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Effectiveness of Scalp Cooling in Preventing Chemotherapy induced Alopecia

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ABSTRACT

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Chemotherapy induced alopecia is the most distressing feature in cancer treatment. The technique of continuous cooling of scalp during chemotherapy reduces the temperature of scalp and causes vasoconstriction of blood vessels thereby decreasing the amount of drug that reaches the blood. This study tested the effectiveness of scalp cooling using the Paxman scalp cooler system. It also attempted to measure simultaneously the relative effectiveness of anthracycline, antimetabolite and taxane group of drugs. Hair loss was assessed using WHO scale and OLSEN/Canfield visual aided scale (VAS). Extent of alopecia was analyzed before and after providing scalp cooling. The study clearly showed that scalp cooling with Paxman scalp cooler was effective in preventing chemotherapy induced hair loss. It was also found that the highest protection was obtained in the case of taxane group of drugs (93.3%), followed by antimetabolite (pemetrexed, gemcitabine) group of drugs (80%) and the least effective was anthracycline group of drugs (30%). Scalp cooling effectiveness was found out using an experimental group and control group consisting of thirty samples each and the study was found to be statistically significant (p□0.001). Association between the three drug groups and scalp cooling efficacy was also found to be statistically significant (p□0.05). Age, gender, number of cycles and sites of cancer did not have any significant association with scalp cooling effectiveness implying that irrespective of age, gender, number of cycles or site of cancer, scalp cooling can be used to prevent chemotherapy induced alopecia.

Keywords: Chemotherapy, Scalp cooling, alopecia, WHO scale, Olsen/canfield scale.

INTRODUCTION

Cancer is a group of neoplastic diseases where there is a transformation of normal body cells into malignant ones. Its two main characteristics are uncontrolled growth of the cells in the human body and the ability of these cells to migrate from the original site and to spread to distant sites. Cancer is the second most common cause of death in the developed countries and a similar trend has been evolving in the developing countries. Chemotherapy is a kind of treatment that uses drugs to attack cancer cells.[1] Cancer chemotherapy targets rapidly growing population of neoplastic cells and other normal cells with a high proliferation rate such as hair matrix cells. Once the cytotoxic drugs reach the cancer cells, they act to retard their growth, eventually resulting in their destruction. Side effects vary, but common ones are nausea, vomiting, tiredness, pain and hair loss.

Chemotherapy induced alopecia is considered to be one of the most devastating factors in cancer patient care. The overall incidence of Chemotherapy induced alopecia is estimated to be 65%. Hair loss can negatively impact patient's self respect because this treatment related outcomes are readily associated with having cancer by the lay public. Chemotherapy induced alopecia can be generally classified into two categories: telogen effluvium and anagen effluvium.

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In telogen effluvium, a large proportion than normal of anagen hair on scalp moves into telogen thereby resulting in increased shedding diffusely over the scalp and a corresponding decrease in hair density. Usually the shedding begins at the end of the normal telogen period so that the loss is almost at about 3-4 months after drug exposure. In anagen effluvium diffuse scalp hair shedding is seen but the time course is earlier, most apparently at the first two months after initiation of therapy and the extent of loss is potentially much greater than that seen in a telogen effluvium[2]. Chemotherapy induced alopecia is nearly reversible, but sometimes permanent. Permanent baldness has been reported with high dose busulphan, cyclophosphomide, thiotepa, melphalan, etoposide, carboplatin, and paclitaxel.[2,3]

Cancer chemotherapy affects rapidly dividing cells and at any given time, 90% of human hair follicles are in the actively dividing anagen phase. Small blood vessels in the scalp supply the cells of the hair follicles with food and oxygen, and carry away waste products. Any chemotherapy drugs in the bloodstream will also be carried to the hair follicles. Hair loss frequently occurs due to partial or total atrophy of the hair root bulb, causing constriction of the hair shaft, which then breaks off easily. It is in this context that scalp cooling becomes effective. Scalp cooling works by lowering the temperature of the scalp (scalp hypothermia). The lowering of temperature results in the constriction of the blood vessels which supply the scalp and hair follicles. This decreased blood flow reduces the amount of drugs that can actually reach the hair roots. Scalp cooling has the advantage over other methods in that it

also depresses the metabolism in the follicular cells leading to reduced cellular uptake of the chemotherapeutic agents in those cells.

