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Symptom Management and Supportive Care

Antiemetic Corticosteroid Rotation from Dexamethasone to Methylprednisolone to Prevent Dexamethasone-Induced Hiccup in Cancer Patients Treated with Chemotherapy: A Randomized, Single-Blind, Crossover Phase III Trial

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Hiccup • Emesis • Dexamethasone • Methylprednisolone • Cancer chemotherapy

Abstract

Background. To assess whether the rotation of dexamethasone to methylprednisolone decreases the intensity of dexamethasone-induced hiccup (DIH) in cancer patients treated with chemotherapy.

Materials and Methods. Adult patients who experienced DIH within 3 days after the administration of dexamethasone as an antiemetic were screened. Eligible patients were randomly assigned to receive dexamethasone ($n = 33$) or methylprednisolone ($n = 32$) as an antiemetic (randomization phase). In the next cycle of chemotherapy, the dexamethasone group received methylprednisolone and vice versa in the methylprednisolone group (crossover phase). The primary endpoint was the difference in hiccup intensity as measured using the numeric rating scale (NRS) between two groups.

Results. No female patients were enrolled, although the study did not exclude them. At the randomization phase, hiccup frequency was 28/33 (84.8%) in the dexamethasone group versus 20/32 (62.5%) in the methylprednisolone group ($p = .04$). Intensity of hiccup was significantly higher in the dexamethasone group than that in the methylprednisolone group (mean NRS, 3.5 vs. 1.4, $p < .001$). At the crossover phase, hiccup intensity was further decreased after the rotation of dexamethasone to methylprednisolone in the dexamethasone group (mean NRS, 3.5 to 0.9, $p < .001$), while it was increased by rotating

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methylprednisolone to dexamethasone in the methylprednisolone group (mean NRS, 1.4 to 3.3, $p = .025$). There were no differences in emesis intensity between the two groups at either the randomization or crossover phases. Clinicaltrials.gov identifier: NCT01974024.

Conclusion. Dexamethasone-induced hiccup is a male-predominant phenomenon that can be ameliorated by rotating dexamethasone to methylprednisolone without compromising the antiemetic efficacy. ***The Oncologist*** 2017;22:1354–1361

Implications for Practice: In this randomized, multicenter, phase III trial, hiccup intensity was significantly lower when the antiemetic corticosteroid was rotated from dexamethasone to methylprednisolone without a change in emesis intensity than that when dexamethasone was maintained. At the crossover phase, hiccup intensity was increased again if dexamethasone was readministered instead of methylprednisolone. The present study demonstrated that dexamethasone-induced hiccup can be improved by rotating from dexamethasone to methylprednisolone without compromising its antiemetic efficacy.

Introduction

Dexamethasone is an established agent for the prevention of chemotherapy-induced nausea and/or vomiting (CINV) in both the acute and delayed phases [1–4]. However, even a short course of dexamethasone can cause many adverse effects, such as insomnia, indigestion, weight gain, and acne [5]. Hiccup is another problem in cancer patients with dexamethasone for CINV. Its incidence is unknown and thought to be low, considering the incidence of hiccup (0.4%) in patients treated with chemotherapy [6]. Although hiccupping may often be regarded trivial and is underestimated by many clinicians, persistent and intractable hiccups can cause depression, insomnia, decrease of oral intake, and malnutrition in cancer patients [7, 8]. Dexamethasone-induced hiccup (DIH) can be resolved with the simple discontinuation of the medication. However, the discontinuation of dexamethasone significantly increases the risk of CINV in patients treated with emetogenic chemotherapy [9].

Methylprednisolone is another corticosteroid that has an antiemetic property when used in combination with a serotonin antagonist or even alone [10–13]. Therefore, the rotation of antiemetics from dexamethasone to methylprednisolone may be an option in patients with DIH. In a previous retrospective study, we reported that this approach effectively reduces the incidence rate of DIH without an increased risk of CINV [14].

To confirm our previous results, we planned a randomized prospective trial for cancer patients with DIH. The objective of the present study was to determine whether the rotation of corticosteroids affects the incidence and intensity of DIH without compromising the antiemetic efficacy.

