

Table 2. Involvement of psychiatric consultation-liaison services in palliative care programs

	Cancer hospitals with approved palliative care teams (<i>n</i> = 80)	Cancer hospitals with non-approved palliative care teams (<i>n</i> = 153)	<i>P</i> -value
Palliative care consultation services			
Availability days per week median (IQR)	5 (3–5)	3 (1–5)	<0.001
Number of referrals (per 2 months)	25	12	<0.001
Frequency of rounds with all team members, <i>n</i> (%)			
>1/week	33 (41)	35 (23)	0.001
1/week	42 (53)	88 (59)	
1–3/month	0 (0)	2 (1)	
None	5 (6)	13 (9)	
Frequency of conferences with all team members, <i>n</i> (%)			
≥1/week	13 (16)	11 (7)	0.008
1/week	60 (75)	109 (73)	
1–3/month	2 (3)	22 (15)	
None	5 (6)	5 (3)	
Contributions to palliative care team, <i>n</i> (%)			
Participating in team rounds			
≥80%	42 (53)	62 (41)	0.003
≥40 and <80%	21 (26)	26 (17)	
<40%	17 (21)	64 (42)	
Participating in team conferences			
≥80%	61 (76)	97 (63)	0.02
≥40 and <80%	7 (9)	27 (18)	
<40%	12 (15)	28 (18)	

involved with palliative care teams provided not only inpatient consultations, but also outpatient clinics and family support. Generally, psychiatrists of approved palliative care teams served more patients, followed up more frequently and responded more readily to referrals compared with psychiatrists on non-approved palliative care teams.

Regarding the total time spent for consultations and follow-up, psychiatrists at cancer hospitals with approved palliative care teams committed more of their time to palliative care consultations compared with psychiatrists at cancer hospitals with non-approved palliative care teams. However, the time devoted to palliative care consultations remained at about 12 h/week at cancer hospitals with approved palliative care teams, which had full-time psychiatrists as core members.

ATTITUDES AND PRACTICES OF PSYCHIATRISTS

Table 4 reveals information about the practice of consultation-liaison psychiatric services involved with palliative care teams provided by consultation-liaison psychiatrists. Table 4 shows the number of hospitals where psychiatric consultation-liaison services adhered to the

consultation practices. In both cancer hospitals with approved palliative care teams and those with non-approved palliative care teams, the adherence rates are various by subjects. The adherence rate was high in assessing psychiatric symptoms directly (99% in cancer hospitals with approved palliative care team and 97% in those with non-approved palliative care teams) and assessing prognostic expectations. On the other hands, the adherence rate was low in educating the nursing and support staff regarding aspects of patient management and care planning (29% in cancer hospitals with approved palliative care team and 18% in those with non-approved palliative care teams). The rate of adherence between cancer hospitals with approved palliative care teams and those with non-approved palliative care teams differed in 16 of the 25 measures. For psychiatric assessment, the adherence rate was high (assessing and managing psychiatric symptoms directly, 99 versus 94%). On the other hand, the adherence rate varied for physical assessment (prognostic expectations, pain, activities of daily life), social assessment (financial, family problems, place of care) and coordination (discussing management with the physician directly, educating the staff regarding aspects of patient management).

Table 3. Availability of psychiatric services in palliative care programs

	Cancer hospitals with approved palliative care teams (n = 80)	Cancer hospitals with non-approved palliative care teams (n = 153)	P-value
Psychiatric service provided by palliative care teams, n (%)			
Inpatient	80 (100)	153 (100)	>0.99
Outpatient	67 (84)	109 (71)	0.04
Family	57 (71)	88 (58)	0.04
Bereaved family	30 (38)	38 (25)	0.043
Availability (inpatient)			
Response time to a request, n (%)			
Within 24 h	60 (75)	77 (51)	<0.001
Within 2–3 days	17 (21)	37 (24)	
Within 1 week	3 (4)	37 (24)	
Responding to an urgent request during business hours	76 (95)	118 (78)	0.001
Responding to an urgent request after office hours, n (%)			
Corresponding directly	19 (24)	33 (22)	0.043
By substitution	46 (58)	70 (46)	
Unsupported	15 (19)	47 (31)	
Emergency care			
Corresponding directly	23 (29)	32 (22)	0.31
By substitution	45 (56)	81 (54)	
Unsupported	11 (14)	34 (23)	
Number of referrals/2 weeks, median (IQR)	5.5 (4–10)	4 (2–8)	0.001
Number of rounds for follow-up/week	2 (1–3)	1 (1–2)	<0.001
Days from referral to discharge, median (IQR)	20 (12–30)	20 (7–30)	0.26
1–7 days	12 (17)	36 (27)	
>1–4 weeks	46 (67)	77 (58)	
>1–3 months	10 (15)	17 (13)	
>3 months	1 (1)	1 (1)	
Percentage of patients who died during intervention	30 (10–50)	50 (20–66.25)	0.040
Total time spent on consultation and follow-up (min/week)	741 (555–927)	516 (393–638)	0.002
Availability (outpatient), n (%)			
Response time to a request			
Within 24 h	26 (37)	39 (33)	0.45
Within 2–3 days	18 (26)	22 (19)	
Within 1 week	25 (36)	56 (48)	
Responding to an urgent request during business hours	64 (92)	90 (77)	0.016
Responding to an urgent request after office hours			
Corresponding directly	12 (17)	24 (21)	0.85
By substitution	33 (47)	52 (44)	
Unsupported	25 (36)	41 (35)	

DISCUSSION

Our survey provides information on the availability of psychiatric consultation-liaison services involved with palliative care programs in Japanese cancer hospitals. Compared with

cancer hospitals with non-approved palliative care teams, those with approved palliative care teams were more likely to integrate psychiatric consultation-liaison services for cancer patients into their palliative care programs. Psychiatrists assessed cancer patients from various

Table 4. Attitudes and practices of psychiatrists

	Cancer hospitals with approved palliative care teams, n (%) (n = 80)	Cancer hospitals with non-approved palliative care teams, n (%) (n = 153)	P-value
Asking the requesting physician directly how you can best help them			
≥80%	56 (70)	90 (59)	0.07
≥40 and <80	19 (24)	43 (29)	
<40%	5 (6)	20 (13)	
Anticipating potential problems			
≥80%	64 (80)	110 (72)	0.16
≥40 and <80%	13 (16)	31 (20)	
<40%	3 (4)	12 (8)	
Assessing and managing psychiatric symptoms directly			
≥80%	79 (99)	144 (94)	0.10
≥40 and <80%	1 (1)	8 (5)	
<40%	0 (0)	1 (1)	
Reviewing medical records			
≥80%	78 (98)	135 (88)	0.02
≥40 and <80%	1 (1)	15 (10)	
<40%	1 (1)	3 (2)	
Assessing prognostic expectations			
≥80%	74 (93)	124 (81)	0.02
≥40 and <80%	6 (7)	23 (15)	
<40%	0 (0)	6 (4)	
Assessing pain			
≥80%	66 (83)	106 (69)	0.02
≥40 and <80%	10 (13)	25 (16)	
<40%	4 (5)	22 (15)	
Assessing physical symptoms			
≥80%	67 (84)	103 (67)	0.004
≥40 and <80%	9 (11)	21 (14)	
<40%	4 (5)	29 (19)	
Assessing activities of daily life			
≥80%	57 (71)	90 (59)	0.04
≥40 and <80%	14 (18)	30 (20)	
<40%	9 (11)	33 (21)	
Assisting the primary care provider in communicating bad news			
≥80%	71 (89)	129 (85)	0.33
≥40 and <80%	7 (9)	15 (10)	
<40%	2 (2)	9 (5)	
Assessing financial resources			
≥80%	37 (46)	54 (35)	0.01
≥40 and <80%	28 (35)	43 (28)	
<40%	15 (19)	56 (37)	
Referrals to hospice, home care and other placements			
≥80%	47 (59)	63 (41)	0.01
≥40 and <80%	15 (19)	39 (26)	
<40%	18 (23)	51 (33)	

