Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China

A clinical study on insomnia in patients with cancer during chemotherapy containing high-dose glucocorticoids

J. Zhao, Y.-H. Dai, Q.-S. Xi, S.-Y. Yu

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Dr. Jing Zhao, Department of Oncology, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China
zhaojingdoc@163.com

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In this prospective, open-labeled study, 240 cancer patients were assigned to either a high-dose glucocorticoids (HDG) group that received chemotherapy containing HDG, or a control group that received chemotherapy without glucocorticoids. The Pittsburgh Sleep Quality Index (PSQI) was chosen to assess insomnia. The results of the study showed that dimensions of sleep latency, sleep duration, and sleep efficiency had the three largest differences in values and numbers of patients, with a score increase in the HDG group compared to the control group ($p < 0.001$). After chemotherapy in the HDG group, the PSQI score significantly increased in patients with stage II cancer (both $p < 0.05$), and patients diagnosed with lymphoma ($p < 0.01$), whereas the complete response and partial response rates ($p < 0.05$) had the smallest elevations. The average score of each dimension did not significantly decrease after hypnotics ($p > 0.05$). Our study suggests that the major clinical manifestations of insomnia in cancer patients receiving chemotherapy containing HDG include difficulty falling asleep, short sleep duration, and low sleep efficiency. however, we cannot definitively state that hypnotics can improve poor sleep quality.

1. Introduction

Insomnia, defined as difficulty falling asleep and/or maintaining sleep throughout the night, which results in clinically significant daytime impairment according to the American Sleep Association (ASA), is the most common type of sleep disorder in patients with cancer (Graci 2005; Kvale and Shuster 2006). It has been reported to occur in 24–95% of cancer patients (O'Donnell 2004; Graci 2005; Kvale and Shuster 2006), which is 7.0–9.5% more than that reported in the general population (Morin et al. 2006). Davidson et al. (2002) reported that insomnia is most common in breast (38%), lung (37%), gastrointestinal (32%), and gynecological (29%) cancer patients. Insomnia can persist for many years after diagnosis or completion of treatment, making it one of the most pervasive problems for cancer patients (Couzi et al. 1995; Lindley et al. 1998). According to a 2010 study by the Society of Clinical Oncology (ASCO), insomnia has become one of the top 12 advances. It has been suggested that its etiology may include poor sleep hygiene, lifestyle habits, type and stage of cancer, as well as pain and side effects from treatment, such as nausea, vomiting, anemia, and urinary frequency (Ancoli-Israel et al. 2001; Lee et al. 2004). Additionally, insomnia usually coexists with other symptoms such as fatigue, depression, and anxiety, which positively correlate with one another ($p < 0.001$) (Redeker et al. 2000; Given et al. 2001), and may have a significant impact on the quality of life in cancer patients (Lee et al. 2004). Glucocorticoids that contain short-acting drugs such as cortisol and hydrocortisone, moderate-acting drugs such as prednisone, and long-acting drugs such as dexamethasone, in combination with other anti-tumor reagents, are widely used during anti-cancer therapy. Recently, Vgontzas et al. (Vgontzas et al. 2001; Rodenbeck et al. 2002) questioned such treatment due to their evidence of an association between glucocorticoid administration and insomnia. They found that patients who take glucocorticoids have a hard time falling asleep at night or awake early during the morning. There are few reports regarding this relationship, partly due to the potential confounding effects of chemotherapeutic agents, which makes it hard to reveal a true association between glucocorticoids and insomnia. As a remedy for insomnia during cancer treatment containing glucocorticoids, hypnotics, benzodiazepines and nonbenzodiazepines, are commonly used (Freedom 2011). In fact, approximately 25–50% of all prescriptions written for patients with cancer are for hypnotics (Stewart and Westra 2002; Espie et al. 2008); however, the response rate is very low. On the other hand, the side effects from hypnotics, such as cognitive impairments, limit its use (Epstein and Dirksen 2007).

The aim of this study was to investigate insomnia in patients with cancer who received chemotherapy containing high-dose glucocorticoids, and to assess the efficacy of hypnotics in those patients.

