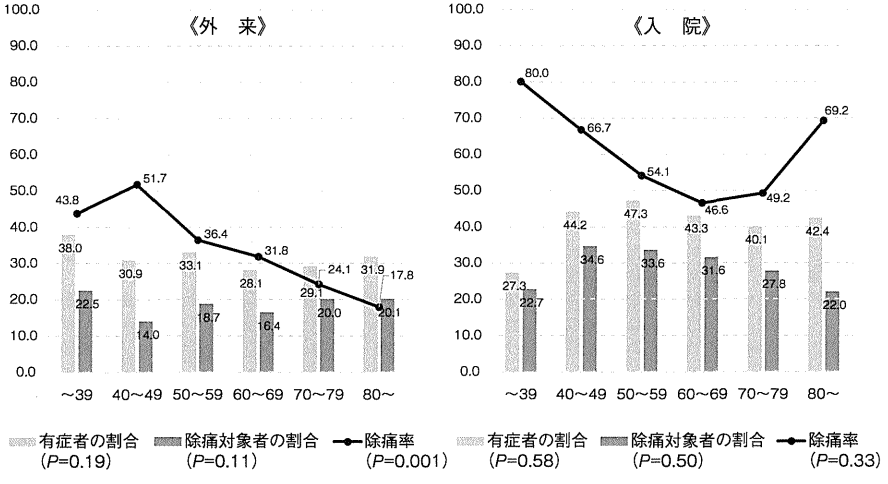
表1　患者の特性

		外　来		入　院	
性　別		*n*	%	*n*	%
女性		322	52.6	90	43.6
男性		290	47.4	119	56.9
年　齢		平均	標準偏差	平均	標準偏差
		67.5	±11.9 (22-95)	64.4	±11.7 (29-87)
診療科		*n*	%	*n*	%
外　科		228	37.3	51	24.4
血液内科		44	7.2	20	9.6
呼吸器科		80	13.1	36	17.2
耳鼻咽喉科		46	7.5	13	6.2
頭頸部外科					
消化器内科		108	17.7	58	27.8
泌尿器科		68	11.1	18	8.6
婦人科		32	5.2	13	6.2
緩和医療科		6	1.0	0	0
治　療		*n*	%	*n*	%
放射線療法	あり	149	24.4	45	21.5
	なし	463	75.6	164	78.5
化学療法	あり	336	54.9	110	52.6
	なし	276	45.1	99	47.4
手　術	あり	333	54.4	74	35.4
	なし	279	45.6	135	64.6



注：P-valueは年齢層別の有症者の割合、除痛対象者の割合、除痛率のχ^2検定によるもの

図2　年齢別にみた有症者，除痛対象者の割合と除痛率

歳おきの年齢層で区切った除痛率は，年齢が上がるにつれ除痛率が低下する傾向があった（外来: 51.7～17.8%，$P=0.001$，入院: 80.0～46.6%，$P=0.33$）．なお，除痛対象者数においては，年齢層別に外来 14.0～22.5%（$P=0.11$），入院 22.0～34.6%（$P=0.50$）であった（図2）．

表2　除痛率と疼痛程度

項　目	外来/入院	全　体 (外来 *n*=612，入院 *n*=209)	高齢者 (外来 *n*=380，入院 *n*=109)	非高齢者 (外来 *n*=232，入院 *n*=100)	*P*
除痛率	外　来	28.9% (177/612) *	24.7% (94/380)	35.8% (83/232)	0.003
	入　院	52.6% (110/209) *	46.8% (51/109)	59.0% (59/100)	0.08
疼痛程度	外　来	NRS 3.9 (SD 2.3) *	NRS 4.2 (SD 2.4)	NRS 3.5 (SD 2.2)	<0.001
			NRS≧5** 27.5% (168/612)	NRS≧5** 10.3% (63/612)	<0.001
	入　院	NRS 2.1 (SD 2.2) *	NRS 2.0 (SD 2.3)	NRS 2.2 (SD 2.2)	0.56
			NRS≧5** 10.5% (22/209)	NRS≧5** 7.7% (16/209)	0.43

*外来/入院の除痛率およびNRSは共に$P<0.001$
**中等度以上の疼痛を持つ者の割合で母数は外来/入院の各合計となる．
痛みの程度はNRS=0: なし，NRS=1～4: 軽度，NRS=5～6: 中等度，NRS=7～10: 強度