Continued

Table 4. Continued

	Cancer hospitals with approved palliative care teams, n (%) (n = 80)	Cancer hospitals with non-approved palliative care teams, n (%) (n = 153)	P-value
Assessing needs in term of discharge support			
≥80%	42 (53)	59 (39)	0.01
≥40 and <80%	21 (26)	35 (23)	
<40%	17 (21)	59 (39)	
Assessing doctor-patient relationship			
≥80%	48 (60)	78 (51)	0.13
≥40 and <80%	17 (21)	33 (22)	
<40%	15 (19)	42 (27)	
Assessing family problems			
≥80%	56 (70)	85 (56)	0.02
≥40 and <80%	18 (23)	45 (29)	
<40%	6 (7)	23 (15)	
Eliciting the patient's understanding and opinions about the disease and its treatment			
≥80%	65 (81)	106 (69)	0.043
≥40 and <80%	9 (11)	24 (16)	
<40%	6 (8)	23 (15)	
Eliciting the family's understanding and opinions about the disease and its treatment			
≥80%	50 (63)	74 (48)	0.03
≥40 and <80%	20 (25)	47 (31)	
<40%	10 (12)	32 (21)	
Making notations on medical charts			
≥80%	76 (95)	147 (96)	0.68
≥40 and <80%	2 (3)	5 (3)	
<40%	2 (3)	1 (1)	
Planning psychiatric treatment with other team members			
≥80%	64 (80)	109 (72)	0.048
≥40 and <80%	14 (18)	31 (21)	
<40%	2 (3)	11 (7)	
Discussing patient management with the physician directly			
≥80%	58 (73)	81 (53)	0.004
≥40 and <80%	16 (20)	50 (33)	
<40%	6 (7)	22 (14)	
Recommending psychiatric pharmacotherapy			
≥80%	60 (75)	114 (75)	0.85
≥40 and <80%	19 (24)	33 (22)	
<40%	1 (1)	6 (4)	
Implementing medical intervention with permission from the primary team			
≥80%	58 (73)	102 (67)	0.51
≥40 and <80%	7 (9)	22 (15)	
<40%	15 (19)	28 (18)	
Implementing psychotherapeutic intervention with permission from the primary team			
≥80%	67 (84)	109 (72)	0.03
≥40 and <80%	11 (14)	30 (20)	
<40%	2 (3)	13 (9)	

Continued

Table 4. *Continued*

	Cancer hospitals with approved palliative care teams, n (%) (n = 80)	Cancer hospitals with non-approved palliative care teams, n (%) (n = 153)	P-value
Participating in patient care, with other team members			
≥80%	72 (90)	118 (77)	0.01
≥40 and <80%	8 (10)	29 (19)	
<40%	0 (0)	6 (4)	
Educating the nursing and support staff regarding aspects of patient management and care plan			
≥80%	23 (29)	27 (18)	<0.001
≥40 and <80%	32 (40)	36 (23)	
<40%	25 (31)	89 (59)	
Coordinating a family meeting to discuss further plans for care			
≥80%	23 (29)	39 (26)	0.40
≥40 and <80%	46 (58)	85 (56)	
<40%	11 (14)	28 (18)	

perspectives with physicians, provided direct patient care, educated team members on the mental health domains and had a highly interdisciplinary approach to their work. Although there remains some variability in the infrastructure and delivery of psychosocial care in cancer settings, our results suggest that the integration model as psychiatric consultation-liaison services involved in palliative care teams is gaining acceptance in palliative care settings.

Although many institutions have developed elaborate support programs for a variety of symptoms, psychiatric symptoms and psychological problems of patients with cancer are still unrecognized, resulting in their not being offered access to the needed services (16,19,20,33). The National Comprehensive Cancer Network guidelines recommend screening for distress, which broadly defines emotional disturbances; however, only half the NCCN member institutions in the USA conducted screening to identify distressed patients (34). In palliative care programs, only half the National Cancer Institute cancer centers assessed and managed psychiatric disorders (4). Although various linkage programs, including screening programs and referrals, have been used in attempt to improve the continuity, the optimal system remains uncertain.

The full integration model aims to facilitate deinstitutionalization of dual assessment and pursues the best continuity and coordination for the complex needs (35). The full integration needs specialized types of interventions, expedited access to each other and close collaboration between professionals.

The involvement of psychiatric services in palliative care programs offers an advantage over conventional support programs in the detection and management of psychiatric disorders and psychosocial problems. First, psychiatrists provide medical care together with the palliative care teams, and a formalized mechanism for providing psychiatric services in

the usual palliative care programs prevents the failure to connect individuals with the referred providers and gain the patients' acceptance of the referral (22,36,37). Second, psychiatrists assess the mental status and evaluate the decision-making capacity of patients, which contributes to enhanced quality of life for patients and families faced with life-threatening illness. Third, palliative care teams often face difficult settings and conflicting ethical issues. Psychiatrists can recognize and mitigate staff stress and address burnout.

Our survey revealed that cancer hospitals with certified palliative care teams offered integrated services between palliative care and consultation-liaison psychiatry; psychiatrists saw cancer patients with the palliative care teams directly, assessed cancer patients in a comprehensive manner and made the coordination process more effective with other staff members.

Although all of the cancer hospitals reported the provision of psychiatric consultation services, some barriers remain at the level of interaction among different clinicians serving the same patient. In our study, 75% of consultation-liaison psychiatrists on certified palliative care teams were ready to respond to urgent requests (within 24 h). About 30% of consultations were urgent requests (20). Many programs provided inpatient services. However, on an outpatient basis, only 40% of cancer hospitals were prepared for referral to consultation on the same day. Most cancer treatment has shifted from inpatient to ambulatory care settings (38) and the structure and processes must be modified accordingly.

On the other hand, a number of barriers to collaboration remain unresolved. The primary problems with attempts to integrate are structural and financial barriers. The integration requires the palliative care teams to expand their knowledge, perspectives and interest. The integrated palliative care teams have to deal with the needs of various patients appropriately, and it takes time to learn about the capabilities of

the other systems, to decide how to work together and to communicate. They often feel 'consultation fatigue'. Also, the integration requires any of various staff to be involved at the clinical management. The cost of support staff can be overwhelming. For this reason, the approval of palliative care teams for national health insurance coverage encourages and facilitates the provision of psychiatric consultation-liaison services in palliative care programs under today's economic circumstances (25).

Most psychiatrists on palliative care teams see patients for direct consultation, assess their condition from various aspects and educate staff members regarding mental health problems. However, the quality and actual frequency of supportive care at each hospital varies. Psychiatrists are actively engaged in providing psychiatric care as well as coordination among physicians, nursing staff and the palliative care teams. On the other hand, educational activities are low in general. The key component to achieve the goal of full integration is the development of common clinical information systems. In previous studies, integrating information system is effective to facilitate communication between professionals (35). For approved palliative care teams, developing the information systems shared in the teams, such as clinical assessment tools, protocols about psychiatric treatment and education programs are needed. Also, for non-approved palliative care teams, establishment of a close contact and improving links between programs might be realistic strategies, rather than building up the full integration by constraint.