Materials and Methods

Patients

The study was performed at 14 centers in Korea between October 2013 and June 2016. Among the cancer patients (age 21 years or older) treated with intravenous chemotherapy, those with DIH were screened within 3 days after an administration of dexamethasone as an antiemetic at a dose of 8–20 mg per day. The cut-off points on the 0–10 numeric rating scale (NRS), in which 0 indicates "no symptoms" and 10 indicates "unbearable symptoms," were used to assess the intensities of hiccup and emesis. In addition to pain, other symptom distress in cancer patients can be assessed using NRS. The Edmonton Symptom Assessment System (ESAS), which has been widely validated in cancer patients, assesses the severity of nine symptoms, including pain, through NRS. Additionally, the ESAS allows any other symptoms to be assessed with NRS [15]. The researchers (health professionals) asked patients "What number describes your average hiccup and emesis from 0 to 10 over the last 24 hours?" at the time of screening.

Eligible patients were those with significant DIH defined as an average hiccup intensity of NRS 4 or more over the last 24 hours at a dose of 8–20 mg of dexamethasone. The exclusion criteria were as follows: (a) history of stroke, epilepsy, and dementia; (b) current central nervous system (CNS) metastases or infection; (c) uncontrolled diabetes mellitus; (d) uncontrolled ischaemic heart disease; (e) gastrointestinal obstruction; (f) uncontrolled gastro-oesophageal reflux disease or active peptic ulcer; (g) organic lesions on the diaphragm; and (h) uncontrolled infection such as pneumonia. The protocol was approved by the institutional review boards of every participating center, and written informed consent was obtained from each participant.

Study Design

This study was a single-blind, prospective, randomized multicenter trial with a crossover design (Fig. 1). Eligible patients were randomly assigned (1:1) to receive dexamethasone or methylprednisolone as an antiemetic corticosteroid using a block randomization scheme (block size of 4). At the first cycle of chemotherapy after the randomization (randomization phase), the dexamethasone group received a dose of 8–20 mg per day of intravenous or oral dexamethasone as an antiemetic according to each institutional protocol. The methylprednisolone group received an equivalent dose of intravenous methylprednisolone instead of dexamethasone, which was used as an antiemetic at the last cycle of chemotherapy performed before the randomization. The recommended conversion rate was 5 mg of methylprednisolone per 1 mg of dexamethasone [16]. All other previously used antiemetics were maintained. The addition of new antiemetics or omission of previously used antiemetics was not permitted except for the management of breakthrough emesis. In the next cycle of chemotherapy (crossover phase), the dexamethasone group received an equivalent dose of methylprednisolone instead of dexamethasone given at the randomization phase, and vice versa in the methylprednisolone group. If clinically indicated, dose reduction of chemotherapy was permitted during the study. However, a change of chemotherapy regimen was not permitted. If the regimen had to be changed due to cancer progression, the patient dropped out.