表3　除痛の有無に関連する要因の検討（ロジスティック回帰分析）

アウトカム:「痛みでできないこと・困っていることがある」

外来 (*n*=612)						入院 (*n*=209)					
変　数		OR	[95%CI]		*P*	変　数		OR	[95%CI]		*P*
性　別	男性である	1.1	0.8	1.7	0.52	性　別	男性である	0.9	0.5	1.7	0.77
年　齢	50 歳代	1.9	0.9	4.1	0.09	年　齢	50 歳代	2.1	0.7	5.9	0.18
	60 歳代	2.4	1.2	4.9	0.01		60 歳代	2.7	1.0	6.8	0.04
	70 歳代	3.6	1.8	7.2	<0.001		70 歳以上	2.4	1.0	6.3	0.06
	80 歳以上	5.3	2.3	12.2	<0.001	活動性	ps1	2.5	1.2	5.0	0.02
活動性	徒　歩	0.9	0.6	1.5	0.71		ps2	2.6	1.1	6.3	0.03
診療科	婦人科	1.7	0.7	4.3	0.26		ps3	2.8	0.9	8.0	0.07
	血液内科	2.8	1.12	6.8	0.03		ps4	16.8	1.8	158.4	0.01
	外　科	1.7	0.9	3.1	0.10	診療科	婦人科	1.7	0.4	7.3	0.48
	耳鼻咽喉科 頭頸部外科	1.7	0.7	3.8	0.23		血液内科	2.3	0.7	7.5	0.18
							外　科	1.2	0.5	3.3	0.67
	泌尿器科	1.2	0.6	2.5	0.64		耳鼻咽喉科 頭頸部外科	7.4	1.6	35.3	0.01
	消化器科	1.1	0.5	2.1	0.86						
	緩和医療科	0.6	0.1	3.5	0.58		泌尿器科	1.2	0.4	4.5	0.74
							消化器科	1.4	0.6	3.6	0.46

3 疼痛の程度

外来と入院では外来の方が痛みの程度（numerical rating scale; NRS: 0～10）が強く（3.9 vs 2.1，$P<0.001$），外来の高齢者は非高齢者よりも疼痛の程度が強かった（4.2 vs 3.5，$P<0.001$）．また，外来の高齢者は中等度以上の疼痛頻度が非高齢者より高かった〔27.5%（168/612）vs 10.3%（63/612），$P<0.001$〕．入院患者の高齢者と非高齢者の疼痛の程度は 2.0 vs 2.2（$P=0.56$），中等度以上の疼痛の分布は 10.5%（22/209）vs 7.7%（16/209）と，統計的な有意差はなかった（$P=0.43$）（表2）．

除痛できていない患者（未除痛）と除痛できている患者（除痛）で2層化した疼痛の程度は，外来，入院共に除痛患者の方が未除痛患者よりNRSが低く，除痛とNRSが連動していることが示された（外来: 未除痛 NRS=4.5 vs 除痛 NRS=2.5，$P<0.001$，入院: 未除痛 NRS=3.1 vs 除痛 NRS=1.2，$P<0.001$）．

4 除痛の有無に関連する要因の検討

外来においては年齢が高くなるにつれリスクが増し，50 歳未満と比べ 60 歳代（OR=2.4，$P=0.01$）～80 歳以上（OR=5.3，$P<0.001$）と年齢が上がるにつれ，リスクの増加を認めた．また，呼吸器科を基準とした診療科によるリスクの違いがあった．入院においても，年齢(60 歳代 OR=2.5，$P=0.04$)や診療科によるリスクの違いを認め，活動性（PS）によるリスクの違いがあった．PS0 を基準に，PS1（OR=2.5，$P=0.02$）～PS4（OR=16.8，$P=0.01$）と活動性低下に伴いリスクが増加する傾向を示した（表3）．

5 QOL

日本語版 EORTC QOL C15-PAL の QOL の項目により 0～100 点で評価した．外来/入院，高齢者/非高齢者共に QOL の得点に差はなかった〔外来平均: 51.7，高齢者（$n=321$）vs 非高齢者（$n=216$）: 51.0 vs 52.7，$P=0.42$，入院平均: 55.0，高齢者（$n=53$）vs 非高齢者（$n=44$）: 54.7 vs 55.3，$P=0.91$〕．しかし，未除痛/除痛で2層化した結果，除痛の方が未除痛より

もQOLが高く，除痛とQOLが連動していることが示された〔外来: 未除痛（$n=379$）48.4，除痛（$n=158$）59.6，$P<0.001$，入院: 未除痛（$n=43$）51.2，除痛（$n=54$）58.0，$P=0.19$〕．

考　察

がん患者の疼痛有症者の割合は全患者の約30%であり，その中で治療により無痛となっている者は約10%にすぎなかった．一方で，無治療で痛みが取り切れないまでも「痛みでできないことや困っていること」が「ない」と答えた者，つまり，有症者であるが除痛対象者とならない者は，全患者の10%程度であり，必ずしも疼痛への対処が必要ではないものの，一定数存在することが判明した．このように，有症者と除痛対象者は集団に一定の相違があり，除痛治療の成績を考えるうえで，分母を明確に設定することが必要であると考えられた．

除痛対象者における疼痛の実態や対処の状況については，入院よりも外来で疼痛を抱える患者の頻度が高かった．入院と外来における結果の違いに関して考えられる要因の一つに，患者を取り巻く環境の違いがある．入院では集学的なケアが行われやすい．現在では多くの病院で緩和ケアチームが設置され，多様なチームアプローチが組織的に可能となっている．そのため疼痛を含め，問題のある患者は抽出されやすく，また，多面的に評価・介入が可能である．一方，外来は入院に比して，関わる医療従事者の数も時間も少なく，患者が疼痛を訴える機会も少なくなる．一度訴える機会を逃してしまうと，次回受診時までに時間が経ち疼痛が増悪している可能性もある．「がん診療連携拠点病院の緩和ケア提供体制における実地調査」において，外来での苦痛スクリーニング体制が確保されていないという指摘がある[17]．今回，入院に比べ外来での除痛率の低さや疼痛の程度が強かったことからも，入院中だけでなく外来においても疼痛の評価・介入の必要性が示唆された．外来での限られた時間やリソースをどのようにして有効に利用し，効果的な評価・介入を行うかが課題である．

