

Kemoterapinin Neden Olduğu Saç Dökülmesinin Engellenmesinde Saçlı Deri Soğutma Yönteminin Etkinliği ve Güvenilirliği

Effectiveness and Reliability of Scalp Cooling in Preventing Hair Loss Caused by Chemotherapy

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ÖZ

GİRİŞ ve AMAÇ: Saç dökülmesi, sitotoksik kemoterapilerin en korkulan yan etkilerinden biri olup çok sayıda hastanın psikososyal durumunu olumsuz yönde etkilemektedir. Çalışmamızda kemoterapi sırasında saçlı deri soğutma yönteminin kemoterapiye bağlı saç dökülmesini önlemedeki etkinliğini, kısa ve uzun dönemdeki istenmeyen etkilerini ve hastanın psikososyal durumunda yarattığı değişiklikleri incelemeyi amaçladık

YÖNTEM ve GEREÇLER: Eylül 2018 ve Ocak 2020 tarihleri arasında saçlı deri soğutma yöntemini kullanan 76 ve kullanmayan 75 olmak üzere toplam 151 hasta çalışmaya dahil edildi. Saç dökülme derecesini belirlemek için National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) treatment related alopecia grading system kullanıldı

BULGULAR: Saçlı deri soğutma sistemini kullanan hastalarda grade 1 saç dökülmesi oranı %77,6 iken kullanmayan hastalarda bu oran %1,3 idi. Yöntemi kullanan ve kullanmayan hastalar arasında izlem süresi boyunca yan etki profili açısından anlamlı bir fark bulunmadı.

TARTIŞMA ve SONUÇ: Saçlı deri soğutma sisteminin kemoterapi ilişkili saç dökülmesini engelleme konusundaki bilgiler gün geçtikçe artıyor olmasına rağmen konu ile ilgili randomize, kontrollü, prospektif çalışma sayısı çok azdır. Bu nedenle çalışmamızın bu yöntemin erkili ve güvenilir olduğuna dair sunduğu verilerin literatür için değerli olduğunu düşünüyoruz

Anahtar Kelimeler: saçlı deri soğutma, soğuk kepler, saç dökülmesinin engellenmesi, kemoterapiye bağlı saç dökülmesinin önlenmesi

ABSTRACT

INTRODUCTION: Hair loss is one of the most feared side effects of cytotoxic chemotherapy and affects the psychosocial status of the patient the most. In our study, we aimed to examine to what extent cooling the scalp with a scalp cooling system can prevent hair loss during chemotherapy, the short- and long-term toxicity of this system, and its effect on the psychosocial status of the patient

METHODS: A total of 151 patients were enrolled; of them, 76 and 75 were sequentially using scalp cooling and the control group. We used National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) treatment related alopecia grading system for grading hair loss

RESULTS: The proportion of grade 1 (less than 50% off hair loss) alopecia was 77,6% in the scalp cooling group and %1,3 in the control group. In the patients who used the system, no short- and long-term side effects that could be considered significant compared to the control group were not detected.

DISCUSSION AND CONCLUSION: Although data on the effectiveness and reliability of scalp cooling used to prevent alopecia caused by chemotherapy is increasing day by day, the number of randomized, controlled, prospective studies on this subject is too few. Our study reveals that scalp cooling reliably and significantly reduces chemotherapy-induced hair loss is well tolerated and improves patients mental health and social condition significantly. However, there is still a need for studies with larger groups.

Keywords: scalp cooling, cold caps, preventing hair loss, preventing alopecia caused by chemotherapy

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INTRODUCTION

As it is known, although hair loss varies according to the drug chosen, it is one of the most common side effects of cytotoxic chemotherapies. In particular, antitumor antibiotics such as microtubule inhibitors, alkylating agents, and anthracyclines often cause hair loss. These drugs are among the most frequently used agents, especially in adjuvant, neoadjuvant, and palliative treatment of breast cancer. In patients with large amounts of hair loss secondary to chemotherapy, mental problems such as social disruption, loss of self-confidence, depression, social phobia, and anxiety occur; as a result, the quality of life decreases significantly (1). It was reported in a study that the most feared side effect among female patients diagnosed with cancer was hair loss, with 77% (2). In terms of the threat, it poses to the body image, hair loss is even more frightening for diagnosed women than mastectomy (3). Perhaps most importantly, since many patients do not want to lose their hair, they can refuse treatment and turn to alternative treatment options (4). Patients with hair loss often shave their heads or wear a wig during treatment and participate much less frequently in social activities. Therefore, new searches have gained speed in recent years to reduce hair loss during chemotherapy. One of these is to provide vasoconstriction by cooling the scalp during chemotherapy, thus reducing the perfusion of chemotherapy drugs to the scalp and hair follicles and preventing hair loss. Some scalp cooling devices designed for this purpose have been approved by the U.S. Food and Drug Administration (FDA). However, the use of these devices both in the U.S. and Europe, as well as around the world, is quite limited at this stage. This is because effectiveness data and short- and long-term toxicity data on this subject are relatively scarce. Therefore, we wanted to share the effectiveness and toxicity data of our patients who used a scalp cooling system to be protected from alopecia caused by chemotherapy.