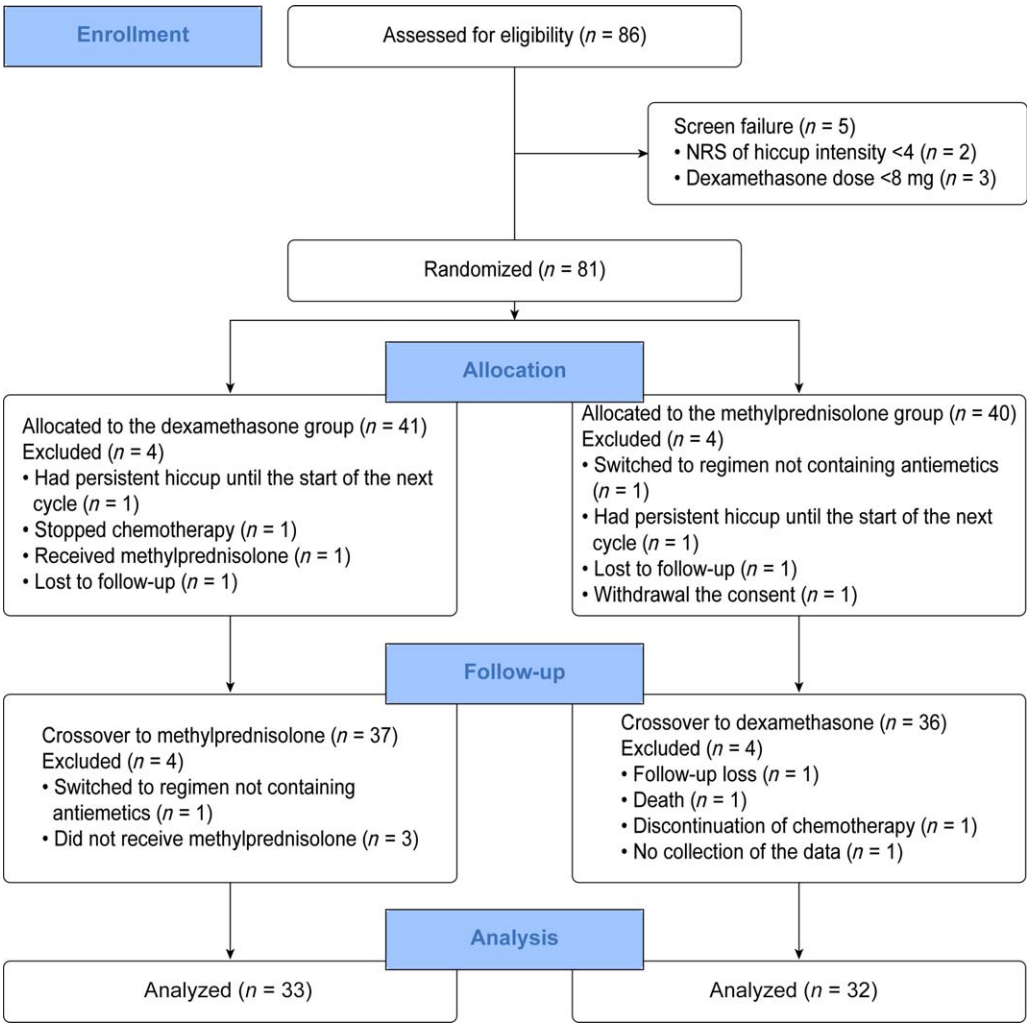

Figure 1. Consolidated Standards of Reporting Trials diagram.
Abbreviation: NRS, numeric rating scale.

Assessments and Endpoints

Baseline assessments at the screening visit included demographics, medical history, laboratory and radiologic tests for screening, the Eastern Cooperative Oncology Group Performance Status (ECOG PS), intensities of hiccup and emesis, and quality of life (QoL), which was assessed using Functional Assessment of Cancer Therapy-General (FACT-G, version 4) [17]. At the randomization and crossover phases, the intensities of hiccup and emesis and the QoL were evaluated once between 24 and 72 hours after the administration of last dose of antiemetic corticosteroids. The researchers asked patients about average NRS of hiccup and emesis over the last 24 hours as described above. The patients without hiccup at the time of assessment were educated to report the intensity of hiccup to the researchers if this symptom was developed thereafter until 72 hours after the administration of last dose of antiemetic corticosteroids. The primary endpoint was the difference in hiccup intensity as measured using the NRS between the dexamethasone and methylprednisolone groups. Secondary endpoints included differences in the incidences of hiccup and emesis (determined by whether the NRS is zero or not), in the intensity of emesis, and in the QoL between two groups.

Statistical Analysis

This study was designed to prove the inequality in hiccup intensity between the dexamethasone and methylprednisolone groups at the randomization phase. Sample size was calculated to detect an absolute difference of 1.5 points in the mean NRS of hiccups between two groups at the randomization phase. Assuming a two-sided type I error rate of 5% and a power of 90%, 54 patients were required in each group to detect this difference. When the attrition rate is expected to be 20%, 68 patients were required in each group. An interim analysis by an independent data monitoring board was planned when 80 patients were enrolled. A Lan and DeMets alpha spending function approach was used for the early rejection of the null hypothesis [18]. All analyses were based on the per-protocol population. The Mann-Whitney U test for continuous variables and chi-squares or Fisher's exact test for categorical variables were used to compare two groups. The Wilcoxon signed-rank test for continuous variables and McNemar's test for categorical variables were used to compare paired values. Two-way analysis of variance (ANOVA) was performed to evaluate the effects of the types of corticosteroids and chemotherapy or other antiemetics with their interaction on the intensity of