また，高齢者の除痛率は非高齢者よりも低く，疼痛の程度も強かった．特に外来では中等度以上の疼痛を有する高齢者が多く，若年層よりも高齢層になるにつれて除痛ができていないリスクが高く，高齢者がリスク要因であることが明らかとなった．これらの結果は，Cleelandら[18]による研究の除痛が不十分となるリスク因子に高齢者が挙げられている点に一致する．高齢者は痛みを我慢する傾向があり[8]，疼痛に関して無治療となっている高齢者は，睡眠や可動性，社会性の低下，うつの増加などを心配している可能性が高いという報告もある[19]．わが国における調査において，高齢者は非高齢者と比べてオピオイドへの誤解（依存性や命の短縮）する割合が高かった（$P=0.007$）[4]．高齢者は長年の経験や信念などから，不必要な我慢をしたり誤解をしている可能性がある．こうしたことを踏まえて，高齢がん患者に特化したコミュニケーション方法やパートナーシップの構築の重要性がうかがえる．

今回の調査結果から，がん患者が抱える疼痛への対処は不十分であることが明らかとなった．それを改善するにあたり優先度が高いのは外来であり，特に高齢者における介入の必要性が高い．外来高齢者が疼痛を抱えて生活する場合，疼痛の増悪，生活への影響や二次的な医療介入を招く恐れもあり，効果的な疼痛の評価・介入方法の検討が急務である．これは，除痛患者の方が未除痛患者に比べQOLが高く，疼痛はがん患者のQOLに影響しうる観点からも，その重要性が強調される．

本調査は単施設調査であったが，がん患者全体から情報を得たことで，病期やがん種に捉われることなく，広く実態を把握した．また，本研究における疼痛は，がん性疼痛に限定せず，がん患者が抱える痛みのすべてが含まれていた．がん疼痛は進行がん患者の8割は複数の痛みを抱えていると報告されていることからも[16]，疼痛へのスクリーニングと対処は，がん性疼痛に限定することなく実施されることが望ましい．がん患者が抱える疼痛は医療全体的な課題であり，疼痛の原因を的確に見分けた対処が必要である．たとえば，がん性疼痛があり各診療科で対処困難な場合であれば緩和ケア専門家，がん性疼痛以外であればその身体部位や痛みの専門家へ紹介するなど，関連専門領域が密接に協力して治療をしていくことが必要である．

本研究の限界として，外来と入院で痛みの情報収集方法が異なることによる影響点においてバイアスが生じた可能性がある．聞き取りにより，「痛みでできないことや困っていること」を訴えることに遠慮する可能性があるとすれば，除痛率が入院で外来よりも高い可能性もあることは留意すべきである．また，今回の疼痛への対処の必要性は患者主観であるため，専門的な関わりによって潜在的な患者のニーズを引き出し，適切な疼痛の対処により患者の生活がより良くなる可能性もありうる．たとえば，寝ていれば痛くないので困っていないという患者もいるかもしれないが，これは，高齢者を寝たきりにしてしまう要因にもなりかねない．患者が疼痛を訴えることにはさまざまなバリアが存在する[20]．そのため，患者の訴えを契機とした患者の同定には限界がある．より患者を理解し，スクリーニングの精度が増せば，除痛への介入が可能となる．スクリーニングする者によってその精度が異なる現実は否めない．どの程度の痛みまでを対処すべきかということやスクリーニングの質については，今後の検討課題である．

結　論

がん患者の疼痛への対処には課題が多い．入院と比べると外来における疼痛への対処が不十分であり，外来での疼痛の評価・介入に工夫が必要である．特に，外来高齢者は疼痛を抱えている頻度が高く，高齢であることは不十分な除痛のリスク要因となり得る．高齢がん患者への介入の優先度は高く，きめ細かな配慮が必要となる．

付記　本研究は，国立がん研究センター がん研究開発費「がん患者の緩和療法の開発と多施設共同研究システムの構築に関する研究」（課題番号: 23-A-29），および，厚生労働科学研究費補助金「がん政策研究緩和ケアセンターを軸としたがん疼痛の評価と治療改善の統合に関する多施設研究」（課題番号: H26-がん政策-一般-003）により実施した．