2. Investigations, results and discussion

Patients were eligible for participation if they were 18 years of age or older, and had a primary diagnosis of lung cancer, breast cancer, lymphoma, alimentary tract cancer, or nasopharyngeal cancer. In addition, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Patients were excluded if they had psychiatric disorders, complaints of pain, received prior systemic chemotherapy, had

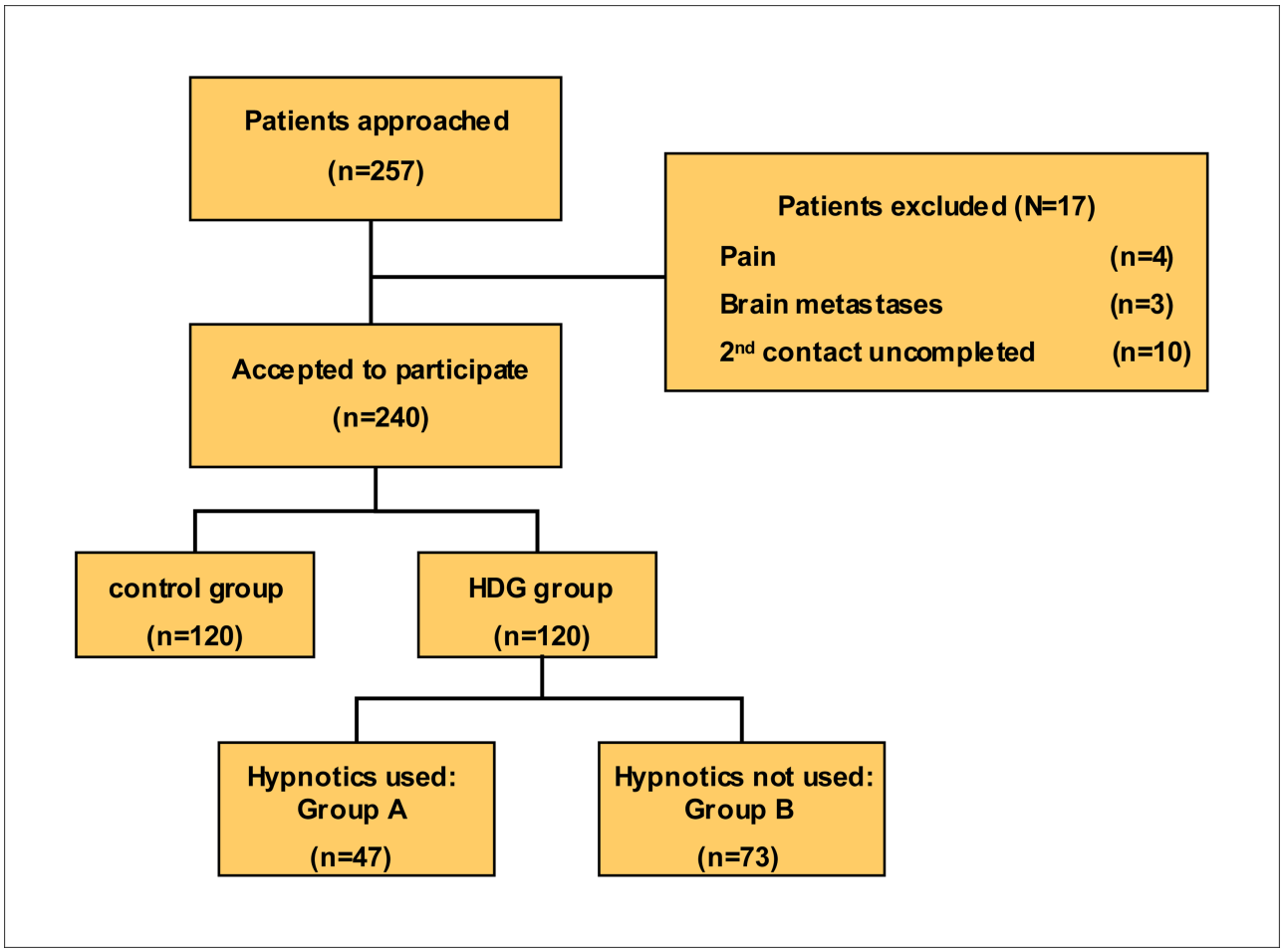

Fig. 1: Participant flow chart. HDG, high-dose glucocorticoids

metastases of the central nervous system, or had severe visual defects that impaired their capacity to complete the scales,