Our study had several limitations. First, the responses from our survey could be biased, because they were based on self-assessment and recalled information. Secondly, the response rate of the cancer hospitals with non-approved palliative care teams was low, possibly because low-activity institutions may be reluctant to participate in this type of survey. This may result in an overestimation of psychiatric consultation-liaison services and palliative care programs in cancer hospitals with non-approved palliative care teams. Third, the gold standard of psychosocial support has not yet been obtained. Although the questionnaire was generated based on a literature review and an expert panel, it has not been validated. The sphere of action of consultation-liaison psychiatry is complex, and it is difficult to identify new measurements for assessing the quality of the programs. It was recently suggested that the patients' subjective well-being and the medical team's difficulty in helping patients might be used to measure the effectiveness of consultation-liaison psychiatry. Further research is needed to improve the measurements applied to the consultation-liaison processes. Fourth, some results of this survey may reflect the impact from differences in country of practice and education.

In conclusion, these results suggest that the integration model between psychiatric consultation-liaison services and palliative care services holds some promise as an acceptable model for improving supportive care for patients with cancer. Although most designated cancer hospitals have a

psychiatric consultation-liaison service, significant gaps remain in the delivery of care. Additional research is needed to establish the level of synergistic effect between the psychiatric service and the palliative medicine.

Acknowledgements

We thank the staff who assisted in data management, including Ms. Nobue Taguchi and Ms. Yasuko Uchimura. We are also grateful to all respondents for completing the surveys.

Funding

This study was supported by the Cancer Foundation, Japanese Ministry of Health, Labour and Welfare.

Conflict of interest statement

None declared.

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Regular Article

Chronic repetitive transcranial magnetic stimulation increases hippocampal neurogenesis in rats

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Aim: While the underlying therapeutic mechanisms of repetitive transcranial magnetic stimulation (rTMS) treatment for depression remain unclear, recent animal studies have suggested that hippocampal neurogenesis might be required for the effects of antidepressant treatments including antidepressant drugs and electroconvulsive therapy. The aim of this study was to examine chronic rTMS effects on hippocampal neurogenesis in rats.

Methods: Using a 70-mm figure-of-eight coil, the stimulating parameters were set to 25 Hz and 70% of the rTMS device's maximum power. For 14 consecutive days, bromodeoxyuridine (BrdU) and 1000

pulses of rTMS were administered daily. Cell proliferation in the dentate gyrus was examined with immunohistochemistry.

Results: In the rTMS-treated group, BrdU-positive cells were significantly increased in the dentate gyrus.

Conclusion: Our results suggest that hippocampal neurogenesis might be involved in the antidepressant effects of chronic rTMS.

Key words: depression, hippocampus, neurogenesis, rat, transcranial magnetic stimulation.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION (rTMS) is a technique to repeatedly induce electric currents in a small area of the brain non-invasively. Recently, this technique has been applied to the treatment of several psychiatric and neurological diseases. Many clinical trials of rTMS have been conducted, most of which are for patients with depression.^{1,2} Sachdev *et al.* showed antidepressant effects of chronic rTMS in a forced swim test in rodents,³ and while many studies have examined the neurobiological therapeutic mechanisms of rTMS, they remain unclear.^{4,5}

Recent studies have suggested that hippocampal neurogenesis might be required for the effects of antidepressant treatments, although it may not be a major contributor to the development of depression.⁶ In mice, antidepressant drug effects were disturbed by X-ray ablation of hippocampal neurogenesis.⁷ As well as the chronic administration of several antidepressant drugs, electroconvulsive shock (ECS), analogous to human electroconvulsive therapy, increased hippocampal neurogenesis in rodents^{8–10} and non-human primates.¹¹

The aforementioned studies suggest that chronic rTMS could increase hippocampal neurogenesis and that this increase might be related to its therapeutic mechanisms on depression. However, to date, only one study has examined the effects of chronic rTMS on hippocampal neurogenesis in rodents and it did not show any significant increase of neurogenesis.¹² The lack of significant effects of rTMS in this study

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Received 30 June 2010; revised 3 November 2010; accepted 14 November 2010.

might be related to non-optimal rTMS conditions, considering that the optimal conditions for rTMS in the treatment of depression in humans and in experimental rodent models are still unknown. Hence, in this preliminary study, we examined chronic rTMS effects on hippocampal neurogenesis in rats using conditions similar to those of Sachdev *et al.*, which showed the antidepressant effects of chronic rTMS in the forced swim test in rats.³

METHODS

Animals

Sixteen-week-old male Sprague–Dawley rats (SLC Japan, Shizuoka, Japan) were used for all experiments. Rats were kept under standard conditions with a controlled 12-h light/dark cycle and fed standard diet and tap water *ad libitum*. The experimental protocol was approved by the Committee for Animal Experimentation of Osaka University Medical School. All efforts were made to minimize the number of animals used and their suffering.

rTMS treatment

Rats were randomly assigned to the control group ($n = 5$) or the rTMS-treatment group ($n = 5$). rTMS was administered with a 70-mm figure-of-eight coil using a Magstim Super Rapid (Magstim, Whitland, UK). The rTMS parameters were as follows: stimulating frequency = 25 Hz, stimulating pulse intensity = 70% of the rTMS device's maximum power, train duration = 10 s. Four successive trains of rTMS (1000 pulses per day) were administered daily for 14 consecutive days (14 000 pulses in total). The coil was placed horizontally over the scalp and its handle was aligned parallel with the body of the rat. For sham stimulation of the control group, the coil was placed perpendicular to the scalp and all other conditions were identical to the conditions in the rTMS group. The real and sham rTMS treatments did not induce seizures or any apparent behavioral changes.

Administration of bromodeoxyuridine

Bromodeoxyuridine (BrdU) (40 mg/kg in saline, Sigma, St. Louis, MO, USA), a thymidine analog that labels DNA during the S phase, was intraperitoneally administered to the two groups following the rTMS treatments daily (Fig. 1).

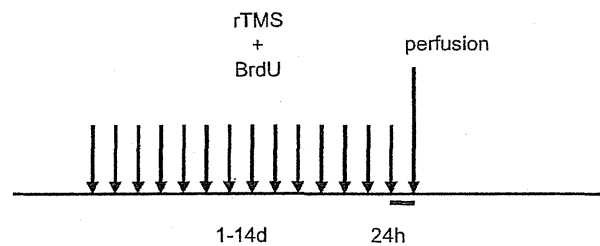


Figure 1. Experimental schema. Repetitive transcranial magnetic stimulation (rTMS) and bromodeoxyuridine (BrdU) were administered daily for 14 consecutive days. Rats were killed 24 h after the last BrdU administration.

Tissue preparation

Twenty-four hours after the last BrdU administration, the rats were deeply anesthetized with sodium pentobarbital and transcardially perfused with saline, followed by 4% paraformaldehyde in 0.1 M phosphate-buffered saline. The brains were removed and postfixed in the same fixative at 4°C overnight and consecutive hippocampal paraffin sections 5 µm thick were prepared.