文　献

1) World Health Organization. National cancer control programmes, Policies and managerial guidelines. 2nd edition, WHO, Geneva, 2002; 84.
2) 厚生労働省ホームページ．拠点病院に求められる緩和ケアの提供体制について（とりまとめ）．アクセス日2015年3月26日．[http://www.mhlw.go.jp/stf/shingi/2r9852000031eac-att/2r98520000031ee0.pdf]
3) Duthey B, Scholten W. Adequacy of opioid analgesic consumption at country, global, and regional levels in 2010, its relationship with development level, and changes compared with 2006. J Pain Symptom Manag 2014; 47: 283-97.
4) Akiyama M, Takebayashi T, Morita T, et al. Knowledge, beliefs, and concerns about opioids, palliative care, and homecare of advanced cancer patients: a nationwide survey in Japan. Support Care Cancer 2012; 20: 923-31.
5) Morita T, Miyashita M, Shibagaki M, et al. Knowledge and beliefs about end-of-life care and the effects of specialized palliative care: a population-based survey in Japan. J Pain Symptom Manag 2006; 31: 306-16.
6) Yamagishi A, Morita T, Miyashita M, et al. Pain intensity, quality of life, quality of palliative care, and satisfaction in outpatients with metastatic or recurrent cancer: a Japanese, nationwide, region-based, multicenter survey. J Pain Symptom Manage 2012; 43: 503-14.
7) Cancer Worldwide. Cancer Research UK; 2011．アクセス日2015年3月26日．[http://publications.cancerresearchuk.org/downloads/Product/CS_CS_WORLD.pdf]
8) Gloth FM 3rd. Pain management in older adults: prevention and treatment. J Am Geriatr Soc 2001; 49: 188-99.
9) McMurdo ME, Roberts H, Parker S, et al. Improving recruitment of older people to research through good practice. Age Ageing 2011; 40: 659-65.
10) Watts G. Why the exclusion of older people from clinical research must stop. BMJ 2012; 344: e3445.
11) McMurdo ME, Witham MD, Gillespie ND. Including older people in clinical research. BMJ 2005; 331: 1036-7.
12) Van Lancker A, Velghe A, Van Hecke A, et al. Prevalence of symptoms in older cancer patients receiving palliative care: a systematic review and meta-analysis. J Pain Symptom Manage 2014; 47: 90-104.
13) Mercadante S, Giarratano A. Assessing age and gender in studies of breakthrough pain medications. Curr Med Res Opin 2014; 30: 1353-6.
14) Dunham M, Ingleton C, Ryan T, et al. A narrative literature review of older people's cancer pain experience. J Clin Nurs 2013; 22: 2100-13.
15) 総務省統計局ホームページ．高齢者の人口．アクセス2015年3月26日．[http://www.stat.go.jp/data/topics/topi721.htm]
16) Twycross RG, Fairfield S. Pain in far-advanced cancer. Pain 1982; 14: 303-10.
17) 厚生労働省ホームページ．拠点病院の緩和ケア提供体制における実地調査に関するワーキンググループ報告書（平成26年3月）．アクセス2015年3月26日．[http://www.mhlw.go.jp/file/05-Shingikai-10901000-Kenkoukyoku-Soumuka/0000041481.pdf]
18) Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. N Engl J Med 1994; 330: 592-6.
19) McCarberg BH. NSAIDs in the older patient: balancing benefits and harms. Pain Med 2013; 14(Suppl 1): S43-4.
20) Ward SE, Goldberg N, Miller-McCauley V, et al, Patient-related barriers to management of cancer pain. Pain 1993; 52: 319-24.

著者の申告すべき利益相反なし

Original Research

Current status of pain control for older cancer patients in comparison to younger patients in outpatient and inpatient settings: a report from one prefectural cancer care hospital

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Background: While the number of older cancer patients increases as the society ages, the current status of the pain control is not well characterized among older patients. To improve the quality of care, it is necessary to understand the current status. **Objectives:** The aim of this study was to describe the pain control for older cancer patients in comparison to younger counterparts and characterize it. **Methods:** During four months in 2013, Aomori Prefectural Central Hospital started asking all hospitalized cancer patients about their pain every day using a standardized pain questionnaire. In addition, a questionnaire adopted to the outpatient setting was distributed to the patients who visited outpatient department of the hospital. The information about pain, quality of life (QOL) and the medical histories were included in the data analyses. Their responses were compared between outpatients versus inpatients and older (≥65 years) versus younger (<65 years) patients. **Results:** The response rate was 57.0%. Pain management was less adequate among outpatients than among inpatients, with pain relief rate of 28.9% for the former and 52.6% for the latter ($P<0.001$). Among outpatients, the pain relief rate for the older patients was particularly low (older: 24.7% vs younger: 35.8%, $P<0.01$). **Conclusion:** Pain management for older patients in the outpatient settings needs a particular attention for improvement. Resources should be allocated to enable better detection and relief of pain among outpatients.
Palliat Care Res 2015; 10(2): 135-41

Key words: palliative care, older, cancer, pain, pain relief

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◎青森県立中央病院がん診療センターの活動を中心に，地域におけるがん診療拠点病院の現状と課題について述べる．当院のような総合病院の枠組みのなかでがん診療を展開しようとする場合，センター化は有用な手法であり，センター会議(および企画室)の存在は円滑な運営と，各診療科を越えた各種委員会の activity を支え，診療実績の質と量の向上に大きく寄与することができる．しかし，全国的な傾向とはいえ，地方における放射線科医や病理医の激減は目を覆うばかりであり，多忙のため必要最小限の日常業務にしか貢献できていない．情報通信技術(ICT)を活用した telepathology や teleradiology の積極的な導入が，国のがん対策事業の課題として積極的に取り上げられるべきと思われる．なお，診療連携パスなどこれまでの受療行動(習慣)の変化を伴う課題については，患者の広い理解が求められることから，時間的な猶予も必要と思われる．

Key word　がん診療センター，がん患者データベース，SPARCS，青森県がん診療連携協議会，DOC率

青森県では県立病院改革の一環として，平成19年度(2007)より地方公営企業法を全部適応(全適)し経営効率の向上をはかるとともに，県立病院の組織を一新した．このとき，中央病院(695床)の医療機能については，①県立唯一の総合病院であること，②県内他施設との区別化が求められること，さらには，③青森県が全国一の短命県であることなどに鑑み，政策医療(4疾病5事業)に特化する病院として，がん診療センター，循環器センター，脳神経センター，糖尿病センターを設置し，4疾病の拠点を確保することとした．がん診療センターは病棟再編が完了した平成20年(2008)4月から稼働を開始し，同年6月には第1回青森県がん診療連携協議会を開催している(県のがん診療連携拠点病院としての認定は同年2月)．