Table 1. Baseline characteristics

Characteristic	All $n = 65$, n (%)	Dexa → Dexa → mPd $n = 33$, n (%)	Dexa → mPd → Dexa $n = 32$, n (%)	p value
Male sex	65 (100.0)	33 (100.0)	32 (100.0)	
Age, median (range)	61 (28–80)	61 (28–79)	61.5 (36–80)	.778
ECOG PS				.613
0–1	61 (93.9)	30 (90.9)	31 (96.9)	
2	4 (6.2)	3 (9.1)	1 (3.1)	
Primary site of tumor				.203
Lung	13 (20.0)	10 (30.3)	3 (9.4)	
Gastrointestinal	28 (43.1)	12 (36.4)	16 (50.0)	
Genitourinary	10 (15.4)	5 (15.2)	5 (15.6)	
Others	14 (21.5)	6 (18.2)	8 (25.0)	
Intent of chemotherapy				>.99
Adjuvant	13 (20.0)	7 (21.2)	6 (18.8)	
Palliative	48 (73.9)	24 (72.7)	24 (75.0)	
Others	4 (6.2)	2 (6.1)	2 (6.3)	
Type of chemotherapy				
Fluoropyrimidine-based	27 (41.5)	13 (39.4)	14 (43.8)	.722
Platinum-based	48 (73.9)	23 (69.7)	25 (78.1)	.440
Type of antiemetic regimen				.543
For high emetogenic potential chemotherapy[a]	37 (56.9)	20 (60.6)	17 (53.1)	
Others	28 (43.1)	13 (39.4)	15 (46.9)	
Dose of dexamethasone, mean ± SD, mg	9.8 ± 2.3	9.6 ± 2.1	9.9 ± 2.5	.961
Hiccup intensity, NRS, mean ± SD	6.3 ± 1.7	6.5 ± 1.7	6.1 ± 1.6	.247
Emesis intensity, NRS, mean ± SD	1.7 ± 2.2	1.2 ± 1.9	2.3 ± 2.4	.089
FACT-G questionnaire, mean ± SD ($n = 58$)				
Total	73.2 ± 15.1	74.2 ± 15.1	72.2 ± 15.2	.597
PWB	21.1 ± 5.6	20.9 ± 5.9	21.3 ± 5.4	.809
SWB	16.3 ± 5.4	17.0 ± 5.3	15.5 ± 5.5	.303
EWB	18.2 ± 4.8	18.6 ± 4.6	17.8 ± 5.0	.696
FWB	17.6 ± 6.1	17.7 ± 6.3	17.6 ± 6.0	.969

[a]Neurokinin-1 antagonist-containing regimens were used through each institutional protocol (cisplatin-based [$n = 36$], doxorubicin/ifosfamide [$n = 1$]).

Abbreviations: Dexa, dexamethasone; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EWB, emotional well-being; FACT-G, functional assessment of cancer therapy-general; FWB, functional well-being; mPd, methylprednisolone; NRS, numeric rating scale; PWB, physical well-being; SD, standard deviation; SWB, social well-being.

hiccup. A value of $p < .05$ was considered significant. All statistical analyses were conducted using Stata software (ver. 14.0; Stata Corp., College Station, TX, http://www.stata.com).

Results

Baseline Characteristics

Interim analysis was performed in June 2016 to determine whether the study was likely to achieve its primary objective. At that time, enrollment reached 60% of the planned recruitment, and early stopping to reject the null hypothesis required a p value $\leq .007$. Because this condition was met in the interim analysis ($p < .001$), the study was terminated early.

Eighty-six patients were recruited in the study (Fig. 1). Of these, 21 patients were ineligible. The remaining 65 patients were randomly assigned to the dexamethasone ($n = 33$) and methylprednisolone groups ($n = 32$). The baseline characteristics of the analyzable patients are described in Table 1. All enrolled patients were male, although the exclusion criteria did not specify the sex of the patients. The majority of patients had been treated with palliative-intent chemotherapy ($n = 48$, 73.9%) and had a good ECOG PS of 0–1 ($n = 61$, 93.9%). With the mean dose of 9.8 mg of dexamethasone, the intensity of hiccup was moderate (mean NRS 6.3), and the intensity of emesis was mild (mean NRS 1.7). The mean doses of corticosteroids used at the randomization (9.7 mg in dexamethasone, 49.9 mg in methylprednisolone) and crossover (9.9 mg in dexamethasone, 47.1 mg in methylprednisolone) phases were similar to those used at the screening. There were no significant differences in the demographics, primary site of the tumor, prior medication, intensities of hiccup and emesis, and QoL between the groups.