Participants were recruited from the oncology wards of Tongji Hospital in middle China from September 2010 to June 2011. Of all 257 patients, 17 patients were excluded, and the remaining 240 patients were assigned to two groups: 120 were in the HDG group and received high-dose dexamethasone and prednisone during chemotherapy. The usage of HDG included 20 mg dexamethasone (before 12 and 6 hours respectively) of paclitaxel used; 8 mg dexamethasone twice daily before, on, and after the day docetaxel is used; 12 mg dexamethasone on the day cisplatin used; 100 mg prednisone daily for five successive days in the CHOP chemotherapy regimen for lymphoma patients. The other 120 patients were in the control group and received therapy without any glucocorticoids. Forty-seven patients in the HDG group received hypnotics including estazolam, midazolam, and zolpidem at least once (Fig. 1).

Table 1 summarizes the information about the recruited 240 patients. The three main types of diseases were lung cancer (30%), breast cancer (20.8%), and lymphoma (16.7%). The major side effects of chemotherapy included nausea (16.7%), vomiting (38.8%), neutropenia (35.4%), and alopecia (51.3%); other side effects included itching, peripheral neuropathy, and constipation. In the HDG group, glucocorticoids were mainly used for pre-medication (54.2%), antiemesis (21.7%), and as one of the drugs in the chemotherapy regimen for lymphoma patients (24.2%).

2.1. Differences in PSQI scores between the two groups before and after chemotherapy

Table 2 shows that 51.67% and 48.33% of patients in the HDG and control group, respectively, had a global PSQI score >5 before chemotherapy, while this ratio increased to 85.00% and 70.83%, respectively, after chemotherapy. The average global PSQI score was 5.9 in the HDG group and 6.0 in the control group before chemotherapy, while this number increased to 9.4 and 6.8, respectively, after chemotherapy. In the HDG group, scores in every dimension, except daily function, significantly increased after chemotherapy compared to the control group ($p<0.05$). However, to our surprise, in 17 patients, the global score in the HDG group decreased after chemotherapy, and six patients had a score <3 (Table 3).

2.2. Major clinical symptoms of sleep disorders after HDG treatment

We used profile analysis to do more research on the most important dimension related to sleep disorders. It showed that after chemotherapy, two curves were parallel ($F=2.097$, $p>0.05$), including seven dimensions between the two groups, but were not coincident ($F=48.541$, $p<0.01$). The three largest differences in dimensions after chemotherapy were sleep efficiency (0.8), sleep duration (0.7), and sleep latency (0.5) (Fig. 2). The number of patients in each dimension was added if their scores increased after chemotherapy. Table 4 shows that in the HDG group, the dimension of sleep efficiency had the most patients with a score increase after chemotherapy (68.33%), followed by sleep duration (56.67%), and sleep latency (53.33%), which significantly differed relative to the control group ($p<0.001$).

According to the cancer site, the mean global score of patients in the HDG group after chemotherapy was higher than that of the control group, whereas among the five cancer sites, the increase in mean global score in lymphoma patients was the