In humans chemotherapy induced alopecia begins approximately within 2-4 weeks and is complete at 1-2 months after the initiation of chemotherapy.[4] The degree of chemotherapy induced alopecia depends upon the type of chemotherapy, dosage regimen and route of administration. The pattern of chemotherapy–induced hair loss begins from the crown and sides of the head above the ears. The pattern is believed to be related to the increased friction experienced during sleep and wearing head coverings.[4,5] Hair loss can be diffused or patchy depending on the distribution of hairs in the active anagen phase.

At present, no approved pharmacologic treatment exists for chemotherapy induced alopecia. Among the few new agents that have been evaluated in humans, the immune modulator AS101 and the hair growth promoting agent minoxidil were able to reduce the severity or shorten the duration of chemotherapy induced alopecia, but could not prevent it.[6]

Since 1970's a number of preventive measures have been proposed to reduce Chemotherapy induced alopecia.[7] Of these, scalp cooling has been the most widely used. The scientific rationale behind scalp cooling is twofold: first, vasoconstriction reduces the blood flow to the hair follicles during the peak plasma concentrations of the chemotherapeutic agent, thereby reducing its cellular uptake; and second, reduced biochemical activity makes hair follicles less vulnerable to the damage of chemotherapeutic agents.[8] Scalp cooling is the use of special cold caps that are worn on the head to reduce and/or prevent hair loss caused by some chemotherapy drugs. In the last decade the use of devices providing continual cooling over the scalp has been adopted and has replaced earlier methods for scalp cooling. However, in India the scalp cooling technique is yet to become popular.

This study tries to determine the effectiveness of cool cap therapy in preventing chemotherapy induced Alopecia between experimental and control group and also analyze which amongst the three drug groups, namely anthracycline combination, antimetabolie combination, taxane combination shows maximum benefit with cool cap in preventing alopecia. We have also attempted to identify any association between the effectiveness of cool cap therapy with age, site of cancer, gender and number of cycles received.

MATERIAL AND METHODS

This was a quasi experimental study design; non randomized with pre test and post test conducted in the Department of Oncology, Kovai Medical Center and Hospital, a multispecialty hospital in Coimbatore, Tamil Nadu over a period of six months from March to August 2012.In this study 60 patients had participated with 30 being offered scalp cooling. The experimental group patients had received one of the Group A (anthracycline combination), or Group B (antimetabolite combination) or Group C (taxanes combinations) drugs. Scalp hypothermia was achieved with Paxman scalp cooling system. Patient's hair was dampened before fitting the cap in order to achieve a closer contact with the scalp. A pre-cooling of thirty minutes was recommended to allow time for sufficient reduction in scalp temperature. The cap remained on the scalp during the infusion period which varied according to regimen and then for the recommended time after infusion of the agent causing alopecia. The same cooling cap was worn throughout the whole period of pre-cooling, infusion and post infusion cooling.

Patients undergoing chemotherapy with anthracycline combination, antimetabolite combination and taxane combination were included in the study. Patients should undergo at least two cycles of chemotherapy to be analyzed for effectiveness. Patients with scalp metastasis, presence of baldness or significant hair loss were excluded from the study.

Measurement of the degree of hair loss was analyzed by using WHO criteria for alopecia that divided the degree of alopecia into four categories, viz., grade 0 for no hair loss, grade 1 for mild hair loss, grade 2 for moderate hair loss and grade 3 for complete hair loss.[9] Olsen/canfield visual aided scale, ranging from 0 for no hair loss to 100 for total baldness, was also employed.

Data were analyzed using SPSS 20.0 software. Pearsons chi-square test has been applied to find out the statistical significance between the treatment group and the control group. Chi-square was also used to determine the association between scalp cooling effectiveness and number of cycles, age, and site of cancer. Gender-wise association with scalp cooling was analyzed by Fishers exact test. Pearson's chi-square test was used to prove the existence of any associations between the effectiveness in the three different drug groups. Values of $p<0.05$ and $p<0.001$ were considered statistically significant.

RESULTS

In our study we have analyzed an experimental group of 30 patients and a control group of 30 patients each. According to sex, majority of the samples in both experimental and control groups with 26 samples (86.6%) each were female. The mean age of the total population was 54.02±12.126.The mean age of male and female were 53.52±11.186 and 57.25±17.718 respectively.