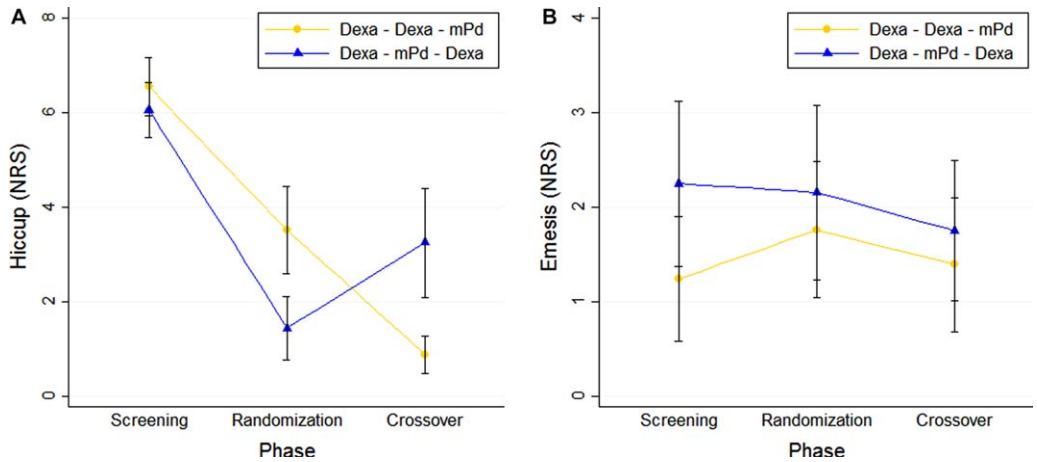

Figure 2. Absolute change (mean ± 95% confidence interval) in the intensities of hiccup **(A)** and emesis **(B)** in each group according to the study phase.

Abbreviations: Dexa, dexamethasone; mPd, methylprednisolone; NRS, numeric rating scale.

Hiccup

Figure 2A shows the change in hiccup intensity according to the study phase by each group. At the randomization phase, hiccup intensity was decreased in both the dexamethasone group (mean NRS ± standard deviation [SD]; 95% confidence interval [CI], 6.5 ± 1.7 [5.9–7.2] to 3.5 ± 2.6 [2.6–4.4]; $p < .001$) and the methylprednisolone group (mean NRS ± SD [95% CI], 6.1 ± 1.6 [5.5–6.6] to 1.4 ± 1.9 [0.8–2.1]; $p < .001$) compared with the level noted at screening. In contrast to the randomization phase, the change pattern in the hiccup intensity was different in each group at the crossover phase. The hiccup intensity of the dexamethasone group was decreased again after the rotation of dexamethasone to methylprednisolone (mean NRS ± SD [95% CI], 3.5 ± 2.6 [2.6–4.4] to 0.9 ± 1.1 [0.5–1.3]; $p < .001$), while that of the methylprednisolone group was increased by rotating the methylprednisolone to the dexamethasone (mean NRS ± SD, 1.4 ± 1.9 [0.8–2.1] to 3.3 ± 3.2 [2.1–4.4]; $p = .025$) at the crossover phase.

In addition to the comparison between the study phases in each group, intergroup comparisons were also performed. At the randomization phase, there was a significant difference in the hiccup intensity between the dexamethasone and methylprednisolone groups (mean NRS ± SD [95% CI], 3.5 ± 2.6 [2.6–4.4] vs. 1.4 ± 1.9 [0.8–2.1], respectively; $p < .001$, primary endpoint), although the hiccup intensity was decreased in both groups compared with that at the screening level. In two-way ANOVA for the hiccup intensity at the randomization phase, there was a significant main effect for the type of corticosteroid without interaction with the type of chemotherapy or other antiemetics (Table 2).