Immunohistochemistry

After deparaffinizing, slide-mounted sections were incubated in 2 N HCl for 2 h and washed in Tris-buffered saline (TBS). Sections were blocked in TBS containing 10% normal rabbit serum at room temperature (RT) for 1 h and incubated overnight at 4°C with anti-BrdU antibody (1:100, OBT0030, Oxford Biotechnology, Oxford, UK) in TBS containing 10% normal rabbit serum. The next day, the sections were washed and incubated with biotinylated rabbit anti-rat immunoglobulin G (IgG) antibody (1:400, Vector Laboratories, Burlingame, CA, USA) at RT for 1 h. After washing, the sections were incubated with avidin-biotin peroxidase complex (Vectastain Elite ABC Kit, Vector Laboratories) at RT for 1 h. Peroxidase was visualized with 0.05% 3,3'-diaminobenzidine tetrahydrochloride (Sigma) in TBS containing 0.01% hydrogen peroxide. Counterstaining was performed with hematoxylin.

For double immunofluorescence staining, sections were preincubated in TBS containing 5% normal donkey serum and 0.1% Triton X-100 at RT for 1 h, and then incubated with primary antibodies in 3%

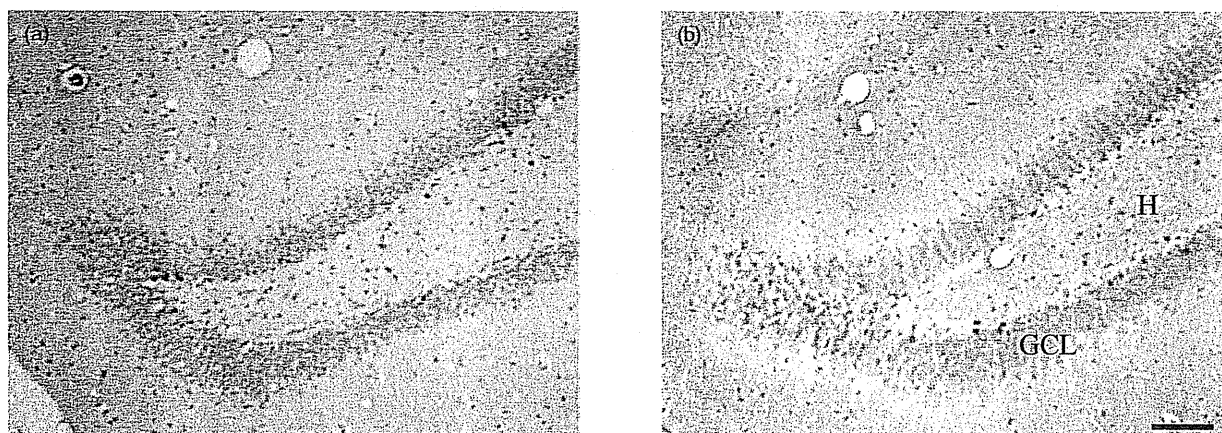


Figure 2. Bromodeoxyuridine-positive cells in the hippocampal dentate gyrus of (a) sham-treated control and (b) repetitive-transcranial-magnetic-stimulation-treated rats. Scale bar: 100 μ m. GCL, granule cell layer; H, hilus.

bovine serum albumin (BSA) and 0.1% Triton X-100 overnight at 4°C. The primary antibodies used for immunofluorescence staining were as follows: anti-BrdU, and anti-neuron-specific class III β -tubulin (TuJ1, 1:500, MMS-435P, Covance, Berkeley, CA, USA). After washing, sections were incubated at RT for 1 h with biotinylated donkey anti-rat IgG (1:400, Jackson ImmunoResearch, West Grove, PA, USA) and Cy3-conjugated donkey anti-mouse IgG (1:400, Jackson ImmunoResearch), containing 1% BSA and 0.1% Triton X-100. After rinsing, the sections were incubated with Cy2-conjugated streptavidin (Jackson ImmunoResearch) at RT for 1 h.

Quantitative analysis

Images of immunostained sections were captured from a microscope (Eclipse E800, Nikon, Tokyo, Japan) equipped with a color 3CCD camera (C5810, Hamamatsu Photonics, Hamamatsu, Shizuoka, Japan). The number of BrdU-immunoreactive cells in the granule cell layer (GCL) and the subgranular zone (SGZ, defined as two cell widths below the GCL) of the dentate gyrus was counted in six representative sections (−2.8 mm to −4.5 mm, relative to bregma according to the coordinates of Paxinos and Watson¹³) per animal using Adobe Photoshop software (Adobe Systems, San Jose, CA, USA) in a blinded fashion. The area of the GCL and the SGZ was quantified using NIH Image to estimate the number of BrdU-positive cells per unit area of the dentate gyrus. Statistical analysis was performed on the average number of BrdU-positive cells per section.

For immunofluorescent double labeling, sections were photographed using a Nikon Eclipse E800 microscope equipped with a VFM epi-FL attachment (Kawasaki, Kanagawa, Japan). At least 50 BrdU-positive cells per animal were analyzed to determine the proportions of BrdU-positive cells co-labeling with TuJ1.

The results are expressed as mean \pm SEM. Differences between groups were compared using the Student's *t*-test. Statistical significance was defined as $P < 0.05$.

RESULTS

Immunohistochemical staining showed that the majority of BrdU-positive cells were in the SGZ. There were significantly more BrdU-positive cells in the dentate gyrus of the rTMS-treated group as compared with the control group (Figs 2,3). Double immunofluorescence staining showed that most of the BrdU-positive cells were co-labeled with the neuronal marker TuJ1 (Fig. 4). The proportion of cells co-labeled with TuJ1 did not differ significantly between the rTMS-treated and control groups (TuJ1 co-labeled cells, $81.3 \pm 2.5\%$ and $80.4 \pm 3.1\%$, respectively).

DISCUSSION

In the present study, we examined the effects of chronic rTMS on neurogenesis in the dentate gyrus of adult rats. Our results showed that the number of

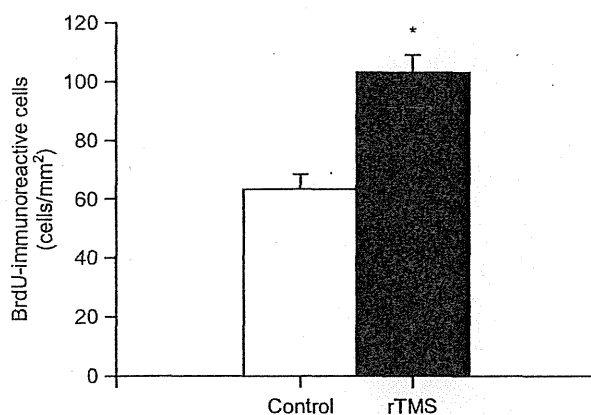


Figure 3. Quantification of bromodeoxyuridine (BrdU)-positive cells in the dentate gyrus. Chronic repetitive transcranial magnetic stimulation (rTMS) treatment significantly increased BrdU-positive cells (Control, 63.1 ± 5.1 cells/mm²; rTMS, 102.3 ± 6.4 cells/mm²). Results are shown as mean \pm SEM. * $P < 0.05$ vs control.

subgranular progenitor cells was significantly increased in the dentate gyrus. To our knowledge, this is the first report that chronic rTMS increased hippocampal neurogenesis.

Our results are in line with previous studies that showed that chronic treatments with ECS or various antidepressant drugs increase hippocampal neurogenesis in rodents,^{6,8–10} and non-human primates.¹¹ Hence, it appears that hippocampal neurogenesis

might be involved in the antidepressant effects of chronic rTMS, although our study did not utilize an animal model of depression or behavioral assessment.