Analyses of employment status showed that majority of the patients (56.6%) in the experimental group as well as in the control group (60%) were employed. While for the socioeconomic status, majority of the patients in the experimental group was in the upper class (76.6%) and in the control group the lower class patients (63.3%) constituted the majority.

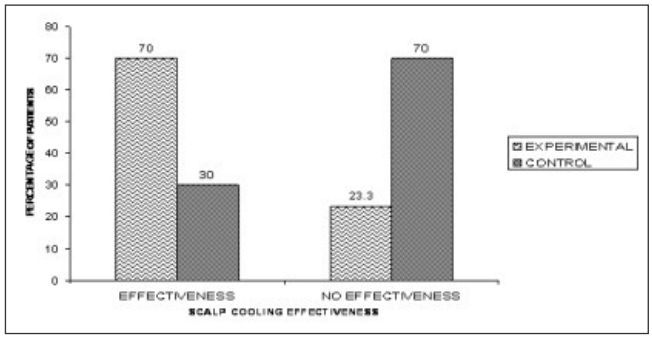
When we saw the distribution of patients according to their site of cancer both in our experimental group and control group 19 of them(63.3%) had breast cancer,2 patients (6%) had fallopian tube cancer,6 (20%) had lung cancer,1 each (3%) had ovarian cancer, prostate cancer and stomach cancer.

In the experimental and control groups 10 patients (33.3%) had received group A drugs which included anthracycline group of drugs, while 5 patients (16.6%) had received group B drugs which belonged to antimetabolite class of drugs (gemcitabine, pemetrexed), and 15 patients (50%) had received group C drug, namely taxane. Regarding the distribution of patients between experimental group and control group there was no difference in the number of cycles undergone.

In the control group out of 30, only 7 patients (23.3%) had show significant hair protection, while the rest of 23 patients (76.7%) had profuse hair fall whereas in the experimental group of 30 patients who received scalp cooling, 21(70%) of them had their hair preserved and only 9(30%) had hair loss. By using Pearsons chi-square test it was found that there was a significant difference between the control group receiving no scalp cooling and experimental group receiving scalp cooling, clearly indicating that scalp cooling offered protection to chemotherapy induced alopecia ($p < 0.001$) (Table 1).

Table 1: Effectiveness of scalp cooling between experimental group and control group(n=60)

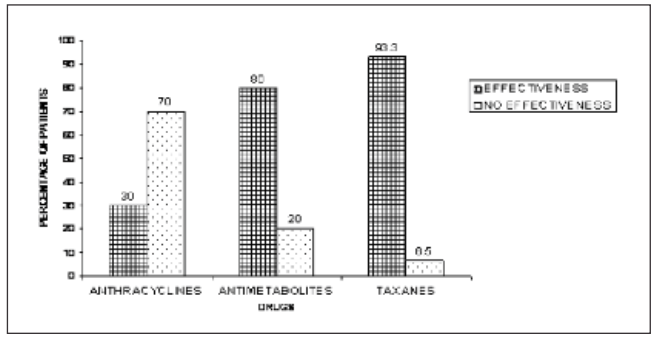
Sl No	Scalp Cooling	Experimental Group	Control Group
1	Effectiveness	23(70%)	9(30%)
2	No effectiveness	7(23.3%)	21(70%)
Chi square = 13.125 p<0.001			



The association between the three drug groups and effectiveness of scalp cooling was found out by Pearsons chi-square test (Table 2). Among the 30 patients included, 21 patients (70%) showed effectiveness in scalp cooling and 9 patients (30%) did not attain protection from hair loss. In patients receiving group A drugs only in 3 cases (30%) protection was achieved while the rest of the 7 patients (70%) did not get protection from hair loss. Patients who received B drugs 4(80%) of them had their hair protected by scalp cooling, while the remaining one (20%) was affected with hair loss. 14 (93.3%) patients who received group C drugs had their hair protected and only 1 (6.7%) had hair loss. In short, we can conclude that group C receiving patients showed the greatest hair protection by using scalp cooling, followed by group B and the least effectiveness was seen in group A receiving patients ($p<0.05$) . This proves that there exists a strong favorable relationship between scalp cooling and chemotherapy treatment. Amongst the three groups, group C with taxanes showed the best results (93.3%), followed by group B (antimetabolites) and group A with anthracyclines showed the least effectiveness.