The hiccup intensity at the crossover phase was also different between the dexamethasone (methylprednisolone used) and methylprednisolone (dexamethasone used) groups (mean NRS ± SD [95% CI], 0.9 ± 1.1 [0.5–1.3] vs. 3.3 ± 3.2 [2.1–4.4], respectively; $p = .003$).

Similar results with the intensity analyses were observed in the comparison of the hiccup incidence rate (Table 3). The incidence rates of hiccup were 84.8% and 62.5% in the dexamethasone and methylprednisolone groups, respectively, at the randomization phase ($p = .040$). In the dexamethasone group, the incidence rate exhibited a greater decrease after the rotation of dexamethasone to methylprednisolone at the crossover phase (84.8% to 48.5%; $p = .003$). In the methylprednisolone group, there was no difference in the incidence rate of hiccup between the randomization and crossover phases. There were no significant differences in grade 3 or more adverse events other than hiccup between two groups (data not shown).

Emesis

We investigated whether the rotation of corticosteroids affects its antiemetic efficacy. In the dexamethasone group, there was a small difference in the emesis intensity between the screening and randomization phases (mean NRS ± SD [95% CI], 1.2 ± 1.9 [0.6–1.9] to 1.8 ± 2.0 [1.0–2.5]; $p = .041$). Otherwise, there were no differences in the emesis intensity between the study phases in each group (Fig. 2B). In the analysis for intergroup comparison, there were also no differences in the emesis intensity between the two groups at the randomization ($p = .694$) and crossover ($p = .441$) phases.

The incidence rates of emesis were also not different in the interphase comparison or in the intergroup comparison except in the comparison between the screening and randomization phases in the dexamethasone group (Table 3).

Quality of Life

The information from the FACT-G questionnaire was available for 29 patients in each group. Overall, there were no differences in the QoL between the dexamethasone and methylprednisolone groups (Table 4). The mean total scale scores at the randomization phase were 71.5 (SD 16.3) and 71.7 (SD 15.8) in the dexamethasone and methylprednisolone groups, respectively ($p = .969$). In the analyses of the subscale scores, the social well-being (SWB) score was higher when methylprednisolone was used than when dexamethasone was used at the crossover phase, without significance (mean SWB ± SD, 16.9 ± 5.3 in the dexamethasone group vs. 14.4 ± 5.7 in the methylprednisolone group; $p = .095$). Differences in the three subscales, physical well-being (PWB), emotional well-being (EWB), and functional well-being (FWB), were not observed between the study groups. Next, we performed post hoc analysis to assess whether the difference in the SWB score was significant in the linear

Table 2. Two-way ANOVA to evaluate the effects of the type of corticosteroid on the intensity of hiccup at the randomization phase

		F-statistics				*p* value		
Factor 1	**Factor 2**	**Model**	**Factor 1**	**Factor 2**	**Interaction**	**Factor 1**	**Factor 2**	**Interaction**
Type of corticosteroid (dexamethasone or methylprednisolone)	Type of chemotherapy (fluoropyrimidine-based or others)	5.3	13.4	2.0	0.4	<.001	.161	.550
	Type of chemotherapy (platinum-based or others)	4.7	12.3	0.7	0.3	<.001	.410	.565
	Type of antiemetics regimen (for high emetogenic potential[a] or others)	5.2	12.6	2.1	0.04	<.001	.149	.844

[a]Neurokinin-1 antagonist-containing regimens were used through each institutional protocol (cisplatin-based [$n = 36$], doxorubicin/ifosfamide [$n = 1$]).
Abbreviation: ANOVA, analysis of variance.

mixed-effect model. The FACT-G scores and individual participants were considered as a fixed and random effect, respectively. The patients with dexamethasone had a decrease of 1.1 (95% CI, 0.2–1.9; $p = .016$) in the SWB score compared with those with methylprednisolone. The total scale score and PWB, EWB, and FWB scores were also not different by the type of corticosteroid used in this analysis.