爾後7年以上を経過したが，さまざまな試行錯誤を経て，ようやく拠点病院らしい活動がみえるようになった．その一端を紹介するとともに，地域特有の課題についても言及してみたい．

がん診療センターの概要

センターを構成する診療科は，①外科(消化器・乳腺)，②呼吸器外科，③耳鼻咽喉科・頭頸部外科，④泌尿器科，⑤歯科・口腔外科，⑥消化器内科，⑦呼吸器内科，⑧血液内科，⑨腫瘍放射線科，⑩腫瘍心療科(精神科)，⑪緩和医療科，の計11科である．なお，婦人科については県内の厳しい産科医不足のため，総合周産期母子医療センターの業務を優先し，オブザーバーの扱いとなっている．また，県内の骨軟部腫瘍患者は国立病院機構弘前病院に集約することとなっており，当院では治療対象としていない．また，小児がんについては小児科(特定診療部門)で担当している．

病棟配置であるが，6階・7階の東西病棟に8階西病棟を加えた5つの病棟を使用しており，病床数は確定分で275床であるが，他病棟の共有ベッドも使用可能である．入院患者の大部分はがん患者であるが，非がん患者の入院も許容されている．また，病棟業務に従事する医師は56名(2015年2月末現在)を数えている．また，外来には通院化学療法センター(30床)を有し，認定看護師5名

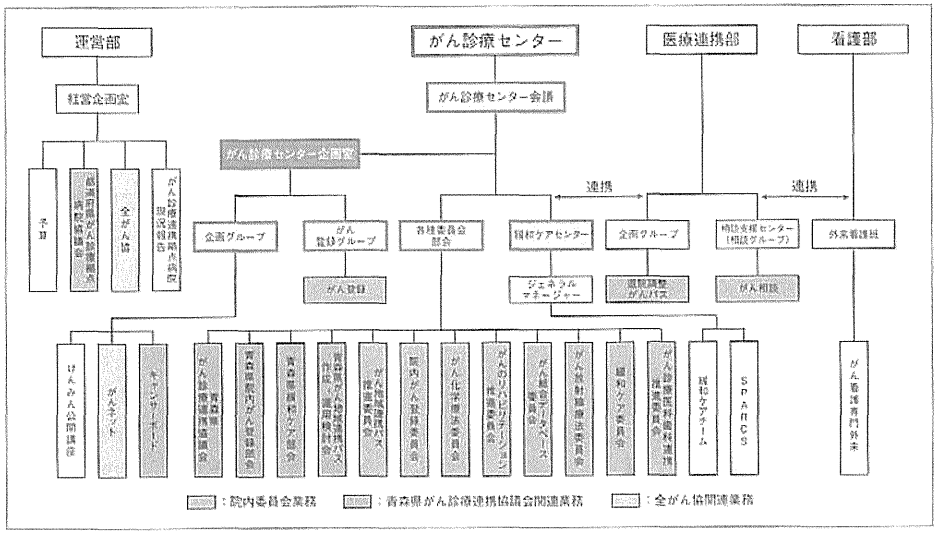

図 1　がん診療センターの組織および院内組織関連図

が配置されている．

図1はがん診療センターの組織図を示したものである．がんセンター会議は，がん診療に従事するすべての職員(医師，薬剤師，看護師，歯科衛生師，放射線技師，理学療法士，臨床心理士，事務職など，だれでも参加可能)を対象として隔月に開催され，緑で示す8つの委員会(毎月開催)，および赤で示す地域がん診療連絡協議会関連部会からの報告事項や検討事項を討議し，最終的な運営方針を決定している．また，センター会議の事務量は膨大かつ多岐にわたる(年報作成を含む)ため，専従の事務部門(がん診療センター企画室)を設置し，円滑な運営を支えている．

がん患者データベースの構築

当院のような総合病院では診療対象が広範にわたるため，そのなかから誤りなくがん患者情報を抽出することは困難をきわめる．院内がん登録の場合は診療情報管理士が電子カルテ上に特定のマークを付記することで選別可能であるが，これだけでは詳細な解析に耐えられるデータベースとはいえない．平成24年(2012)，後述の厚労科研費によるSPARCS(Special Project for Awareness and Relief of Cancer Symptoms)研究の進展に伴い，除痛率の算出に際して，母集団(医療上，除痛介入が必要と判断される全がん患者)の詳細な診療情報が求められた．これを機に医療情報部内にプロジェクトチームを立ちあげ，電子カルテと院内の各部門システム(がん登録，SPARCSデータベース，病理レポート，放射線診断レポート，放射線治療記録システムなど)とをファイルメーカーを介して連結・統合し，がん患者にかかわるすべての診療情報を即座に提供しうる“がん患者データベース”を開発した．以下に示す診療実績は本データシステムにより算出したものであるが，症例の確定作業を完了した平成25年度以前のデータを用いている．

平成25年度(2013)の診療実績

表1は，平成25年度の診療実績をがん種別，主たる治療法別にみたものである．総手術例数は798例(うち体腔鏡手術が128例)，化学療法例数は686例，内分泌療法163例，放射線治療295例，消化管がんの内視鏡治療が181例となっている．

