

CLINICAL STUDY

Effects of granulocyte colony-stimulating factor administration time on pain

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ABSTRACT

OBJECTIVE: This study was aimed at evaluating the effect of administration time of granulocyte colony-stimulating factor (G-CSF) on the level of pain related to G-CSF.

METHODS: This study was carried out with 48 cancer patients divided into A and B groups. In the first stage of the study, the groups A and B were planned to be administered with G-CSF at 10: 00 and 14: 00, respectively. In the second stage, patients in groups A and B were asked to self-administer filgrastim at 14: 00 and 10: 00, respectively. Patients were also asked to assess their pain level after G-CSF administration for a total of 4 times. **RESULTS:** According to the findings, the incidence of pain related to G-CSF was 91.7 %. The pain score after G-CSF being administered at 10: 00 was significantly higher compared to administration at 14: 00 in both groups (group A after 4, 8, and 12 hours: $p < 0.05$; group B after 4 and 8 hours: $p < 0.05$).

CONCLUSIONS: The results of the present study have demonstrated that the pain score related to G-CSF administration at 14:00 p.m. was significantly reduced. Thus, in order to minimize the pain, it will be more beneficial to administer G-CSF at 14: 00 (*Tab. 4, Ref. 31*). Text in PDF www.elis.sk.

KEY WORDS: cancer, G-CSF, pain, nurse.

Introduction

Neutropenia is a commonly seen serious adverse effect of cancer treatment (1, 2, 3). The incidence of neutropenia decreases by 50 % with the use of granulocyte colony-stimulating factor (G-CSF) (4, 5). The most commonly used G-CSF preparations in Turkey and worldwide are filgrastim and lenograstim (6). Patients may experience adverse effects including headache, bone pain, myalgia and arthralgia related to G-CSF which are usually managed using pharmacological agents (3, 7–11).

Pain management varies, and is complex because of individual differences and circadian pain behavior (12, 13). It has been suggested that pain varies with individuals and different diseases, and because the circadian rhythm influences the pharmacodynamic and pharmacokinetic properties of the drugs, pain management should be conservative and individualized (12). In a study on circadian changes during a 24-h period induced by CFU-GM in bone marrow, the production of myeloid progenitor cells has been reported

to start to increase at 04.00, peak at 12.00 p.m. and start to decrease at 16.00 p.m. (14). During the 24-h circadian rhythm of bone marrow, the percentage of bone marrow cells at the DNA synthesis phase is 188% higher in the midday compared to midnight with a similar circadian change seen in granulocyte/macrophages during the DNA synthesis phase (15).

Although there are several previous studies investigating the relationship between the circadian rhythm and proliferation of bone marrow cells or pain (12,14, 15), to the best of our knowledge, no studies have investigated the circadian rhythm in pain induced by G-CSF treatment used to induce neutrophil proliferation. This semi-experimental study was planned in order to investigate the influence of administration time of G-CSF on myalgia and arthralgia induced by the drug used to prevent neutropenia in cancer patients.

Material and methods*Study design*

This semi-experimental, self-controlled study was conducted in order to investigate the effect of administration time of filgrastim on myalgia and arthralgia induced by filgrastim used to prevent neutropenia in cancer patients.

Study setting and population

The study was carried out at the chemotherapy unit of hospital at Eskisehir between November 31, 2014 and July 31, 2015.

Study population consisted of patients who had received G-CSF treatment the day after chemotherapy. The study sample con-

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sisted of patients meeting inclusion criteria and agreeing to participate in the study. Study sample excluded the patients who reported to have used analgesic medication during filgrastim application.

Inclusion criteria:

- Being literate,
- Having no mental or communication problems,
- Being over 18 years and under 74 years of age,
- Having ability to self-administer subcutaneous 30 MIU G-CSF (filgrastim)
- Agreeing to participate in the study.