Discussion

This is the first randomized, prospective study to demonstrate that DIH in patients receiving chemotherapy could be controlled by rotating dexamethasone to methylprednisolone. Both the incidence and intensity of DIH were significantly decreased with this method without compromising antiemetic efficacy. The extent of the decrease in hiccup intensity was substantially more in the methylprednisolone group (77% reduction) than in the dexamethasone group (38% reduction) at the randomization phase. In addition, at the crossover phase, the hiccup intensity was increased by rotating methylprednisolone to dexamethasone in the methylprednisolone group, whereas it was further decreased when dexamethasone was rotated to methylprednisolone in the dexamethasone group. This pattern of change in the methylprednisolone group was consistent with that observed in our previous retrospective study [14]. These results strongly support that DIH intensity can be attenuated with maintenance of the antiemetic effect by rotating dexamethasone to methylprednisolone.

There are potential mechanisms to explain how corticosteroids can cause hiccups. The hiccup reflex arc comprising the afferent limb, central part of the midbrain, and efferent limb can be stimulated by many drugs and neurotransmitters [19]. Corticosteroids may stimulate the central part of the hiccup reflex arc and lower the synaptic transmission threshold in the midbrain [20, 21]. Although it has been suggested that corticosteroids competitively bind to the steroid receptors of the hiccup reflex arc [8, 22], why the hiccup intensity differs between dexamethasone and methylprednisolone remains unclear. This observation may be explained by the different permeabilities of the blood brain barrier (BBB) according to the type of corticosteroid. Given that there was no difference in the intensity of emesis between the two corticosteroids, however, the difference in the permeability of the BBB may not fully explain the difference in the hiccup intensity according to the type of corticosteroid. Further comprehensive experimental studies are needed to elucidate the mechanism of this finding.

Two interesting phenomena were observed. Compared with the screening phase, the hiccup intensity was also decreased in the dexamethasone-allocation group at the randomization phase. This finding is similar to that observed in a previous report showing that the hiccup intensity was lower when dexamethasone was readministered compared with the baseline level [14]. Given that possible confounding factors were controlled using the crossover design in the present study, we hypothesize that tolerance to dexamethasone may develop following the readministration of dexamethasone. The other finding is male predominance, which has been observed sporadically in other reports [8, 9, 14, 23]. Although the difference may originate from the nature of dexamethasone or gender itself, the disparity could be attributed to sexual vulnerability to hiccups. We previously reported that men are more susceptible

Table 3. Incidence rate of hiccup and emesis

		Randomization phase			Crossover phase		
Group	**Screening *n* (%)**	***n* (%)**	***p* value (vs. screening)**	***p* value (intergroup)**	***n* (%)**	***p* value (vs. randomization phase)**	***p* value (intergroup)**
Hiccup							
Dexa → Dexa → mPd	33 (100.0)	28 (84.8)	.025	.040	16 (48.5)	.003	.163
Dexa → mPd → Dexa	32 (100.0)	20 (62.5)	.001		21 (65.6)	.739	
Emesis							
Dexa → Dexa → mPd	14 (42.4)	20 (60.6)	.014	.875	18 (54.6)	.564	.694
Dexa → mPd → Dexa	19 (59.4)	20 (62.5)	.706		19 (59.4)	.706	

Abbreviations: Dexa, dexamethasone; mPd, methylprednisolone.

Table 4. Quality of life

FACT-G questionnaire	Phase	Score, mean ± SD: Dexa → Dexa → mPd ($n = 29$)	Score, mean ± SD: Dexa → mPd → Dexa ($n = 29$)	p value
Total	Screening	74.2 ± 15.1	72.2 ± 15.2	.597
	Randomization	71.5 ± 16.3	71.7 ± 15.8	.969
	Crossover	71.8 ± 15.9	69.9 ± 16.6	.697
PWB	Screening	20.9 ± 5.9	21.3 ± 5.4	.809
	Randomization	20.7 ± 5.2	20.9 ± 5.6	.845
	Crossover	20.0 ± 5.6	20.6 ± 5.1	.815
SWB	Screening	17.0 ± 5.3	15.5 ± 5.5	.303
	Randomization	15.9 ± 5.4	15.6 ± 5.0	.773
	Crossover	16.9 ± 5.3	14.4 ± 5.7	.095
EWB	Screening	18.6 ± 4.6	17.8 ± 5.0	.696
	Randomization	19.4 ± 3.4	18.4 ± 4.7	.622
	Crossover	18.6 ± 4.1	18.0 ± 4.8	.767
FWB	Screening	17.7 ± 6.3	17.6 ± 6.0	.969
	Randomization	15.4 ± 6.6	16.8 ± 6.3	.441
	Crossover	16.3 ± 6.2	16.9 ± 6.0	.629