In the present study, we used the similar conditions of chronic rTMS to those described by Sachdev *et al.*, who showed the antidepressant effects of rTMS in the forced swim test.³ We used the same rTMS device and the same figure-of-eight coil placed over the scalp with identical alignment. The rTMS parameters were also similar to them (25 Hz stimulating frequency, 70% of the rTMS device's maximum power, 1000 pulses per day). The stimulating frequency was set to 25 Hz because Sachdev *et al.* showed that this frequency was most effective among the four frequencies tested (1, 5, 15, and 25 Hz). However, while they assessed the effects of rTMS on the second day after the five daily rTMS treatments, we conducted rTMS treatment for 14 consecutive days according to the schedule of the most recent human clinical trials on depression.^{1,2}

Only one study, reported by Czéh *et al.*, has examined chronic rTMS effects on hippocampal neurogenesis in rats, and it showed that neurogenesis was not significantly increased.¹² In contrast with this study, we used a faster stimulating frequency (25 Hz vs 20 Hz) and more total pulses (14 000 pulses vs 5400 pulses). Our use of more powerful chronic rTMS treatment seems to be more appropriate for increasing hippocampal neurogenesis in rats.

The set of the conditions that modulate the intensity and distribution of electric currents and fields

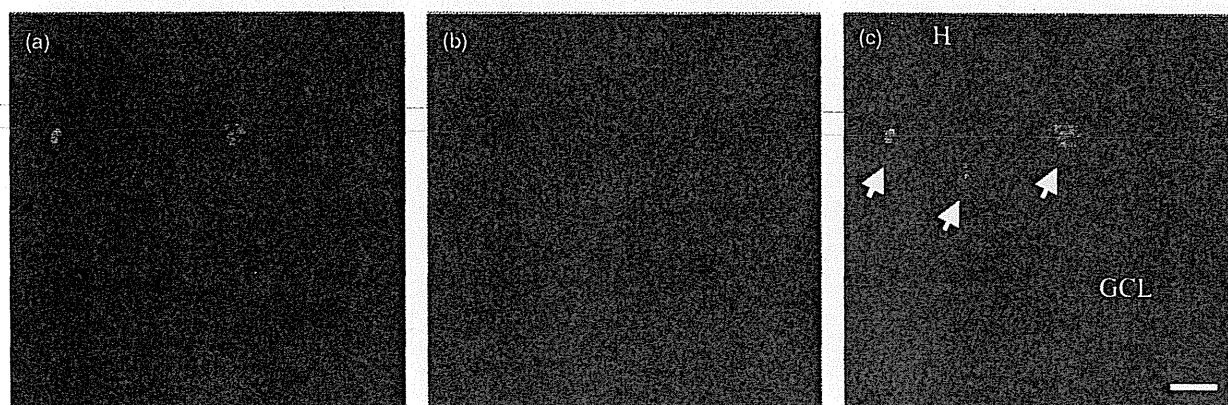


Figure 4. Double labeling with bromodeoxyuridine (BrdU) and neuronal marker anti-neuron-specific class III β -tubulin (TuJ1) after chronic repetitive transcranial magnetic stimulation (rTMS) treatment. Co-localization of (a, green) nuclear BrdU staining and (b, red) cytoplasmic TuJ1 staining. (c) The merged image shows TuJ1-positive cytoplasm surrounding BrdU-labeled nuclei (arrows). Scale bar: 10 μ m. GCL, granule cell layer; H, hilus.

induced by a single pulse in the rat brain (e.g. the shape, size, and location of the coil relative to the rodent small brain) is another important consideration.¹⁴ Czéh *et al.* used a smaller round coil over the left frontal brain region and theoretically estimated the characteristics of the intensity and distribution of electric currents and fields.¹² Further studies are needed to evaluate their characteristics in the present study conditions and how they influence the effect of rTMS on hippocampal neurogenesis in rodents.

While most of the previous studies examined hippocampal neurogenesis roughly 1 month after a single or several injections of BrdU, our examinations were conducted on the next day after completion of 14 daily rTMS and BrdU treatments, and we assessed the overall proliferation during the daily treatments. Therefore, our results should be interpreted cautiously when comparisons are made with the results of the previous studies. In addition, the survival of nascent cells was not examined in our study. For more exact comparisons and discussions, further studies will be necessary to set the protocol of the BrdU treatment according to the previous studies under similar conditions of the chronic rTMS of our study.

In conclusion, the present study demonstrated an increase of hippocampal neurogenesis in rats using 14-day chronic rTMS, and it appeared that this increase might be related to the antidepressant effects of rTMS. To examine this relationship more exactly, further studies are needed using an animal model of depression and antidepressant drug-treated animal groups. While a standard rTMS protocol for the treatment of human depression has not been established, our results, even though not directly applicable to humans, could contribute to determining the optimal clinical rTMS conditions for such treatment.

ACKNOWLEDGMENTS

This research was supported in part by a Grant-in-Aid for Scientific Research from the Ministry of Education, Culture, Sports, Science, and Technology of the Japanese Government (13671001) and in part by a grant from Mitsubishi Pharma Research Foundation.

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Review Article: Palliative Care

Importance of Rehabilitation in Cancer Treatment and Palliative Medicine

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Received January 11, 2011; accepted March 16, 2011

Although rehabilitation for cancer patients is being practiced in clinical settings, it has not been very well recognized in cancer care. However, interest has been turning to cancer rehabilitation in recent years in association with advances in palliative care and the increasing numbers of patients who survive for long periods, while enduring symptoms caused by cancer or adverse effects associated with treatment. The fact that cancer patient rehabilitation fees were newly established in the 2010 revision of the Japanese medical service fees has propelled interest in this topic. Rehabilitation can be applied throughout the entire phase from the time of diagnosis to the terminal stage, and it is an approach that can involve psychosocial aspects as well as physical aspects. Although its effectiveness has not been adequately demonstrated, especially in the area of palliative medicine, rehabilitation for cancer patients is expected to be an important means of supporting the hopes of patients and their families, and attempting to maintain and improve patients' quality of life.

Key words: ADL – QOL – rehabilitation

INTRODUCTION

Advances in treatment techniques have been associated with increases in cancer patient survival rates, and the numbers of long-term cancer survivors have been rising. Nevertheless, many cancer patients experience impairments in everyday living as a result of adverse effects or sequelae associated with treatment or as they reach the terminal stage of their disease. Rehabilitation may play a role as one approach to maintaining and improving the quality of life (QOL) of such cancer patients.

Approaches to cancer patient rehabilitation that take both psychosocial aspects and physical aspects into consideration are important, based on 'adequately understanding the strong connections between the patients' physical, psychological and social aspects (1)'. Thus, the involvement of representatives of a variety of occupations, including psychologists, clinical psychologists and nurses, and not just such rehabilitation specialists such as physical therapists, occupational therapists or speech therapists is important for the

rehabilitation of cancer patients; thus, a multidisciplinary team care is required. However, not many reports on the rehabilitation of cancer patients have appeared since the comprehensive research reports on the need for rehabilitation were first published by Lehmann et al. (2) and by Harvey et al. (3) in 1982. One reason for this lack of research is that as rehabilitation was originally performed mainly for the purpose of improving and raising the level of activities of daily living (ADL), there has been little demand from either healthcare providers or patients for proactive intervention in cancer care with regard to rehabilitation, which has had a strong image of being intended to improve ADL and return patients to their former lives. In recent years, however, interest has turned to the association between cancer rehabilitation and the increasing numbers of patients who survive for long periods, while enduring symptoms caused by cancer or the adverse effects associated with treatment or the association with advances in palliative care.