The repeated measures of Anova statistical power analysis was conducted in order to determine the adequacy of sample size. In the statistical power analysis based on Quantitative Pain Assessment Scale value, the number of units for each group was determined as 7 for the effect power of 0.99 % with a α value of 0.05, and β value of 0.0033.

Outcome measures

Data were collected through observation, face-to-face- interview and measurement methods, and by using Patient Identification Form and Quantitative Pain Assessment Scale.

Patient Identification Form: The form prepared by the researchers consists of 16 items regarding sociodemographic features and disease- and treatment-related factors (16, 17).

Quantitative Pain Assessment Scale (QPAS): This scale assessing the pain severity aims to quantify the pain of patient. The scores of the scale range from 0 to 10 with 0 indicating no pain and 10 indicating intolerable pain severity (18).

Data collection procedure

The patients who met the inclusion criteria were systematically assigned into two groups (A and B) by using a simple randomization method. First and second stages of the study were carried out in both groups of patients.

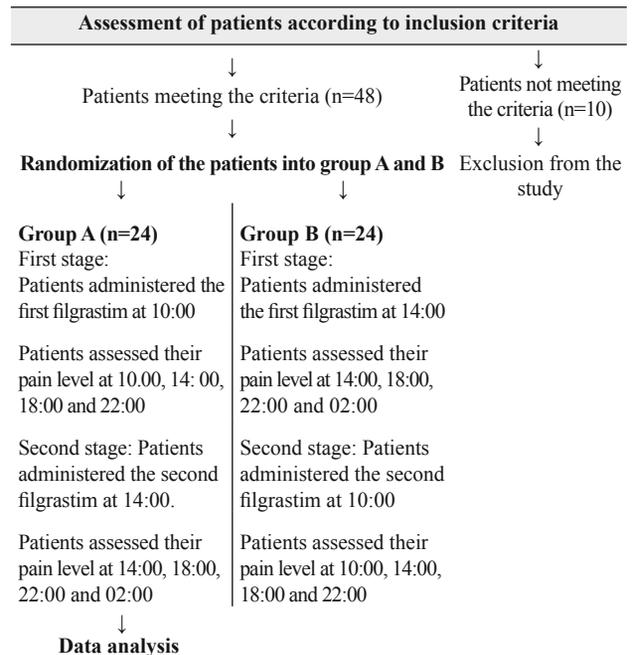
First stage: The filgrastim treatment was planned to be self-administered the day after chemotherapy by the patient according to the decision of physician who instructed the administration to be carried out at 10: 00 in group A and at 14: 00 in group B. Patients were also asked to assess their pain level by using Quantitative Pain Assessment Scale every four hours after the drug administration for a total of 4 times (Tab. 1).

Second stage: In this stage, patients in group A and B were asked to self-administer filgrastim at 14: 00 p.m. and 10: 00, respectively. Again, patients were instructed to assess their pain level by using Quantitative Pain Assessment Scale every four hours after the drug administration for a total of 4 times (Tab. 1). Because the drugs in our country are most commonly administered at 10: 00 and 14: 00, filgrastim was instructed to be administered at these particular points of time.

Data analysis

All data were analyzed by using SPSS 21.0 package program (19). Continuous quantitative data are given as n, mean and standard error while qualitative data are given as n, median, 25th and

Tab. 1. A schematic view of study.



75th percentiles. Kruskal-Wallis and Mann-Whitney U tests were used for data series consisting of independent measurements or scoring and Wilcoxon Signed Ranks test was used for dependent variables. The significance level was set at $p < 0.05$.

Ethical considerations

This study was approved by Ethical Committee of Hospital (approval date/number: November 14, 2014/2014–210). After giving written and verbal information, all study subjects gave written consent. They were informed on the fact that if they wanted to discontinue participation, they could leave the study without stating their reason.