Table 1: Patient demographic and clinical characteristics

Characteristic	HDG group (n = 120) No. of patients (%)	Control group (n = 120) No. of patients (%)	χ^2	*p*
Age, mean (Standard deviation), y	48.3(11.3)	50.4(11.5)	—	0.28
Sex			0.82	> 0.05
Male	54(45.0)	61(50.8)		
Female	66(55.0)	59(49.2)		
Cancer site			2.05	> 0.05
Breast	22(18.3)	28(23.3)		
Lung	35(29.2)	37(30.8)		
Lymphoma	29(24.2)	16(13.4)		
Alimentary tract	13(10.8)	24(20.0)		
Nasopharynx	21(17.5)	15(12.5)		
Stage			3.29	> 0.05
I	12(10.0)	17(14.3)		
II	26(21.7)	30(25.0)		
III	51(42.5)	38(31.7)		
IV	31(25.8)	35(29.2)		
Intervals from tumor diagnosed			0.94	> 0.05
< 6 months	42(35.0)	47(39.2)		
6 to 12 months	34(28.3)	36(30.0)		
> 12 months	44(36.7)	37(30.8)		
Side effects of therapy				
None	15(12.5)	20(16.7)	0.84	> 0.05
Nausea	13(10.8)	27(22.5)	5.88	< 0.05
Vomiting	64(53.3)	29(24.2)	21.51	< 0.01
Anemia	17(14.2)	15(12.5)	0.14	> 0.05
Neutropenia	53(44.2)	32(26.7)	8.03	< 0.01
Alopecia	67(55.8)	56(46.7)	2.02	> 0.05
Itchy	3(2.5)	5(4.2)	0.52	> 0.05
Neuropathy	4(3.3)	23(19.2)	15.07	< 0.01
Constipation	21(17.5)	23(19.2)	0.11	> 0.05
Others	5(4.2)	7(5.8)	0.35	> 0.05
HDG applications				
Pre-medication	65(54.1)	—	—	—
One drug of regimen	29(24.2)	—	—	—
antiemesis	26(21.7)	—	—	—
Treatment outcome			3.67	> 0.05
CR/PR	26(21.7)	15(12.5)		
SD	57(47.5)	65(54.2)		
PD	37(30.8)	40(33.3)		

CR: complete remission, PR: partial remission, SD: stable disease, PD: progression disease.

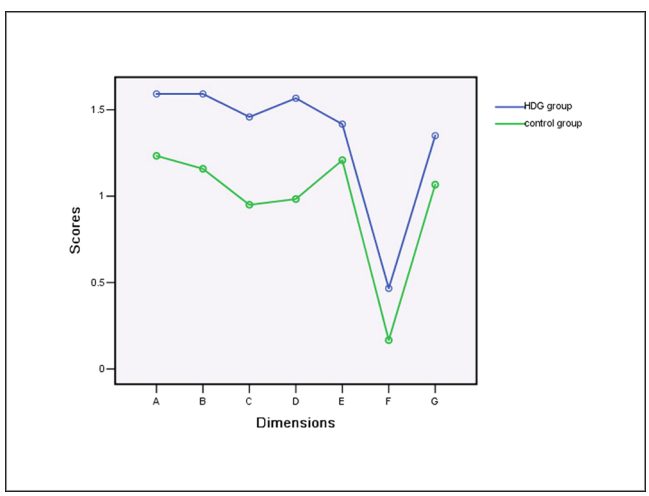

Fig. 2: Profile analysis for patients after chemotherapy A: Subjective sleep qualities; B: Sleep latency; C: Sleep duration; D: Sleep efficiency; E: Sleep disturbances; F:Sleep medications; G: Daily functions

Table 2: Accumulative ratio of PSQI scores

Scores	HDG group				Control group			
	Pre-treatment		Post-treatment		Pre-treatment		Post-treatment	
	N	%	N	%	N	%	N	%
15	0	0	7	5.83	0	0	0	0
14	0	0	6	10.83	0	0	0	0
13	0	0	23	30.00	0	0	0	0
12	0	0	16	43.33	0	0	0	0
11	0	0	2	45.00	0	0	2	1.67
10	0	0	6	50.00	0	0	4	5.00
9	5	4.17	10	58.33	4	3.33	20	21.67
8	29	28.33	10	60.00	29	27.50	17	35.83
7	12	38.33	10	66.67	16	40.83	31	61.67
6	16	51.67	12	85.00	9	48.33	11	70.83
5	26	73.33	0	85.00	46	86.67	14	82.50
4	29	97.50	11	94.17	13	97.50	19	98.33
3	3	100	1	95.00	3	100	1	99.17
2	0	100	6	100	0	100	1	100

lowest, and the difference was significant (F = 36.21, $p < 0.01$) (Fig. 3). Figure 4 shows that among the four stages of cancer, patients with stage II had the highest elevation in mean global