1. 外科手術療法

臓器別に症例数をみると，大腸がんが最多で226例(うち直腸がんは95例)，ついで乳がん119例，胃がん104例，泌尿器領域94例(膀胱35，腎26，前立腺25，尿路6，その他2)，肺がん89例，婦人科領域70例(子宮頸部23，子宮体部19，卵巣その他28)，口腔および頭頸部外科領域56例(口腔10，咽頭13，喉頭13，甲状腺20)と続いている．なお，食道がんと膵がんについては大学に手術例の集積をはかっていることもあり，それぞれ5例および17例と少なくなっている．また，脳神経腫瘍の手術例が16例を数えている．

平成25年度の全身麻酔下総手術件数は2,613例であり，総がん手術例数798例はその30.5%に相当した．なお，平成26年(2014)8月より前立腺がんに対してはダヴィンチ手術を導入している．

2. 化学療法と内分泌療法

診療領域別に全身化学療法症例数(補助化学療法例を除く)をみると，消化器領域が最多で276例(大腸79，胃71，肝および胆嚢胆道66，膵30，食道28，小腸2)，ついで呼吸器領域(縦隔を含む)133例，血液領域93例(造血器54，悪性リンパ腫39)となり，以下，乳房59例(内分泌療法を加えると168例)，泌尿器領域48例(内分泌療法を加えると101例)，婦人科領域33例と続いている．

また，外来化学療法件数をみると，平成20年度は4,968件にすぎなかったが，年々増加し25年度以降は約9,000件で推移している．なお，外来化学療法についてはレジメン登録を前提としており，現在その登録数(入院分を含む)は305種を数えている．もっとも多いのが血液疾患で119種(白血病その他84，悪性リンパ腫35)，ついで消化器63種，呼吸器47種，乳がん32種と続いている．

なお，平成25年に血液病棟(8階西病棟)の無菌

表 1　平成25年度(2013)のがん診療実績

診断名	外科的治療	体腔鏡治療	内視鏡的治療	放射線治療	化学療法	内分泌療法	他の全身療法	他の局所療法	総計
口腔の悪性新生物	1			6	3				10
舌の悪性新生物	9			6	4				19
頭頸部の悪性新生物	26			38	21				85
甲状腺の悪性新生物	20			4	3				27
食道の悪性新生物	5		6	20	28				59
胃の悪性新生物	104		44		71			1	220
小腸の悪性新生物	3		1		2				6
大腸の悪性新生物	184	42	130	2	79			9	446
肝，胆嚢，胆道の悪性新生物	18		20		66			42	146
膵の悪性新生物	4		7		30				41
気管支・肺・縦隔の悪性新生物	11	74	4	90	133			7	319
造血系および細網内皮系の悪性新生物				1	54	2	2		59
悪性リンパ腫	1			7	39			1	48
皮膚・皮下組織の悪性新生物	22			2	2			1	27
乳房の悪性新生物	119			89	59	109	1	4	381
婦人科領域の悪性新生物	69	1		1	33				104
前立腺の悪性新生物	25			17	3	53		1	99
腎の悪性新生物	18	8		2	4				32
腎盂・尿管の悪性新生物	3	3			4				10
膀胱の悪性新生物	6		29		36		4		75
その他の泌尿器の悪性新生物	2			1	2				5
髄膜・脳・脊髄の悪性新生物	16			7	6				29
その他の内分泌腺および関連組織物，不明確な部位の悪性新生物	1			1	1				3
原発部位不明の悪性新生物	3			1	2			1	7
総計	670	128	241	295	683	166	7	69	2,259

(青森県立中央病院)

化に取り組み，全体の病床数を60床から51床に減じるなかで，あらたにクラス100を2床，クラス10000を30床整備した(以前は小児科病棟内のクラス100が2室のみ)．当院の骨髄移植あるいは造血幹細胞移植症例は年間およそ25～30例を数えているが，これにより大量化学療法に伴う合併症や感染エピソードは激減し(約40%減)，平均在院日数も40日から28日へ短縮するなど，改めてその有効性を再確認するところとなった．

3. 放射線療法

常勤医師が1名のみであるため，症例数を限らざるをえない部分もあるが，治療総数295例中もっとも多いのは気管支，肺および縦隔の90例で，乳腺の89例と合わせ全治療例の半数を超え，ついで，口腔および頭頸部の50例，泌尿器科領域の20例となっている．また，当院では主として前立腺がんと頭頸部がんに対して強度変調放射線治療(IMRT)を行っている．これまで，年間30例程度であったが，常勤医が1名体制となったにもかかわらず，平成25年度から増加傾向となり，26年度は61例を数えている．なお，青森県では子宮頸がんが少なく，当院でも婦人科からの照射依頼が極端に少ない．当該年度の子宮頸がん症例は1例のみであった．

4. 緩和ケア(SPARCS研究の進展)

当院では緩和ケア病棟を有していないこともあり，がん患者の除痛治療は基本的に担当医によって行われている．この場合，各担当医による除痛治療の有効性評価には一定の基準が求められる．SPARCSはこのような有効性評価の集大成として算出される“除痛率”(除痛治療の有効例数/[全除痛介入例数＋除痛介入が必要と考えられる全がん患者数]×100)が施設全体の除痛活動に対する評価指標となりうるか否かを明らかにするために行われた臨床研究である．本研究では実にさまざまな成果が得られたが，これらの知見に基づき，がん診療センターの入院患者に対しては以下の手順をルーチンワークとしている．