Results

Socio-demographic and clinical characteristics of the sample

The total of 48 patients with cancer were included in the analysis (22 men and 26 women). During the study period, a total of 15 patients were excluded from the study because 11 patients were reported to have been using analgesic medication regularly, and 4 patients did not complete the study. The mean age of the study population was 56.52 ± 12.08 years (57.66 ± 11.76 years in group A and 55.38 ± 12.54 years in group B). Of the patients, 54.2 % were female, 45.8 % were male, 41.7 % were secondary school graduates and majority (89.6 %) were married. Of the patients included in the study, 33.3 %, 25 %, 12.5 %, and 8.4 % had breast carcinoma, gastrointestinal cancers, lung cancer, hematological cancers, soft tissue cancer, respectively and 41.7 % were at the second stage of the disease. Chemotherapy-induced neutropenia was seen in 83.3 %, while 81.3 % of patients had filgrastim administered previously (mean 2.47 ± 1.68) (Tab. 2).

Tab. 2. Sociodemographic characteristics and disease- and treatment-related factors.

Informative characteristics	Group A		Group B		Total	
	n	%	n	%	n	%
Age (year)	57.66±11.76		55.38±12.54		56.52±12.08	
Course	4.42±4.95		3.21±2.17		3.81±3.82	
Previous G-CSF administrations (number)	2.12±1.75		2.83±1.58		2.47±1.68	
Gender						
Female	11	22.9	15	31.3	26	54.2
Male	13	27.1	9	18.8	22	45.8
Marital status						
Married	22	45.8	21	43.8	43	89.6
Single	2	4.2	3	6.3	5	10.4
Educational status						
Solely literate	6	12.5	2	4.2	8	16.7
Primary school	4	8.3	4	8.3	8	16.7
Secondary school	9	18.8	11	22.9	20	41.7
High school	5	10.4	7	29.2	12	25
Employment						
Civil servant	3	6.3	4	8.3	7	14.6
Worker	2	4.2	1	2.1	3	6.3
Housewife	11	22.9	8	16.7	19	39.6
Retired	8	16.7	11	22.9	19	39.6
Diagnosis						
Gastrointestinal cancers (esophageal, gastric, colon, rectal)	7	14.6	5	10.4	2	25
Lung cancer	1	2.1	5	10.4	6	12.5
Breast cancer	7	14.6	9	18.8	16	33.3
Soft tissue cancer	2	4.2	2	4.2	4	8.3
Hematological cancers (CLL, NHL)	4	8.4	0	0	4	8.4
Prostate cancer	2	4.2	1	2.1	3	6.3
Testicular cancer	0	0	2	4.2	2	4.2
Ovarian cancer	1	2.1	0	0	1	2.1
Stage						
1	5	10.4	7	14.6	12	25
2	10	20.8	10	20.8	20	41.7
3	5	10.4	5	10.4	10	20.8
4	4	8.3	2	4.2	6	12.5
Previous neutropenia						
Yes	17	35.4	23	47.9	40	83.3
No	7	14.6	1	2.1	8	16.7
Previous use of G-CSF						
Yes	17	35.4	22	45.8	39	81.3
No	7	14.6	2	4.2	9	18.8
Adverse effects in previous G-CSF usage						
None	8	16.7	2	4.2	4	20.9
Bodily pain	16	33.3	22	45.8	44	79.1
Methods of coping with previous pain						
Analgesic medications	15	31.3	9	18.8	24	50.4
Relaxation techniques	1	2.1	0	0	1	2.1
Massage	0	0	1	2.1	1	2.1
Other (analgesics, relaxation techniques, massage, resting)	0	0	13	27.1	13	27.1
Nothing	8	16.7	1	2.1	9	18.8

Effectiveness of administration time of filgrastim in pain

Previous filgrastim was reported to cause diffuse bodily pain in 79.1 %. Of these patients, 50.4 % used analgesic medication, 27.1 % used analgesics, relaxation techniques, massage, and resting for pain management while 18.8 % used no intervention in prior usage of filgrastim (Tab. 2). In group A, the pain score in the first

stage (filgrastim administered at 10: 00) was significantly higher compared to filgrastim administered at 14: 00 in the second stage (0th hour: $p = 0.020$; 4th hour: $p = 0.01$; 8th hour: $p < 0.001$; 12th hour: $p < 0.012$) (Tab. 3). On the other hand, in group B patients, the pain score in the first stage (filgrastim administered at 14: 00 p.m.) was significantly lower than that in the second stage (fil-

Tab. 3. Pain scores by the administration time of G-CSF. Wilcoxon Signed Ranks test.