Table 3: Scores of participants measured by PSQI

Dimensions	HDG group		Control group		Effects	
	Mean	SD	Mean	SD	F	*p*
Subjective sleep quality					12.726	<0.01
Pre-treatment	1.2	0.382	1.2	0.389		
Post-treatment	1.6	0.930	1.2	0.530		
Sleep latency					20.718	<0.01
Pre-treatment	1.1	0.290	1.1	0.322		
Post-treatment	1.6	0.893	1.1	0.389		
Sleep duration					24.829	<0.01
Pre-treatment	0.7	0.463	0.8	0.403		
Post-treatment	1.4	0.916	1.0	0.563		
Sleep efficiency					24.045	<0.01
Pre-treatment	0.5	0.580	0.6	0.517		
Post-treatment	1.6	1.035	1.0	0.889		
Sleep disturbances					6.831	=0.01
Pre-treatment	1.2	0.395	1.2	0.382		
Post-treatment	1.4	0.544	1.2	0.408		
Sleep medications					10.710	<0.01
Pre-treatment	0.2	0.382	0.2	0.389		
Post-treatment	0.5	0.819	0.2	0.374		
Daily functions					1.081	>0.05
Pre-treatment	1.0	1.045	0.9	1.062		
Post-treatment	1.3	1.186	1.1	0.905		
Global score					39.203	<0.01
Pre-treatment	5.9	1.694	6.0	1.569		
Post-treatment	9.4	3.743	6.8	1.917		

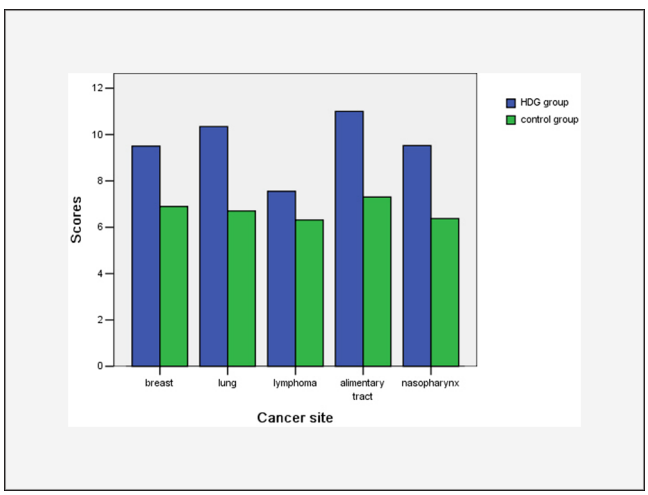

Fig. 3: Mean global score after chemotherapy according to cancer site

score after chemotherapy in both groups (F = 13.25, $p < 0.05$). The same results were found with treatment outcome, as shown in Figure 5. Patients who obtained a CR or PR after chemotherapy had the smallest change in mean global score in both groups (F = 20.56, $p < 0.05$).

2.3. Effect of hypnotics in patients in the HDG group

In our study, patients in the HDG group were divided into subgroups A and B, according to whether hypnotics were used. Forty-seven (39.2%) patients in subgroup A used hypnotics; specifically, 28 patients used estazolam (23.3%), 12 patients used midazolam (10.0%), and seven patients used zolpidem (5.8%). The remaining 73 patients (60.8%) were in subgroup B and did not use hypnotics during chemotherapy.