Table 2: Effectiveness of scalp cooling among different drug groups(n=30)

Sl No	Drugs	Effectiveness	No effectiveness
1	Group A(Anthracyclines)	3(30%)	7(70%)
2	Group B (Antimetabolites)	4(80%)	1(20%)
3	Group C(Taxanes)	12(93.3%)	1(6.7%)
Chi square =11.746 p-value=0.003			



The association between age group and scalp cooling was found out by Pearsons Chi-square test. In patients with their age ranging between 30-45yrs, 7(70%) of them had their hair preserved, while 8 patients (72.7%) in the age group of 46-60yrs had their hair preserved and in the case of those in 61 and above age group, 6patients (66.7%) had no hair loss ($p = 0.958$). This indicates that scalp cooling is equally effective for all age groups (Table 3).

In our study a total of 26 female patients had participated, and among them 18(69.2%) did not suffer any hair loss and

Table 3:Relationship of scalp cooling effectiveness with mean age, gender, site of cancer, and number of cycles

Variable	Effectiveness	No effectiveness
Mean age		
31-45	7(70%)	3(30%)
46-60	8(72.7%)	3(27.3%)
61-75	6(66.7%)	3(30%)
	Chi square=0.08 p =0.958	
Gender		
Female	18(69.2%)	8(30.8%)
Male	3(75%)	1(25%)
	Fischer exact test p=1	
Site of cancer		
Breast cancer	11(57.9%)	8(42.1%)
Fallopian tube cancer	2(100%)	0(0%)
Lung cancer	5(83.3%)	1(16.7%)
Ovarian cancer	1(100%)	0(0%)
Prostate cancer	1(100%)	0(0%)
Stomach cancer	1(100%)	0(0%)
	Chi square=3.977 p=0.553	
Number of cycles		
2	7(50%)	7(50%)
3	5(71.4%)	2(28.6%)
4	5(100%)	0
5	2(100%)	0
6	2(100%)	0
	Chi square =6.531 p =0.163	

8(30.8%) had considerable hair loss. Only 4 male patients had participated in the study and among them 3(75%) had attained hair protection and 1 (25%) dropped out from the study due to cold intolerance and he suffered hair loss. The Fischer exact value obtained was 1 which shows that there exist no relationship between gender and scalp cooling, thereby proving that irrespective of gender, scalp cooling provides hair protection.

The association between the site of cancer and effectiveness of scalp cooling was found out by Pearsons Chi-square test. Out of a total of 19 patients with breast cancer, 11(57.9%) of them had hair protection and 8(42.1%) suffered hair loss. Among the 2 patients with fallopian tube cancer, both of them had their hair protected. Among the 6 patients with lung cancer, 5(83.5%) of them had their hair protected while 1(16.7%) had hair loss. There was 1 patient each with ovarian cancer, prostate cancer, endometrial cancer and all 3 of them had attained hair protection (p=0.553). Thus we can conclude that irrespective of the sites of cancer mentioned above scalp cooling is equally beneficial.

The association between number of cycles undergone and scalp cooling effectiveness was analyzed by Chi-square test. In patients who had undergone 2nd cycle, hair preservation was seen in 7(50%) patients. In the case of patients in 3rd cycle, 5 of them (71.4%) had shown effectiveness in scalp cooling while in cycle 4, all the 5 patients (100%) had shown effectiveness by using cool cap. In cycles 5 and 6, all of the patients (2 each) had shown effectiveness of scalp cooling. In cycle 6, both the patients (100%) had shown effectiveness of scalp cooling (p=0.163).

DISCUSSION

Chemotherapy induced alopecia is a distressing side effect common to chemotherapy regimens in oncology. Unfortunately, chemotherapy induced alopecia is an often overlooked factor among the current research priorities. Cooling the scalp during selected chemotherapy regimens has been shown to reduce or prevent otherwise inevitable total hair loss. Commercially available systems used were frozen gel caps, cooled air blown over the scalp, and a liquid coolant circulated through a refrigeration unit attached to a cap. It was only after 1970s that the technique of continuous cooling of the scalp was introduced and the results were amazing.

In a study conducted by Lemenager et al[10] on the prevention of alopecia by using a cool cap, 98 patients received 100mg/m^2 docetaxel by 1 hour IV infusion over 3 weeks. Here 83 patients (86%) were evaluated as a success as they obtained WHO grade alopecia of $\leqslant$ 2 and had no need to wear a wig while 14 patients (14%) had to wear a wig, with seven among them withdrawing before the evaluation at three cycles and one was lost to follow up. The study concluded that cool cap is a very effective technique with a minimal side effect for docetaxel treated patients. In our study we have found that scalp cooling was very much effective with taxane based drugs (93.3%).