Pain assessment time	n	Pain score														
		A group							P	B group						
		First stage (10: 00)			Second stage (14: 00)					First stage (14: 00)			Second stage (10: 00)			
		25%	Median	75%	25%	Median	75%	25%		Median	75%	25%	Median	75%	P	
0 th hour	24	0	0	1	0	0	0	0.020	0	0	0	0	0	0	0	0.564
4 th hour	24	1	2	3	1	1	2	0.01	1	1	2	1	2	2	0.016	
8 th hour	24	2	2.5	4	1	1	1.75	0.001	1	1	2	1	2	2.75	0.027	
12 th hour	24	1	1	2	1	1	1	0.012	0	1	1	1	1	2	0.012	

Tab. 4. G-CSF administration time-related pain scores by informative characteristics of patients.

Informative characteristics		Pain score																
Group	Gender	n	0 th hour				4 th hour				8 th hour				12 th hour			
			25%	Median	75%	p	25%	Median	75%	p	25%	Median	75%	p	25%	Median	75%	p
A	Female	11	0	0	1	0.384*	1	2	3	0.965*	2	2.5	4	0.079*	1	1	2	0.071*
	Male	13	0	0	0		1	1	2		1	1	2		0	1	1	
B	Female	15	0	0	0	0.905*	1	1	2	0.552*	1	1	1.75	0.888*	1	1	1	0.863*
	Male	9	0	0	0		1	2	2		1	2	2.75		1	1	2	
Marital status																		
A	Married	22	0	0	0	0.960*	1	2	2	0.531*	1	2	3	0.128*	1	1	1	0.052*
	Single	2	0	0	0.5		1	1	1		0.5	1	2		0	0	0	
B	Married	21	0	0	0	0.626*	1	2	2	0.093*	1	1	2	0.864*	1	1	2	0.137*
	Single	3	0	0	0		0.5	1	1.5		1	1	2.5		0	1	1	
Educational status																		
A	Literate	6	0	0	1	0.34**	1	2	3.75	0.075**	2	3	4.75	0.044**	1	1.5	2	0.050**
	Primary school	4	0	0	0.75		1	1	2		1	2	2		1	1	1	
	Secondary school	9	0	0	0		1	2	3		1	2	3		0	1	1	
	High school	5	0	0	0		1	1	2		1	1	2		0	1	1	
B	Literate	2	0	0	0	0.41**	1	2	2	0.34**	1	2	2.75	0.21**	1	1	2	0.61**
	Primary school	4	0	0	0		1	1.5	2		1	1	2.75		0	0.5	1.75	
	Secondary school	11	0	0	0		1	2	2		1	1	2		1	1	2	
	High school	7	0	0	0		1	1	2		1	1	1		0.25	1	1	
Previous use of G-CSF																		
A	Yes	17	0	0	0	0.508*	1	1	2	0.203*	1	1	1	0.228*	0	0	0	0.827*
	No	7	0	0	0		1	2	3		0	1	1		0	0	0	
B	Yes	22	0	0	0	0.815*	1	2	2	0.141*	1	1	2	0.114*	1	1	1	0.550*
	No	2	0	0	0		1	1	1.5		1	1	1		1	1	2	

*Mann–Whitney U test; **Independent Samples Kruskal–Wallis test

grastim administered at 10: 00; 0th hour: p = 0.564; 4th hour: p = 0.016; 8th hour: p = 0.027; 12th hour: p = 0.012) (Tab. 3).