① 看護師は，検温の際，すべての担当患者に対して「痛みでできないことや困っていることはありませんか」〔この質問がVisual Analogue Scale(VAS)ともっともよく対応する〕と声がけし，痛みがあるとした患者についてはVASのスケールを用いてその程度を記録するとともに，担当医に報告する．

② 担当医は鎮痛剤を処方し，その有効性を担当看護師(VAS)がふたたび評価し，軽快していれば除痛治療を継続する．

③ 一方，除痛治療が無効で，担当医が対応困難とした場合には緩和ケアチームに頓診し，専門的な治療を求める．

というものである．この方式により，いわゆるがんの初期段階からの緩和ケアが可能となるとともに，当院における入院患者の除痛率も年々向上していることが明らかとなった．現在，さらなる展開を求めて外来患者への介入を試みているが，人的・空間的・時間的制約により残念ながらルーチンワークとなりえてはいない．外来診療体制の見直しを行うなかで解決すべく，あらたな整備計画を展開中である．

都道府県がん診療拠点病院としての活動

青森県では弘前大学医学部附属病院，八戸市立病院，市立三沢病院，十和田市立中央病院，市立むつ総合病院の5施設を地域がん診療連携拠点病院に指定している．したがって通常であれば，がん診療連携協議会はこの5施設に当院を加えた6施設で構成されるが，協議会発足当時，他県に比べて地域がん登録の立後れが著しかったため，医療圏とは関係なく，がん診療に携わる機会の多い10施設を協力メンバーとし，計16施設で運営することとした．協議会では，①院内がん登録の推進，②がん診療連携パスの推進，③キャンサーボードの開催，④がん相談センターの機能拡充，⑤緩和ケア講習会の開催状況などについて協議を重ねているが，紙幅も限られるため，地域ならではと思われる①②③の活動を紹介したい．

1. 院内がん登録の推移

図2はがん登録用診断名(C00～C80)をおおよそ18のカテゴリーに分け，平成18年度から23年度までの当院の登録実績を示したものである．当初は1,300例程度にすぎなかったが，年々増加傾向を示し，平成24年度以降は2,000件以上を登録している．図中の各カテゴリーの動向をみると，

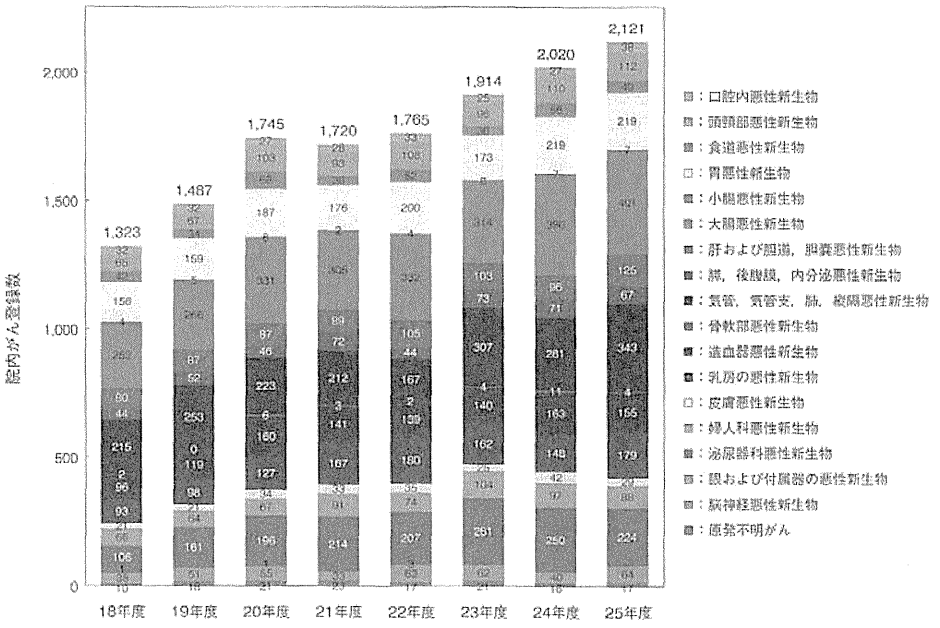

図2 院内がん登録の年代別登録数とその内容

特定のがん種に増加傾向はみられず，これまでの登録が全体として不調であったことがわかる．なお，登録例数の増加は診療情報管理士による人力が奏功したためであるが，その普及を目的として各協議会メンバー施設で勉強会や研修会を開催していたところ，平成21年度の青森県のDOC(death only certificate：死因となる臓器がんが特定できず，死亡の確認だけに終わる)率は前年度の42.6%からいきなり5.1%にまで減じ，23年度にはさらに2.6%にまで改善した．協議会参加施設のカバー率が高い(92%)ことがその最大要因と思われるが，一方では過疎であることが幸いしている可能性も否定できない．

2. がん診療連携パスへの取組み

五大がんにかかわる地域連携パスの運用は，当初から拠点病院の指定要件とされた(平成20年3月1日，健康局長通知)．その理由には，患者の利便や地域連携の普及という側面もあるが，がん治療後の経過観察(与薬を含む)をかかりつけ医に任せることで，拠点病院にさらに多くの新患診療の余力を与えることのほうがむしろ本線と思われる．当県では当初，かかりつけ医の理解を得るのに時間を要し，全体に取組みが遅れたが，平成23年度の試行期間を経て，24年度から稼働を開始した．