Dietz (4) has classified cancer rehabilitation according to cancer patients' physical and individual needs into four

categories: preventive, restorative, supportive and palliative (Table 1). Based on these categories, the effectiveness of rehabilitation has been reported for each stage of cancer treatment, from physical rehabilitation during the acute stage of treatment (5–8) to the rehabilitation of physical aspects and psychological aspects during the terminal stage (9–12), but it remains difficult to claim that cancer rehabilitation is generally acknowledged adequately. In view of these situations, Dietz (13) has pointed out that it will be necessary to focus on a concept of care that asks, ‘What is the best support that can be provided to enable cancer patients to readapt to society’, and DeLisa (14) has stated that ‘now that cancer patients’ survival rate has increased, attention should be turned to maintaining cancer patients’ QOL and prolonging it’. In other words, a shift to an approach that aims to maintain the QOL of patients at a high level and not just improve their function and prognosis has become necessary.

On the other hand, the recognition or practice of rehabilitation in the cancer area is not adequate. In this article, I will first outline the rehabilitation that is performed during each phase and the points to bear in mind while performing such rehabilitation. Next, I will report on rehabilitation needs, then on the current state of affairs with regard to cancer rehabilitation in Japan, including the results of our own research. Finally, I will describe the current problems and perspectives regarding rehabilitation for cancer patients.

REHABILITATION DURING EACH PHASE

The areas in which rehabilitation can be applied during the various phases of disease have been summarized in a table (Table 2) (15). Below, I have summarized the kinds of rehabilitation that are performed during each phase as well as some points to bear in mind.

REHABILITATION BEFORE AND AFTER SURGICAL TREATMENT

First, promoting early postoperative ambulation and improving physical functions so that patients can return as closely as possible to their lives before surgery is a goal common to rehabilitation for all diseases. During this phase, many patients have just started treatment, and rehabilitation should be conducted with sufficient consideration of the fact that many patients have a tendency to become psychologically depressed during this phase as a result of their ‘cancer’ diagnosis or changes in their body image as a result of surgery. When performing rehabilitation, it is important to first determine how a patient’s disease has been explained to him or her and how the patient perceives his or her disease. In addition, determining what issues patients and their families are concerned about at present and with regard to their future makes it possible to provide them with information to allay their concerns.

Now that the length of hospital stays in Japan has been shortened, the time available to conduct inpatient rehabilitation has also been limited. Thus, some problems may arise, while the patients are going about their daily lives after their discharge from hospital that were not recognized, while the patients were hospitalized. Patients often spend the next several years being concerned about recurrence, and another role of rehabilitation is to provide patients with a place to go for consultation when they have concerns after being discharged.

REHABILITATION DURING CHEMOTHERAPY

Physical strength tends to diminish during chemotherapy as a result of the adverse effects, such as nausea/vomiting, myelosuppression or peripheral neuropathies. Rehabilitation aims to encourage ambulation consistent with the patient’s condition even during chemotherapy and to prevent disuse

Table 1. Classification of cancer rehabilitation

(1) Preventive rehabilitation

Starts soon after cancer has been diagnosed. Performed before or immediately after surgery, radiotherapy or chemotherapy. No impairments of function present yet. Preventing impairments is the purpose of the rehabilitation measures

(2) Restorative rehabilitation

Aims for the maximal recovery of function in patients with remaining function and ability Attempts to achieve maximal functional recovery in patients who have impairments of function and decreased abilities

(3) Supportive rehabilitation

Increases self-care ability and mobility using methods that are effective (e.g. guidance with regard to self-help devices, self-care and more skillful ways of doing things) for patients whose cancer has been growing and whose impairments of function and declining abilities have been progressing. Also includes preventing disuse, such as contractures, muscle atrophy, loss of muscle strength and decubitus

(4) Palliative rehabilitation

Enables patients in the terminal stage to lead a high QOL physically, psychologically and socially, while respecting their wishes. Designed to relieve symptoms, such as pain, dyspnea and edema and to prevent contractures and decubitus using heat, low-frequency therapy, positioning, breathing assistance, relaxation or the use of assistive devices

Quoted from ref. no. 4.

Table 2. Possible contributions of rehabilitation in the various phases of the disease

Phase of disease	Possible contributions of rehabilitation
I. Treatment	<ol style="list-style-type: none"> 1. Evaluating the effects of treatments on function 2. Preserving and restoring function through exercise, edema management and increased activity 3. Controlling pain using heat, cold and transcutaneous electrical nerve stimulation
II. Posttreatment	<ol style="list-style-type: none"> 1. Developing and supporting a program to help restore daily routines and promote a healthy life-style 2. Educating the patient about what to self-monitor 3. Supervising a maintenance program of exercise, edema management, and mobility management and mobility
III. Recurrence	<ol style="list-style-type: none"> 1. Educating the patient about the impact of recurrence and its effect on function 2. Educating the patient about what to monitor in the context of the new clinical status 3. Supervising the patient in an appropriate program to restore function or prevent its decline
IV. End of life	<ol style="list-style-type: none"> 1. Educating patient/family regarding mobility training, good body mechanics and assistive devices 2. Pain management (non-pharmacologic treatment) and symptom control 3. Maintaining independence and quality of life

Quoted from ref. no. 15.

syndrome and maintain physical and muscle strength by performing mild exercise therapy and sedentary occupational therapy. Failure to resume ambulation during treatment and the development of severe disuse syndrome often occur, especially among infants and the elderly. It is important for the rehabilitation staff to visit the patient regularly and to make movement a habit, even if only a little at a time, by incorporating activities that the patients enjoy.

Moreover, many patients today receive outpatient chemotherapy as well as inpatient chemotherapy, and treatment is expected to shift even further toward an outpatient setting. Patients undergoing outpatient chemotherapy continue their daily lives at home while receiving treatment. Continuing to work and keep house, while experiencing the adverse effects of treatment often imposes a major burden on patients. The rehabilitation staff should determine which activities a patient considers to be important in his or her life so that the patient can recognize their own symptoms and acquire his or her desired ADL, with the rehabilitation staff proposing activities that will help the patient to do what he or she wants to do. Giving the patients the sense that they are able to control their own activities in this way is an important link to preserving their self-confidence.

REHABILITATION DURING THE RECURRENCE AND ADVANCED STAGES

Patients with recurrent and advanced cancer experience a variety of symptoms associated with cancer progression. Because patients also sometimes develop disuse syndrome and their general condition rapidly deteriorates when they are deprived of opportunities to move as a result of general malaise and feeling tired, it is desirable to maintain a minimum of self-care in their everyday lives, i.e. feeding, elimination and bathing, whenever possible.

As the disease progresses, patients are compelled to cope with physical symptoms that develop one after another. Faced with these circumstances, caution is required when dealing with patients during this phase, when they are also often confronted with situations that may make the cure of their disease difficult. Because many patients are trying to concentrate on treatment during the phase, with the aim of a cure, the improvement of physical functions is often ranked first among patient's hopes with regard to rehabilitation. However, when they approach the transition period, it becomes necessary to consider what it is that they really want to do in anticipation of the future deterioration of their physical condition. It takes time for this transition to occur, and the feelings of patients and their families may change markedly. It is important to recognize that fluctuating feelings are natural, and it may be necessary to listen closely to the patients and their families from time to time and await their choices. In terms of the goals of rehabilitation, the rehabilitation staff should interact with the patients and their families in a manner that will enable them to accept reality and to identify their goals. The rehabilitation approach should also take into consideration the environment surrounding the patient, including the patients' own remaining functional activities as well as the human support that is available, the utilization of healthcare devices, and the utilization of social resources, so that patients are able to achieve whatever they hope to do.