Socio-demographic characteristics of effectiveness of administration time of filgrastim relative to pain

There was no significant relation between pain severity scored after different filgrastim administration times and gender, marital status, educational status and previous filgrastim administrations (p > 0.059) (Tab. 4), while mean pain scores were found to be significantly lower in higher educated subjects compared to solely literate subjects (p = 0.034).

Discussion

Pain is a well-known complication of G-CSF administration. In the present study, filgrastim was reported to cause diffuse bodily pain in 91.7 %, while previous use of filgrastim was reported to

cause diffuse bodily pain in 79.1 %. The mechanisms of bone pain secondary to G-CSF are not fully known but recent studies have been reported to range from 19 % to 59 %. Bone pain develops in patients treated with pegfilgrastim and filgrastim (2, 7, 8, 11, 20, 21). On account of bone pain is a well-known complication of G-CSF, pain is treated with drugs (8, 9, 11, 20, 21, 22). Accordingly, in the study by Ogata et al (2005), G-CSF administration resulted in bone pain in 10 % of patients in whom the pain management included nonsteroidal antiinflammatory drugs (NSAIDs) and hydroxyzine. In the study by Kirshner et al (2012), bone pain associated G-CSF should be treated with naproxen while pain relief in patients managed with hydroxyzine but not in those managed with NSAIDs in the study of Ogata et al (2005) (11, 21). According to Carr (2012), mild bone pain induced by G-CSF should be treated with paracetamol but the number of G-CSF administration days and/or G-CSF dose should be changed in the case of intoler-

able severe pain (9). Some works also reported that patients were treated with loratadine (8, 20). It has been emphasized that paying attention to circadian rhythm with determination of the dose and administration time of the drug is essential for the best pharmacokinetic results of the drugs (23, 24). It has been also suggested to the drug administering health professionals to consider the factors that are associated with the pharmacokinetic features of the drug, such as the activity and resting periods of the patient, posture, meal times and meal contents, and galenic formulations particularly when using the drugs with a narrow therapeutic window (25). However, literature search revealed no studies assessing the relationship between G-CSF administration time and pain level. Authors of this study planned the present a study with the hypothesis that G-CSF administration time affects the level of G-CSF-associated pain and found that the pain was statistically significantly lower when G-CSF was administered at 14: 00 compared to administration at 10: 00

In the study by Mendez-Ferrer et al (2008), circulation of hematopoietic stem cells has been reported to peak 5 hours after sunrise, decrease 5 hours after sunset and circulate during the day (26). The authors have also suggested that activation of the nervous system also changes in relation to these circadian rhythms. Saba et al (2013) have also reported similar findings (27). In studies examining the effects of circadian rhythm and exercise on homeostasis, exercise was found to influence platelet synthesis (28, 29) with increased platelet synthesis during daylight (29). Mora-Rodriguez and Coyle (2000) have reported significantly increased plasma norepinephrine level with exercise (30) with another study reporting that G-CSF and adrenergic signal collaborate to trigger the output of hematopoietic stem cells to the peripheral area (31). In our study, it has been considered that the reason of lower pain level with G-CSF administered at 14: 00 p.m. may be associated with the effect of circadian rhythm and exercise via increasing the concentration of hematopoietic stem cells in daytime (26, 28, 29, 31) and that with G-CSF administered at 10: 00, pain level might increase 4 and 8 hours after injection because of overstimulation of bone marrow. Accordingly, the decreased hematopoietic stem cell circulation after sunset (26) may be associated with lower pain level assessed 4 and 8 hours after G-CSF administration at 14: 00 p.m.

Conclusion

It was determined in the present study that in order to minimize the pain, it will be more beneficial to administer G-CSF at 14: 00. This should be of importance in the nursing practice aimed at pain reduction and sustenance of the quality of life of patients, thus enabling uninterrupted treatment.

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