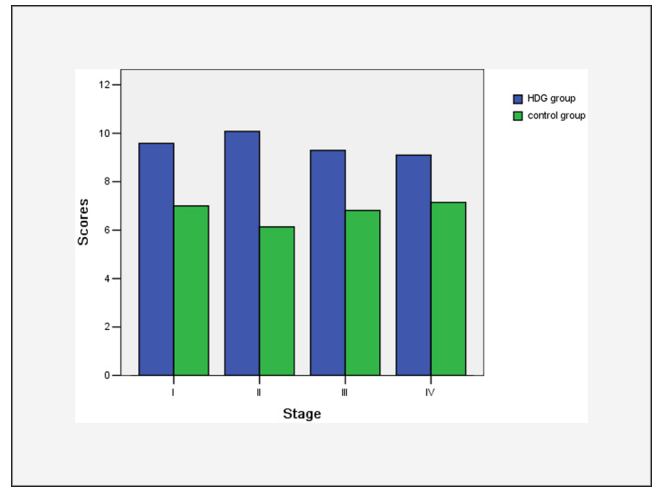

Fig. 4: Mean global score after chemotherapy according to stage

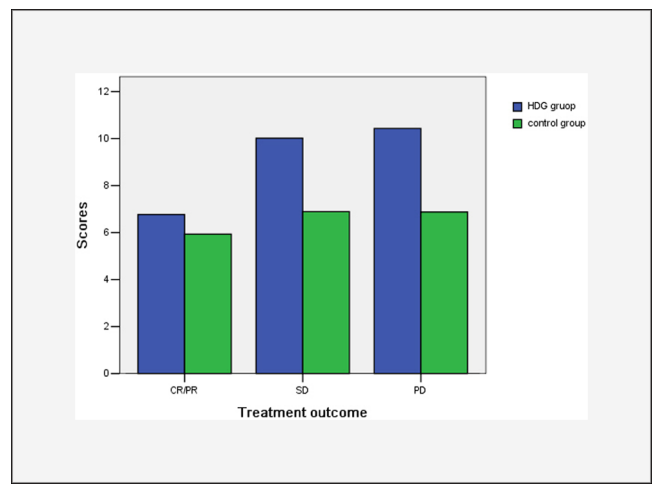

Fig. 5: Mean global score after chemotherapy according to treatment outcome

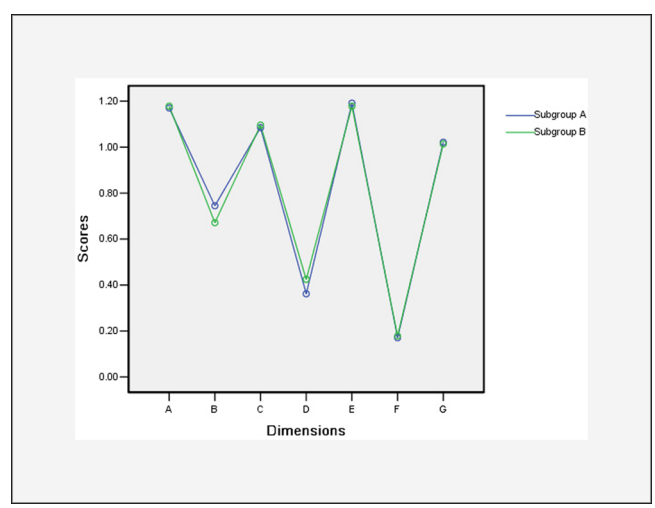

Fig. 6: Profile analysis for patients in HDG group before chemotherapy A: Subjective sleep qualities; B: Sleep latency; C: Sleep duration; D: Sleep efficiency; E: Sleep disturbances; F:Sleep medications; G: Daily functions

We also used profile analysis to compare scores between the two subgroups before chemotherapy. As shown in Fig. 6 , two curves, including seven dimensions, were parallel (F = 0.164, $p > 0.05$) and coincident (F = 0.000, $p > 0.05$). As shown in Table 5, after chemotherapy, subjective sleep quality, sleep latency, sleep dura-

Table 4: Numbers of patients with score increase after chemotherapy

Dimensions	Numbers of Patients with score increase in HDG group %	Numbers of Patients with score increase in control group %	χ^2	*P*
Subjective sleep qualities	37.50	19.17	9.927	< 0.01
Sleep latency	53.33	15.00	39.191	< 0.01
Sleep duration	56.67	20.00	34.130	< 0.01
Sleep efficiency	68.33	35.83	25.394	< 0.01
Sleep disturbances	31.67	15.83	8.313	< 0.01
Sleep medications	25.83	11.67	7.897	< 0.01
Daily functions	41.67	40.83	0.017	> 0.05