REHABILITATION DURING THE TERMINAL STAGE

Patients' and their families' needs are most important during the terminal stage. When patients express strong wishes, such as 'I want to go to the bathroom' and 'I want to walk', up until the very end, it is sometimes possible to satisfy their wishes by teaching family members how to assist them,

making adjustments to the environment around the bed and around the bathroom, and by making walking aids available, even when there is no prospect for improvement in the patients' functions. Communication with patients and their families also becomes important during this phase, and when communication becomes difficult for patients, providing support designed to achieve understanding among patients, their families and the staff by introducing communication aids or assisting with conversation is another important role of rehabilitation.

Moreover, even when a patient's general condition deteriorates, it is possible to perform rehabilitation until the very end by going to the patient's bedside and touching the patient's body through palliative interventions, such as range of motion (ROM) exercises for the patients' limbs, massage for swollen lower limbs or breathing assistance.

As stated earlier, rehabilitation can be applied throughout the entire phase of disease from the time of diagnosis until the terminal stage, and involvement with psychosocial aspects not just physical aspects can be included as one possible approach.

REHABILITATION NEEDS

Several studies have already been conducted regarding the needs of cancer patients in relation to rehabilitation. A survey of the rehabilitation needs during the initial stage of treatment in the USA revealed that 87% of the patients had rehabilitation needs, and recovery from deconditioning; improvement of impaired mobility, restricted ROM and impaired ADL, and a need for distraction were cited as rehabilitation needed (16). In the Netherlands, it was reported that 26% of the participants desired specialized support to strengthen physical functions, to deal with their physical and social situation, and to find new goals in their lives (17). In addition, broader needs were cited in relation to the lives of those living at home, including with respect to financial matters, the performance of housework and means of transportation (18). However, the results of interventions to meet such needs have never been elucidated.

Moreover, in a questionnaire survey of the families of patients who had died in a palliative care unit in Japan, pain, impaired mobility and ADL impairments were mentioned as problems during the hospital stay, and it was shown that even during the terminal stage 85% of the patients wanted to be able to walk or to move about in a wheelchair, and interventions with regard to these aspects were said to be effective and satisfactory (12). However, what patients themselves feel is effective and satisfactory has never been elucidated in proxy evaluations by bereaved families, and there have been no reports of investigations of the families' degree of satisfaction or changes in their emotions.

We therefore provided rehabilitation to 23 inpatients of a cancer hospital for 2 weeks and conducted a survey of the patients and their families to determine what changed before

and after the rehabilitation (19). The performance status (PS) of the patients was 3 in 12 cases (52.2%) and 4 in 8 cases (34.8%); thus, 87% of the patients had a PS of 3–4. The rehabilitation that was performed consisted mainly of standing training, gait training and upper limb function training. The results of the rehabilitation interventions included changes in several physical aspects and considerable changes in the emotional states of both the patients and their families (evaluated using a face scale). Thus, psychological suffering was alleviated by the rehabilitation efforts. When the patients and their families were surveyed separately with regard to how they felt about the effectiveness of the rehabilitation, the patients mentioned 'a feeling of relief as a result of receiving guidance' and 'psychological support', while the families mentioned content related to the impact of the rehabilitation on the psychological aspects of the patients, such as 'effective in terms of mental aspects', 'fun' and 'restoration of self-confidence'. Based on the earlier-mentioned findings, rehabilitation for cancer patients may be effective not only in terms of physical aspects, but also in terms of psychological aspects.

CURRENT STATUS OF CANCER REHABILITATION IN JAPAN

In March 2006, we conducted a survey on the current status of cancer rehabilitation by mailing questionnaires to 1693 nationwide healthcare institutions certified as general hospitals, long-term care hospitals or multi-unit hospitals according to evaluations performed by the Japan Council for Quality Health Care in December 2005. The survey asked whether the institutions had performed rehabilitation for cancer patients in 2005, and the institutions that had performed cancer rehabilitation were surveyed as to the nature of the rehabilitation that was performed, the stage of the cancer patients' disease, the type of cancer, the number of patients who received rehabilitation, the occupations of the personnel who provided the rehabilitation and whether the institution had a specialized cancer rehabilitation facility or equipment. In addition, the institutions where cancer rehabilitation was not being performed were asked about whether there was a need for cancer rehabilitation, the settings in which they felt that there was a need, the reason why rehabilitation was not being performed, and whether there were any plans to perform rehabilitation in the future (20).

Valid replies were received from 1045 (62.0%) of the healthcare institutions nationwide, and 864 (82.7%) of them were institutions that had performed rehabilitation for cancer patients in 2005. However, we could not clarify the exact number of cancer patients who received rehabilitation. In terms of the nature of the rehabilitation, large percentages replied that they had performed rehabilitation for physical functions: gait training in 92.1%, muscle strength training in 88.9% and joint ROM training in 85.6%. A large percentage of the institutions (73.6%) also provided training with regard

to ADL. Small percentages of the institutions performed specialized rehabilitation for lymphedema care, postoperative head and neck cancer care, colostomy care after colorectal cancer surgery, urostomy care after surgery for urinary tract cancer or rehabilitation that focused on mental and psychological aspects. Of the 181 institutions that had not performed rehabilitation for cancer patients, 171 (94.5%) replied that they felt a need for rehabilitation for cancer patients. The most common settings in which a need was felt were when 'patients would say that they wanted to stand up and walk again' and 'patients would say that they wish they could go to the bathroom without needing help from anyone'.

The above results indicated a large need for rehabilitation for cancer patients, but it was not concluded to what extent the current status met the needs of cancer rehabilitation. This survey also showed that the system for performing cancer rehabilitation is inadequate and that it is needed to assess strategies designed to develop and disseminate rehabilitation programs for cancer patients.

CURRENT PROBLEMS AND PERSPECTIVES

As stated already, although the need for the rehabilitation of cancer patients has been recognized, the degree of recognition in the field of oncology remains somewhat low. The fact that there have been few reports demonstrating its effectiveness can be cited as one of the reasons for this state of affairs. Recently, a systematic review regarding the health effects of exercise during cancer rehabilitation has been established (21). Ten studies were reviewed, and improvements in physical functioning, strength, physical activity levels, QOL, fatigue, immune function, hemoglobin concentrations, potential markers of recurrence and body composition were reported. However, all the studies were limited by incomplete reporting and methodological limitations.

We also systematically reviewed the effectiveness of cancer rehabilitation in palliative care using the keywords 'cancer' AND 'palliative care' AND 'rehabilitation' to search a medical literature database (PubMed) on 17 August 2009. We restricted the study design to intervention studies (retrospective studies and case reports were excluded, and music therapy was also excluded) and to studies that focused on physical functions and daily living functions. After conducting discussions twice a year (a total of four times), we performed a systematic review of the following survey items: lead author, name of the country, journal name, year of publication, number of subjects, cancer site, proportion of females, age, composition of the rehabilitation team, intervention (method, frequency and time per day), main outcomes and main results. As a result, only eight documents were retrieved, and three of them were randomized controlled trials (in submission). Thus, although rehabilitation is being practiced in the palliative care area, the evaluation of its outcome will be a future task.