MATERIALS AND METHODS

The period between September 2018 and January 2020 was examined. In 76 patients, the scalp was cooled to -20 degrees Celsius with the device for one hour before, during, and after

chemotherapy, for a total of three hours. In the control group, 75 patients did not use the system. Patients with migraine, sickle cell anemia, chronic sinusitis, and chronic headache, as well as patients receiving chemotherapy agents with low alopecia potential, were excluded. Each patient received at least four cycles of chemotherapy, except for patients who could not tolerate the device and patients who stopped using the device due to hair loss despite the use of the scalp cooling system. We used National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) treatment related alopecia grading system for grading chemotherapy caused hair loss

Grade 1: those who lost less than 50% of their hair

Grade 2: those who lost 50% or more of their hair (Table 1)

Table 1: Treatment-related alopecia is provided in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE)

Advers event	Grade 1	Grade 2
Alopecia	Hair loss of <50% normal for that individual that is not obvious from a distance but only on close inspection; a different hairstyle may be required to cover the hair loss, but it does not require a wig or hair piece to camouflage	Hair loss of ≥50% normal for that individual that is readily apparent to others; a wig or hair piece is necessary if the patient desires to completely camouflage the hair loss; associated with psychosocial impact

The psychological and social conditions of patients who used the system and patients who did not use the system were compared using the Hospital Anxiety and Depression Scale (HADS) (Table 2).

Patients were divided into groups in accordance with the chemotherapy regimens and forms of chemotherapy (adjuvant, neoadjuvant, curative, or palliative) they received and the stage of the disease.

After the first week, when the side effects such as nausea, weakness, and loss of appetite were expected to decrease, it was questioned whether these toxicities had persisted and if they had persisted to what extent. Besides, the needs for head shaving and wig-wearing were asked and noted. It was also questioned which part of the hair those who had had grade 3-4 hair loss had lost and whether it had been accompanied by eyebrow and eyelash loss. Also, in order to evaluate the acute toxicity, it was questioned whether headache,

numbness in the face and scalp, problems in the facial skin and scalp had been experienced during or after the procedure. The Paxman Hair Loss

Prevention System was used in our study as a scalp cooling system.

Table 2: HADS score

D	A		D	A	
		I feel tense or wound up			I feel as I am slowed down
	3	Most of the time	3		Nearly all the time
	2	A lot of the time	2		Very often
	1	From time to time,occasionally	1		Sometimes
	0	Not at all	0		Not at all
		I still enjoy things i used to enjoy			I get a sort of frightened feeling like butterflies in the stomach
0		Definitely us much		0	Not at all
1		Not quite so much		1	Occasionally
2		Only a little		2	Quite often
3		Hardly at all		3	Very often
		I get a sort of frightened feeling as if something awful is about happen			I have lost interest in my appeance
	3	Very definitely and quite badly	3		Definitely
	2	Yes,but not too badly	2		I dont take as much care as i should
	1	A little,but it doesnt worry me	1		I may not take quiteas much care
	0	Not at all	0		I take just as much care as ever
		I can laugh and see funny side of things			I feel restless as I have to be on the move
0		As musc as i always could		3	Very much indeed
1		Not quite so much now		2	Quite a lot
2		Definitely not so much now		1	Not very much
3		Not at all		0	Not at all
		Worrying thoughts go through my mind			I look forward with enjoyment to things
	3	A great deal of the time	0		As much as ever did
	2	A lotof the time	1		Rather less than I used to
	1	From time to time,but not too often	2		Definitely less than I used to
	0	Only occasionally	3		Hardly at all
		I feel cheerful			I get sudden feelings of panic
3		Not at all		3	Very often indeed
2		Not often		2	Quite often
1		Sometimes		1	Not very often
0		Most of the time		0	Not at all
		I can sit at ease and feel relaxed			I can enjoy a good book or radio or TV program
	0	Definitely	0		Often
	1	Usually	1		Sometimes
	2	Not often	2		Not often
	3	Not at all	3		Very seldom
SCORING:					
Total score Depression:					
Total score Anxiety:					
0-7: Normal					
8-10: Borderline Abnormal					
11-21: Abnormal					

Statistical methods

SPSS 23.0 package program was used in the statistical analysis of the data. Categorical variables were summarized as numbers and percentages, while continuous variables were summarized as means and standard deviations. The chi-square test or Fisher's exact test was used to compare categorical variables.