A randomized clinical trial was performed by Barbara Satterwhiteet al[11] to determine the effectiveness of scalp hypothermia in the prevention of hair loss associated with doxorubicin. In that study, 26 patients were randomized to receive scalp hypothermia for chemotherapy induced alopecia. Data was analyzed in 25 patients; 12 in the treatment group and 13 in the control group. There was acceptable hair preservation in 75% of patients who received scalp hypothermia and only 8% patients of the control group had acceptable hair preservation (p=0.0009). In our study we have found that scalp cooling is less effective for anthracycline based chemotherapeutic regimen (30%).

In the study by Katsimbri et al[12] on the prevention of chemotherapy induced alopecia using an effective scalp cooling system 70 patients were recruited and were classified into four groups based on different drug regimens viz.,

Group A (taxane based regimen without anthracyclines), Group B (taxanes with anthracyclines), Group C (anthracycline based regimen with taxanes), and Group D (etoposide based regimen). Assessment was carried out using WHO grading system from 0 to 4. Grades 0 to 2 were considered as satisfactory hair protection while grade 3 and 4 were considered as failure. A total of 57 patients were evaluated for assessment and over 81% protection was achieved. In groups C and D, 11 of 12 patients (92%) had no alopecia while 30 of 32 (88%) treated with taxanes had adequate hair protection. In group B, 4 of 11 patients (36%) had adequate hair protection. The system was well tolerated and was a very effective method for protection for hair loss caused by taxanes and anthracyclines and etoposide. In our study we have found that maximum hair protection was attained with taxanes (93.3%), followed by antimetabolites (80%) and least effectiveness was shown in anthracyclines (30%).

A multicenter study was conducted by Carolyn S Massey[13] to determine the efficacy or patient acceptability of the Paxman scalp cooler to prevent hair loss in patients receiving chemotherapy. This was an open non randomized observation study conducted at eight sites involving 94% patients. Alopecia was assessed using the WHO grading system. The use of the Paxman scalp cooler was adjudged a success for 89% of all patients by using the WHO grading system for alopecia and for 87% of patients being specifically administered with 5 Flurouracil, Epirubicin, Cyclophosphamide regimen. When asked about the degrees of comfort during scalp cooling process 85% of the patients described it as very comfortable, reasonably comfortable or comfortable with only 15% patients reporting a description of uncomfortable or very uncomfortable. The study concluded that scalp cooling by use of Paxman scalp cooler is effective with minimal side effects. In our study also we found that Paxman scalp cooling system was found to be effective in the selected chemotherapy regimens.

CONCLUSION

Alopecia is a distressing side effect of chemotherapy that affected the quality of life of patients. Cooling the scalp prevents the hair loss caused by the use of chemotherapy drugs. There were several methods of preventing chemotherapy induced hair loss prevailing in the past but these did not offer any significant protection from hair loss. All these methods were based on the principle that scalp circulation is temporarily reduced, either mechanically or by vasoconstriction due to low temperatures achieved by cooling, thus reducing the amount of drug reaching the hair follicle. Also low temperature can reduce the metabolic rate of the follicles, making them less susceptible to the effect of the chemotherapeutic agent.

In this study it was clearly shown that scalp cooling with Paxman scalp cooler was effective in preventing chemotherapy induced hair loss. It was also found that the highest protection was obtained in the case of taxane group of drugs (93.3%), followed by antimetabolite (pemetrexed, gemcitabine) group of drugs (80%) and the least effective was anthracycline group of drugs (30%). Thusit showed that scalp cooling with taxanes, antimetabolites give good results while with anthracyclines it did not work well. This is mainly due to the reason that anthracycline drugs tend to remain in circulation for a longer period of time compared to others. Association between the three drug groups and scalp cooling efficacy was also found to be statistically significant ($p<0.05$). Age, gender, number of cycles and sites of cancer did not have any significant association with scalp cooling effectiveness implying that irrespective of age, gender, number of cycles or site of cancer, scalp cooling can be used to prevent chemotherapy induced alopecia. However, it must be admitted that more studies are needed with larger samples to identify individual drug based degree of protection from hair loss and also to understand gender wise variations.

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