We have not devoted much attention to the particulars of rehabilitation in this review because considerable variation exists in the interventions that are actually being performed for individual patients and because the interventions have been established as rehabilitation techniques and are not specifically performed only for cancer patients. Instead, the task from now on will be to determine how rehabilitation personnel may acquire knowledge about cancer and incorporate established techniques into cancer care.

CONCLUSION

Interest in cancer rehabilitation in Japan has increased since cancer patient rehabilitation fees were newly established in the 2010 revision of medical care service fees. However, it is still hard to say that the need for rehabilitation services has been adequately acknowledged in cancer care and that future research is needed because high-quality literature evidence is still lacking.

Rehabilitation is expected to become an important support that sustains the hopes of patients and their families, as it is said that 'Being able to maintain and improve ADL as much as possible, while skillfully using remaining physical strength is a great joy and is linked to the desire to live'.

Funding

This work was supported in part by the Third Term Comprehensive Control Research for Cancer from the Japanese Ministry of Health, Labour and Welfare.

Conflict of interest statement

None declared.

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Assessment of the efficacy of footbaths as a means of improving the mental health of nurses: a preliminary report

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Key words : 1. chromogranin A 2. footbath 3. stress

Objective: There are few studies that have subjectively and objectively verified the efficacy of footbaths as a means of relieving stress. The purpose of the present study was to validate the stress-reducing efficacy of footbaths both subjectively and objectively by means of a stress indicator, chromogranin A (CgA).

Methods: The subjects were 21 female nurses working at a general hospital. After evaluating their current mental and physical condition, and measuring their salivary CgA levels, the subjects took a 10-min footbath. After the bath their mental and physical condition was evaluated again, and their salivary CgA levels were measured again. The changes in their mental and physical state before and after the footbath were assessed by the Wilcoxon signed-rank test. CgA levels taken before and after the footbath were assessed by the paired *t*-test.

Results: The results showed that both their subjective mental and physical condition improved and their CgA levels were lower after the footbath than before.

Conclusions: These results suggested that footbaths can exert a restorative effect on the stress associated with the performance of nursing duties and are effective in relieving nurses' stress.

Introduction

Nursing work is said to involve greater job stress than other occupations¹⁾, and for that reason there have been many studies examining nurses' stress management²⁻⁷⁾. Relaxation methods are one form of stress management. A variety of relaxation methods are available, e.g., listening to music or massage⁸⁾. In the present study we turned our attention to footbaths, which are familiar as a nursing activity. Footbaths require no special facilities and are more convenient than showers or taking a bath, and, unlike massage, they do not require any special skills. Some previous studies showed that footbaths produced (1) significant changes in the autonomic responses, indicating a shift to increased parasympathetic and decreased sympathetic activity and (2) significant increases in the white blood cell (WBC) count and natural killer (NK) cell cyto-

toxicity, suggesting an improved immune status^{9,10)}. However, few studies have focused on footbaths as a relaxation method for nurses' stress management, and although there have been subjective evaluations by means of questionnaires to assess the efficacy of footbaths, few evaluations have used objective indicators^{11,12)}.

Chromogranin A (CgA) is a protein secreted by the chromaffin cells of the adrenal medulla and by sympathetic neurons¹³⁾. It is present in endocrine organs and sympathetic neurons, where it is stored along with catecholamines, and they are secreted together in response to sympathetic nervous system stimulation¹⁴⁾. CgA is present in salivary glands and released into saliva in response to stimulation of the autonomic nervous system¹⁵⁻¹⁷⁾. According to a report of a study in which salivary concentrations of CgA, catecholamines, and cortisol were measured in association with stress

・看護職者のメンタルヘルス向上を目指した足浴の効果に関する予備的検討

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loading, when subjects were exposed to a stress load, the CgA level rose before the cortisol level, whereas during exercise stress loading the catecholamine levels increased dramatically, but there were no marked changes in the CgA level¹⁸⁾. The testing method is characterized by the advantages of requiring collection of saliva alone and enabling measurements to be made painlessly. Salivary CgA levels react specifically to stress. They rise even when exposed to only minor stress, and they rapidly decline at the conclusion of the stress¹⁹⁾. The major advantage of the use of salivary CgA, therefore, is that the sampling is non-invasive and can be performed in non-stressful conditions. Furthermore, CgA is secreted immediately after stress without the influence of circadian rhythm²⁰⁾.

The aim of this preliminary study was, subjectively and objectively and based on salivary CgA levels, to verify the efficacy of footbaths as a means of relieving the stress of nurses. If the efficacy of footbaths were demonstrated in this study, footbaths could possibly be used as a coping strategy to relieve stress and to contribute to improving the mental health of nurses.

Method

After obtaining the approval of the Institutional Review Board of the institution, the purpose, content, etc., of the study were explained to the candidates in a document requesting cooperation with the study. The study was conducted only on candidates who had given their written consent to participate.

The participants were 21 female nurses, with a mean age of 29.2 years (22 to 47 years). There were nine nurses with fewer than 5 years of nursing experience, seven with 5 to 9 years, and five with 10 or more years of experience.

The survey was conducted on the subjects after they had completed their day duty (8:20-17:00). All experiments were performed in an air-conditioned quiet room between 17:15 and 18:15. First, after basic information, including age and number of years of nursing experience, was taken during an interview when they came off duty, saliva was collected, and they were requested to fill out a questionnaire on their current mental and physical states. Current mental and physical states were evaluated on a 6-point Likert scale that the authors had prepared (1: very poor, 2: poor, 3: somewhat poor, 4: somewhat good, 5: good, 6: very good). Then a

special footbath vessel (MA-226; Marutaka, Tokyo, Japan) was filled with hot water so as to immerse the feet in 40°C water from the ankle joint to the dorsum of the foot and the toes. The footbath was continued for 10 min based on a previous study²¹⁾. After completion of the footbath, saliva was collected again, and the subject was asked to fill out the questionnaire on their current mental and physical states again.

The saliva was collected in the following manner. The subject gently bit on two cotton rolls with the molar teeth for about 1-2 min, allowing saliva to penetrate them thoroughly. The cotton rolls were then removed from the mouth by the subject. They were then returned to the original saliva collection vessel, and it was sealed. The vessel was then immediately stored in a cold place, and after placing it in a cold storage envelope, it was sent to a specialized facility for measurement. The concentration of CgA was determined using an enzyme-linked immunosorbent assay kit (YK070 Human Chromogranin A EIA, Yanaihara Institute, Shizuoka, Japan).

During the footbath the examiner was in the same room, and observed the subjects without speaking to them.

The changes in mental and physical state before and after the footbath were assessed by the Wilcoxon signed-rank test. CgA levels between before and after the footbath were assessed by the paired *t*-test. The *p* values in all of the tests were two-tailed, and *p* values <0.05 were considered significant. Statistical Package for the Social Sciences (SPSS) ver. 14.0J for Windows software was used to perform all of the statistical analyses.

Results

Comparisons between the CgA levels before and after the footbath showed a significant change in levels (Fig. 1).

Regarding their mental and physical states, at the end of duty, two subjects evaluated their mental and physical state before the footbath as "good", but after the bath both changed it to "very good". There were nine subjects who initially evaluated their mental and physical state as "somewhat good". Two of them changed it to "very good", while the other seven changed it to "good". There were three subjects who initially rated their condition as "somewhat poor", and all three changed it to "somewhat good". There were five