RESULTS

The study included 151 participants, 76 patients who used scalp cooling (the scalp cooling group), and 75 patients who did not use scalp cooling (the control group). The mean age of the scalp cooling group was 47.6 (23-71), and the mean age of the control group was 54 (19-86).

96.1% of the scalp cooling group and 92% of the control group were women. 84.2% of the scalp cooling group and 90.7% of the control group were married. 84.2% of the scalp cooling group had breast cancer. This rate was 82.6% in the control group.

In the scalp cooling group, 10.9% of patients with breast cancer were at stage 1, 26.5% stage 2, 54.6% stage 3, and 7.8% stage 4.

In the control group, these rates were 9.6%, 19.3%, 58.06%, and 12.9%, respectively.

In the scalp cooling group, 68.4% of patients received adjuvant, 17.1% neoadjuvant, 3.9% curative, 10.5% palliative chemotherapy.

In the control group, these rates were 46.6%, 26.6% %, 5.3%, and 21.3%, respectively (Table 3).

Table 3: Patient characteristics

	Scalp cooling		Control		p
	n	%	n	%	
Gender					
female	73	96,1	69	92	0,327
male	3	3,9	6	8,0	
Marital status					
Married	64	84,2	68	90,7	0,342
single	12	15,8	7	9,3	
Stage					
1	8	10,5	4	5,3	0,161
2	20	26,3	13	17,3	
3	38	50	40	53,3	
4	10	13,2	18	24	
Chemotherapy form					
adjuvant	52	68,4	35	46,7	0,055
neoadjuvant	13	17,1	20	26,7	
curative	3	3,9	4	5,3	
palliative	8	10,5	16	21,3	

The most commonly used chemotherapy regimens in the scalp cooling group: paclitaxel after doxorobusin+cyclophosphamide (AC), 28.9%; docetaxel after AC, 23.7%; AC, 18.4%; cyclophosphamide+docetaxel (TC), 6.6%.

The most commonly used chemotherapy regimens in the control group: AC+paclitaxel, 30.6%; AC+docetaxel, 24%; TC, 9.3%; AC, 8% (Table 4)

Table 4: Chemotherapy regimes

	Scalp cooling		control		p
	n	%	n	%	
TC	5	6,6	7	9,3	0,0001
AC	14	18,4	6	8	0,0001
AC+Paklitaxel	22	28,9	23	30,6	0,0001
AC+Docetaxel	18	23,7	18	24	0,0001
Others	17	22,4	21	28	0,0001

No statistically significant difference was found between age ($p=0.001$), gender ($p=0.327$), marital status ($p=0.343$), disease stage ($p=0.171$), and chemotherapy ($p=0.055$) in both groups.

Hair loss grades in the scalp cooling group:

Grade 1: %77,6

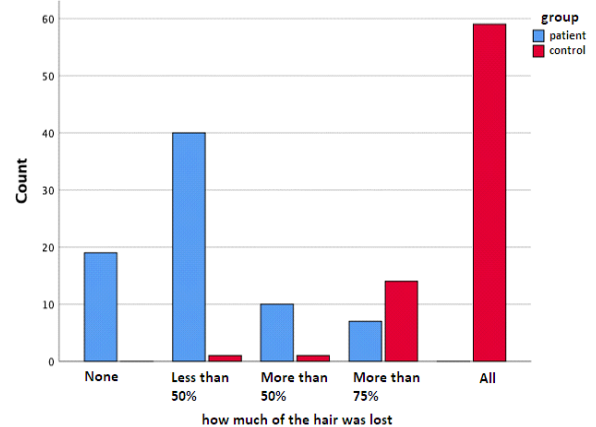
Grade 2 :%22,4

Hair loss grades in the control group:

Grade 1: %1,3

Grade 2 :%98,7

Hair loss statistically significantly decreased in the scalp cooling group (Graphic 1)



Graphic 1: Comparison of hair loss between groups

(%22,4 vs. 98,7 % for grade 2 hair loss, $p=0.0001$).