表2は当院発のパス発行件数を年度別にみたものである．試行段階から順調に展開し，その後もコンスタントな実績を得ている．臓器別にみると，乳がんが最多で264件，ついで大腸の190件，胃がんの155件と続くのに対し，肝がんは試行期間中の4例，肺がんは平成24年度の1例にすぎない．その理由は，前三者の場合，早期段階のがんが多く，手術後の経過観察における拠点病院と地域医療施設との役割分担(連携)が容易であるのに対し，後二者では，①いわゆる根治例が少なく，術後も再発・再燃に備えた検査や支持治療を必要とする，②さらには市中にしかるべき専門医が少ない(とくに呼吸器科)などから，患者が拠点病院を離れにくい状況におかれていることを示している．この点について，平成27年度のがん診療拠点病院現況報告をみると，平成26年6月1日～7月

表 2　がん地域連携パスの臓器別年度別発行状況

施設	胃がん	大腸がん	乳がん	肺がん	肝がん	計
県立中央病院	総数 155	総数 190	総数 264	総数 1	総数 4	総数 614
	23年度 35	23年度 32	23年度 17	23年度 0	23年度 4	23年度 88
	24年度 37	24年度 50	24年度 78	24年度 1	24年度 0	24年度 166
	25年度 41	25年度 66	25年度 89	25年度 0	25年度 0	25年度 196
	26年度 42	26年度 42	26年度 80	26年度 0	26年度 0	26年度 164
他の拠点病院	総数 8	総数 15	総数	総数 2	総数 9	総数 35
	23年度 4	23年度 3	23年度 1	23年度 1	23年度 1	23年度 10
	24年度 2	24年度 6	24年度 0	24年度 1	24年度 4	24年度 13
	25年度 2	25年度 6	25年度 0	25年度 0	25年度 4	25年度 12
	26年度 0	26年度 0	26年度 0	26年度 0	26年度 0	26年度 0
計	総数 163	総数 205	総数 265	総数 3	総数 13	総数 649
	23年度 39	23年度 35	23年度 18	23年度 1	23年度 5	23年度 98
	24年度 39	24年度 56	24年度 78	24年度 2	24年度 4	24年度 179
	25年度 43	25年度 72	25年度 89	25年度 0	25年度 4	25年度 208
	26年度 42	26年度 42	26年度 80	26年度 0	26年度 0	26年度 164

31日の2カ月間に都道府県拠点病院から発行された肝がんのパス数はわずか2例のみであり，肺がんも41例と2番目の少なさとなっている．したがって，今後とも連携パスの普及を図ろうとするのであれば，単に五大がん(症例数が多い)というようなとらえ方ではなく，連携のしやすさといった疾患の特性も考慮することが必要と思われた．

一方，当院以外の拠点5施設の実績をみると，試行期間を含め，全施設を合算してもわずか35例にすぎず，平成26年度はついに実績ゼロの状況に追い込まれた．協議会でその要因を検討しているが，①地域におけるこれまでの受療習慣に対する疑問や問題意識がなく，パスを使用することに積極的な意義を見出せない(患者は拠点を離れたくない，医師はパスの発行が面倒)，②医療過疎地ではそもそも近医，かかりつけ医の数がきわめて少ない，③病院スタッフの人手が足りず，パスの管理まで手が回らない，などさまざまな理由が語られているが，最大の要因は①に尽きると思われる．つまり大都市圏の拠点病院に比べ，当県では一般に外来の新患圧力が弱く，再来患者を調整する必要性が理解されにくい．したがって，わざわざ面倒なパスを発行する必要性はないということになるのであるが，さらにその背景を辿れば，守旧的な土地柄であることも患者の受療行動を変えるうえで大きな障害となっているように思われる．

3. キャンサーボード

診療科を越えたさまざまな専門医が治療方針の決定を論議するキャンサーボードの定期的開催は，拠点病院に求められる重要な要件であることに論をまたない．しかし，青森県では最近の医師不足の影響により病理医や放射線科医がきわめて払底し，当院でも常勤は，病理医が1名，放射線診断医が2名，放射線治療医が1名と，ギリギリの員数で診療に追われており，院内各所で開催される検討会に定期的に参加できるような時間的な余裕は皆無である．したがって，消化器関連以外では単科的なカンファレンスにとどまっており，問題症例については診療依頼という形での対応をとらざるをえない．現在，大学(病理，放射線科)などのメンバーを加えたTV会議方式など，ソフトウェアの開発を検討中である．

おわりに

青森県におけるがん診療連携拠点病院の現状と課題について，地域の特性などを含め，若干の考察を加えて述べた．拠点病院として国によって定められた指定要件自体についてはきわめて妥当なものばかりであるが，めざす内容や方向性については，国立がん研究センターをはじめとするがん専門施設のactivityや大都市圏の医療事情を前提としているように思われる部分も少なくない．ことに，大学病院を含め総合病院の場合，拠点病院の機能を果たすためには組織の変更を含め，これまでとは異なる各科横断的なシステムの導入が不可欠である．当院の取組みが何らかの手がかりにでもなれば幸いである．

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