Abbreviations: Dexa, dexamethasone; EWB, emotional well-being; FACT-G, functional assessment of cancer therapy-general; FWB, functional well-being; mPd, methylprednisolone; PWB, physical well-being; SD, standard deviation; SWB, social well-being.

to any causes that may induce hiccups [23]. The meta-analysis revealed that hiccup occurred over 11 times more frequently in men than in women, suggesting that men have a lower synaptic threshold or easier excitability in the hiccup reflex than women, whereas there was no gender difference in hiccup of CNS origin (odds ratio 1.74; $p = .072$). Several experimental studies have demonstrated that the hormone-binding capacity of brain corticosteroid receptors is higher in men than that in women [24–26]. Steroid receptor coactivator 1, which mediates steroid hormone responses, is known to be expressed at higher levels in the hippocampus and pituitary of male rats than in those of female rats [27].

In terms of the QoL, only marginal differences in the SWB domain existed between the dexamethasone and methylprednisolone groups. The total scale scores of FACT-G were nearly identical between the two groups at the randomization phase. Several reasons may explain this finding. First, the number of enrolled patients with severe hiccups was insufficient to show the difference in the QoL. If mild to moderate hiccup has only a small effect on the QoL, many patients may be needed to demonstrate the significance. Second, no optimal questionnaire exists to address the influential relationship between hiccups and QoL. While FACT-G has established its reliability and is the most widely used tool in cancer research, it may be still insufficient for this type of issue.

We adopted the crossover trial instead of the parallel design. In addition to the items listed in the exclusion criteria of this study, the causes of hiccups are extensive, including electrolyte imbalance, surgical procedures, radiotherapy, and medications other than corticosteroids such as opioids, antibiotics, and chemotherapeutic agents [28]. In the parallel design trial, multivariable analysis, stratification, or propensity score matching may be considered to adjust for these potential confounders [29]. However, the parallel design using the two latter statistical methods is difficult to apply in this study because it requires a large number of patients to demonstrate the noninferiority in the antiemetic efficacy between two corticosteroids, and the rarity of DIH does not allow for the recruitment of sufficient numbers of patients. By contrast, the crossover design has advantages in that intra-individual comparisons reduce confounding factors by allowing each patient to serve as his or her own control, and the same statistical power can be achieved with a smaller sample size [29].

This study has limitations and questions to be resolved. First, the relationship between the dose of corticosteroids and hiccup intensity was not evaluated. Most previous reports have suggested that hiccupping is induced by high-dose corticosteroids [9, 30–32]. The dose of dexamethasone used in this study was in the usually recommended range (8–20 mg) in guidelines to prevent emesis and was lower than the dose described in previous reports. A study to assess the difference in hiccup intensity according to the dose of corticosteroid is warranted. Second, whether the intensity of corticosteroid-induced hiccup is affected according to the type of chemotherapy was not precisely understood, due to the heterogeneity of the chemotherapy protocol in this cohort. A Taiwan study proposed that dexamethasone alone may be insufficient to explain the onset of hiccup [9]. Of note in this study, the type of corticosteroid affected the hiccup intensity independent of the type of chemotherapy as evaluated through the crossover design and multivariable analysis. Third, the NRS has not been validated widely to assess the intensity of hiccup, although the ESAS allows any symptoms to be assessed with NRS [15]. We previously applied the NRS to assess that in a retrospective study for DIH [14]. Nevertheless, more information to validate this scale in the assessment of hiccup is needed. Fourth, investigator bias could be caused by a single-blind design. However, because the primary and secondary outcomes were reported by the patients,

the bias might not be enough to substantially affect the results of the study.

Conclusion

Hiccup can develop in cancer patients, especially in male patients receiving dexamethasone as an antiemetic. Hiccups can be ameliorated by simply rotating dexamethasone to methylprednisolone in the next cycle of chemotherapy without compromising the antiemetic efficacy.

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Disclosures

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