During treatment, the wig-wearing rate was 12% in the control group and 9.2% in the scalp cooling group. There was no statistically significant difference between the groups ($p=0.608$) The rate of head-shaving during treatment was statistically significantly higher in the control group (60% vs. 17.1%, $p=0.0001$). When the hair loss localizations of those who had grade 2 hair loss in both groups were examined, the most common type was found

to be diffuse hair loss in both groups. There was no statistically significant difference between the groups (90.9% vs. 93.2%, $p=0.674$).

Lash loss was statistically significantly higher in the control group than in the scalp cooling group (60% vs. 42%, $p=0.035$).

Again, eyebrow loss was statistically significantly higher in the control group than in the scalp cooling group (72% vs. 44.7%, $p=0.001$).

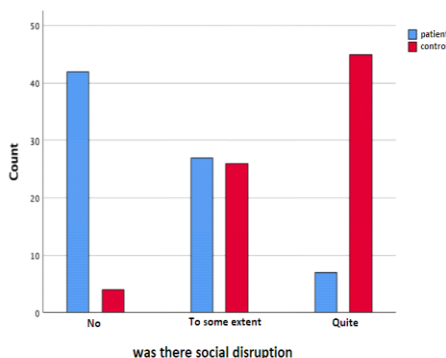
After the week after chemotherapy, when patients' appetite (5.3% vs. 34.9%), nausea (25.1% vs. 54.4%), and weakness (42.1% vs. 70.7%) status were evaluated, all three problems were found to be statistically significantly worse in the control group ($p=0.0001$ for all three).

Hospital Anxiety and Depression Scale (HADS) was used to interpret and compare the psychological and social conditions of patients who used scalp cooling and those who did not.

When the HADS scores of the groups were examined, the mean anxiety score of the control group was 10 points, while the mean anxiety score of the scalp cooling group was 8 points. The mean depression score of the control group was 16 points, while the mean depression score of the scalp cooling group was 11 points. While there was no statistically significant difference between anxiety scores, the depression score was statistically significantly worse in the control group ($p=0,001$).

The rate of antidepressant use in the control group was statistically significantly higher than in the scalp cooling group (26,7% vs. 13,2%, $p=0,043$). The sleep problem was statistically significantly lower in the scalp cooling group than in the control group (39,5% vs. 76%, $p=0,0001$).

The rate of social disruption in the control group was statistically significantly higher than in the scalp cooling group (60% vs. 9,2%, $p=0,0001$) (Graphic 2)



Graphic 2: Changes in social life

The longest follow-up time was nine months, the shortest follow-up time was two months, and the mean follow-up time was five months. During this follow-up period, no patient with metastasis on the scalp was detected.

DISCUSSION

As mentioned before, hair loss is one of the most feared adverse effects of cancer treatment, which disrupts the social life of the patient and causes treatment rejection in some patients. Hair loss caused by chemotherapy varies between 10% and 100% depending on the agents used (5). In a scalp cooling system, a device is used to create vasoconstriction in the scalp of the patient by cooling the scalp in each chemotherapy session so that cytotoxic chemotherapy can not penetrate the hair follicles. Another mechanism of action is slowing the follicle metabolism and thereby decreasing its sensitivity to cytotoxic drugs (6). Although its use is limited in the United States due to the lack of consensus on its effectiveness and reliability, this system has started to become widespread around the world in recent years. So much so that it is used in more than 70 hospitals in the Netherlands alone, in the treatment of over 80% of the patients with solid organ tumors (7). In our study, the safe prevention of hair loss was investigated by using a scalp cooling system in patients receiving cytotoxic chemotherapy with high alopecia potential. As a result of the study, it was found that alopecia caused by chemotherapy can be effectively prevented by a scalp cooling system.

In some previously published studies, it has been reported that hair loss can be prevented by a scalp cooling system. In a study by Nangia et al. on 119 patients with early-stage breast cancer, the patients were randomized at a rate of approximately 2-1, and the effectiveness was determined as less than 50% hair loss. In this study, the success rate was reported to be 50% (8).

In another study published, among patients with early breast cancer, those who received anthracycline were excluded, and the success of scalp cooling was determined to be around 60% (9). In other studies consisting of more heterogeneous patient groups and chemotherapy regimens, the effectiveness of the system in hair protection was determined between 30% and 80% (10-15). In a Japanese HOPE study on 48 patients in which the

effectiveness of scalp cooling systems was analyzed, the rate of no hair loss, which was the primary endpoint, was determined to be 26%, but less than 50% hair loss developed in 85% of the patients (16).