Table 5: Scores of HDG patients measured by PSQI

Dimensions	Subgroup A		Subgroup B		Effects	
	Mean	SD	Mean	SD	F	*p*
Subjective sleep quality					0.075	> 0.05
Pre-treatment	1.2	0.380	1.2	0.385		
Post-treatment	1.6	0.874	1.6	0.930		
Sleep latency					0.084	> 0.05
Pre-treatment	1.1	0.282	1.1	0.296		
Post-treatment	1.6	0.945	1.6	0.893		
Sleep duration					0.356	> 0.05
Pre-treatment	0.7	0.441	0.7	0.473		
Post-treatment	1.4	0.927	1.5	0.916		
Sleep efficiency					1.463	> 0.05
Pre-treatment	0.4	0.486	0.4	0.498		
Post-treatment	1.7	1.044	1.5	1.035		
Sleep disturbances					0.106	> 0.05
Pre-treatment	1.2	0.398	1.2	0.385		
Post-treatment	1.4	0.583	1.4	0.544		
Daily functions					0.002	> 0.05
Pre-treatment	1.0	1.073	1.0	1.034		
Post-treatment	1.4	1.223	1.3	1.186		

tion, sleep efficiency, sleep disturbance, and daily function did not improve between the two subgroups ($p > 0.05$).

Sleep medicine belongs to the domain of palliative care. Although neurologists often use polysomnography (PSG) to diagnose sleep disorders such as insomnia (Iber 2007), in most cases, scales such as the Epworth sleepiness scale, the EORTC QLQ-C30 questionnaire, the Insomnia Severity Index, and the Pittsburgh sleep quality index (PSQI), are used instead. Several authors reported insomnia in cancer patients using those methods (Savard and Morin 2001; Cooley et al. 2003; Roth and Roehrs 2003; Roth 2005). In our study using PSQI, half of the participants had a global score > 5 before chemotherapy, and the average global score was higher than 5 in either group before chemotherapy. These results once again confirm the fact that insomnia is more common in cancer patients than in the general population.

Many predisposing and precipitating factors are associated with insomnia. In fact, in most cancer patients, insomnia is a symptom or consequence of a preexisting primary medical or psychiatric disorder, rather than a primary disease. Above all, symptom clusters (Barsevick 2007; Miaskowski et al. 2007; Roscoe et al. 2007; Stepanski et al. 2009) containing fatigue, anxiety, depression and insomnia are so prevalent in cancer patients that more attention needs to be paid to those comorbidities which may often take effects reciprocally and may play a role in the development or transit of chronic insomnia (Roscoe et al. 2007). In addition, treatment for cancer often leads to complaints of persistent insomnia (Palesh et al. 2010). In our study, most patients had an increase in their global scores, which suggests that more patients had poor sleep quality after chemotherapy. There were also significant differences after chemotherapy in the HDG group in regard to sleep latency, sleep duration, and sleep efficiency with scores increasing by 0.5, 0.7, and 0.8, respectively ($p < 0.01$); similar results were reported by Palesh et al. (2008). Patients and even doctors are often more concerned with decreasing tumor size; however, insomnia is also an important factor to consider during treatment as it seriously affects quality of life (QOL), and thus should not be neglected.

Although insomnia is an important symptom in the clinical population, there has been a paucity of information in the literature on insomnia in cancer patients. Glucocorticoids are drugs that are widely used in oncology wards, and can lead to sleep disorders by reducing the concentration of the inhibitory neurotransmitter GABA, which functions to change Cl^- permeability at cell membranes in the central nervous system. Several *in vitro* experiments have confirmed the correlation between insomnia and glucocorticoids. For example, Sturenburg et al. (1997) found that prednisone and dexamethasone could inhibit the 3α-HSDH metabolic process, and when combined with GABA, there was heightened activity in the cortical neuron. The inhibitory effects related to GABA may increase in the presence of HDG, which is defined as a dose more than 1 mg/kg/d for prednisone and 0.15 mg/kg/d for dexamethasone. In recent years, reports of insomnia caused by high glucocorticoid doses have increased (Sturdza et al. 2008).