In our study, among the patients we used a scalp cooling system, the rate of patients who had grade 1 alopecia was 77,6% (no hair loss was 25%, less than 50% hair loss was 52.6%). These rate of grade 1 alopecia was 1.3% in the control group. Besides, although the cases with breast cancer were in the majority in our study (84% in the scalp cooling group and 82% in the control group), patients with different types of cancer were also taken. Again, no stage distinction was made, although early-stage patients were predominant (86% in the scalp cooling group and 76% in the control group), metastatic patients were also included. Similarly, although approximately three-quarters of patients in both groups received combinations of taxane- and anthracycline-based chemotherapy, other chemotherapy combinations were also examined.

Although it is not an objective criterion, whether patients shave their heads during treatment may be a criterion for evaluating hair loss. In this period, 17% of patients in the scalp cooling group and 60% of patients in the control group had their heads shaved. This information gives a valuable insight into the success of the system used, albeit indirectly. Because this behavior represents a perception of the patient that the hair is successfully protected, for this reason, the lack of need to shave the head during the treatment or need for a wig can be considered as a more useful parameter in this case than the existing objective measurements, which are scarce. In a review by Megan Kruse and Jame Abraham, the need to wear a wig or a headscarf during the chemotherapy and scalp cooling treatment was emphasized. This parameter, that is, the patient's not wearing a headscarf or a wig until the treatment was completed, was interpreted as the success criteria of the procedure (17). Besides, the results of our study showed that eyebrow and eyelash loss was significantly lower in the scalp cooling group compared to the control group. Based on this data, it was concluded that scalp cooling could also prevent eyebrow and eyelash loss, although not as much as hair loss.

Although generally well-tolerated, some patients may develop a headache or cold intolerance during scalp cooling therapy. In our study, four patients

(5%) gave up scalp cooling therapy within the first 15 minutes of the first cycle due to cold intolerance. Scalp cooling is not applied to patients with cold agglutinin disease, cryoglobulinemia, cryofibrinogenemia, sickle cell anemia, migraine, and chronic headache in our clinic.

In this system, the main concern in the long-term is the risk of developing metastasis in the scalp. Some authors have expressed their interests in this regard (18). For this reason, it is inconvenient to use this system in patients receiving curative treatment for malignancies such as lymphoma and leukemia, in which malignant cells are circulating in the blood (19). To date, no significant data have been published in the literature showing that scalp cooling may increase scalp metastasis in the long term. In contrast, scalp metastasis could not be found during follow-up in 3 separate studies with average follow-up times of 12, 14, and 17 months (20-22). In our study, no scalp metastasis was found in an average of 5 months of follow-up (min-max 3-14 months). Long-term results will be tracked and presented by us.

In our study, the psychosocial effect of hair loss on patients was examined, as well as whether scalp cooling was beneficial in this regard. HADS score was used as a method to analyze the mental states of both groups. HADS depression score was significantly higher in the control group. Common side effects of chemotherapy, such as nausea, weakness, and loss of appetite, generally decrease in severity after the first week of chemotherapy. Especially in more anxious and depressive patients, these side effects are prolonged, which is common in medical oncology practice. Based on this, the patients loss of appetite, weakness, and nausea after the first week were examined, and it was observed that all three problems were significantly more common in the control group. The rate of antidepressant use, sleep problems, and social disruption in the groups were questioned; it was concluded that the said problems were significantly more common in the control group.

CONCLUSION

Although scientific data on the effectiveness and reliability of scalp cooling systems used to prevent hair loss caused by chemotherapy and the frequency of use of these systems are increasing day by day, the number of randomized, controlled, prospective

studies on the subject is too few. Our study reveals that scalp cooling reliably and significantly reduces chemotherapy induced hair loss is well tolerated and improves patients mental health and social condition significantly. Studies in the literature mostly covered a limited number of patients and consisted of observational data. Another problem is the inability to evaluate the amount of hair loss objectively. For this reason, subjective data have been mainly used in the studies. Also, though it is still theoretical, the issue of increasing the risk of scalp metastasis in the long term has not been investigated sufficiently, which is worrying. In this regard, studies with more extended follow-up periods and more participants are needed. Nevertheless, scalp cooling gives hope to our patients on this devastating problem that is encountered so frequently. In order for scalp cooling to become a standard in hair protection in terms of effectiveness and long-term results, a large number of prospective, controlled, randomized studies involving more patients are needed.

LIMITATIONS

Although we used a verified alopecia grading method (CTCAE) the most important limitation of our study is difficulties in calculating the amount of hair loss. The second problem is that the follow-up period for long-term toxicity is short. Especially for scalp metastasis

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