However, unlike most patients after chemotherapy, the global PSQI score of 17 patients in the HDG group remarkably decreased. Further analysis showed that this cohort consisted of two breast cancer patients, 12 lymphoma patients, and three nasopharyngeal cancer patients, who were sensitive to chemotherapy with treatment outcomes of CR or PR; no severe adverse events occurred during treatment. As shown in Figs. 3 and 5, these patients had better sleep quality than others. How can these specific results produce? Reasons may be as follows: First of all, these 17 cases can renerve and become more confident from good informations out of chemotherapy, and concomitant symptoms including sadness, depression and angry also alleviated (Roscoe et al. 2007; Dirksen et al. 2009). On the other hand, glucocorticoids have some special functions in patients with cancer such as increasing appetite, gaining weight and alleviating pain. Vardy et al. (2006) reports that appetite increases in 16% of 60 cancer patients after using dexamethasone, and dexamethasone together with morphine can be used to alleviate neuropathic pain syndromes which are associated with sleep disturbances (Mishra et al. 2008). Additionally in some chemotherapy regimens (e.g. CHOP for lymphoma patients), glucocorticoid is an important component to directly kill off tumor cells in combination with other cytotoxic drugs)-comment.

The management of insomnia comprises approaches using pharmacotherapy and cognitive behavioral therapy (CBT), although little is known about the efficacy of these treatments for insomnia in cancer patients. Some psychologists have reported that

benzodiazepines and non-benzodiazepines are effective for both short-term or long-term treatments for insomnia (Freedom 2011). However, both treatments can have side effects, such as tolerance and withdrawal, complex sleep behaviors, and associated cognitive impairments. Currently, nonbenzodiazepine hypnotics are seen as first-line drugs to treat insomnia, which selectively combines ω1 or ω1,2 receptors of GABA, and has a short half-life period, limited risks of drug abuse, rebound insomnia, drug tolerance, and hangover effects (Morrow 1995), although some rare but serious effects, such as anaphylaxis, angioedema, and complex sleep-related behaviors, have been also reported. In addition, the melatonin receptor agonist, ramelteon, has also been introduced (Greenblatt et al. 2007). Investigations have demonstrated significant improvement in sleep following various CBT interventions in cancer patients (Epstein and Dirksen 2007; Espie et al. 2008; Harkless 2008). However, on the whole, these study samples were not large.

Our study also investigated the effects of hypnotics in cancer patients who were treated with HDG. It is worthwhile to note that according to our results, sleep latency, sleep duration and sleep efficiency did not improve after hypnotics were used in the HDG group ($p > 0.05$). The choice of hypnotics should be taken into account. In our study, only seven (5.8%) patients regularly used nonbenzodiazepines, while a double-blind, randomized, and parallel study by Lee et al. (2004) confirmed that sleep disorders in patients taking estazolam tended to recurr after three weeks of therapy compared to those taking nonbenzodiazepines. Sleep quality in cancer patients taking chemotherapy may somewhat differ from non-cancer patients, and the variable effects of hypnotics should also be considered.

3. Experimental

3.1. Experimental design

Patients accomplished the chemotherapy in a week. Eligible patients in either group were invited to complete PSQI questionnaire on the baseline and one week after the first day high-dose glucocorticoids used.

3.2. Measures

We investigated insomnia using the Pittsburgh Sleep Quality Index (PSQI). It was designed by Buysse et al. (1989) and contains 18 major items which can be summarized in 7 dimensions: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, sleep medications, and daily functions. A global score of these dimensions ranges from 0 to 21; a higher score indicates poorer sleep quality. This questionnaire was confirmed in prior studies in cancer patients (Le et al. 2007; Espie et al. 2008), and a PSQI score < 5 is considered good sleep quality which has a sensitivity of 89.6% and specificity of 86.5% in differentiating good sleepers from bad sleepers (Sateria and Lang 2008). All participants finished the assessment sheets in less than 10 min.

3.3. Statistical analysis

Data were analyzed using SPSS 12.0 for windows. The PSQI scores of patients were calculated. Linear regression was used to compare total scores after chemotherapy between the two groups according to patient age. ANOVA and profile analysis for repeated measurement data were used to evaluate each dimension before and after chemotherapy in the two groups and subgroups of the HDG group. We used the chi-square test to analyze the number of patients with a score increase in the two groups. P values less than 0.05 were considered statistically significant.

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