

Site-Dependence Scalp Cooling System to Prevent Hair Loss during Chemotherapy

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Abstract

Hair loss (Alopecia) is regarded as the most distressing side effects of chemotherapy in cancer patients. A reduction in cutaneous cell metabolism as a response to the hypothermia could simply make hair follicles less susceptible to drug damage with subdural cooling. In this study, a detailed three-dimensional finite element of human head model is used to investigate the changes in cutaneous blood flow due to heat transfer during the cooling process. Our finite element model consists of scalp, skull (trabecular and cortical bones), all meningeal layers, flax, tentorium, and the brain. Cooling effect was investigated in three different regions of frontal, superior and occipital of the head. The results showed that frontal region is the most sensitive region during cooling, because of the highest contact area between the scalp and the coolant. In order to keep the normal brain condition, the coolant temperature must not be lower than 2°C. It's also recommended to keep the coolant temperature in range of -5°C to 7°C. With the constant coolant temperature, the results showed different steady state temperatures in different anatomical regions. It is therefore expected to design a new scalp cooling cap to provide site-dependence temperature with respect to different head regions for optimum heat transfer.

Keywords: Heat transfer; Three-dimensional FE head model; Alopecia; Scalp cooling

Introduction

Chemotherapy as a cancer treatment often leads to partial or complete hair loss (alopecia). It is one of the most distressing and traumatic side effects of cancer therapy [1,2]. It causes psychological stress [3]; negative impact on body image [4], self-esteem [2] and social relations [5], which might lead to treatment rejection by some patients [6,7]. Chemotherapy-induced alopecia is caused by the effects of the chemotherapeutic drug on the hair follicle that continuously receive blood supply from the superficial scalp arteries [8]. Cooling the scalp during chemotherapy treatment can reduce or even prevent this hair loss [9] and is generally very well tolerated by the patient [10]. Two possible mechanisms explain how scalp cooling might contribute to hair preservation [11]. First, blood flow reduces due to the cutaneous tissue condensation during cooling which leads to a reduced drug supply to the hair follicle. Second, a reduction in cutaneous cell metabolism as a response to the hypothermia could simply make hair follicle less exposed to drug.

In this study, a cooling cap is used to cool the scalp in which the coolant fluid is adjusted to the desired temperature in flow state by a cooled reservoir. To lower the scalp temperature, the fluid in this system is circulated with specific temperature and flow rate in the cap; therefore, heat is scavenged from the patient's scalp. The brain heat transfers through free convection and evapotranspiration, while heat generation occurs from two perfusion and metabolism sources. Considering the brain sensitivity, empirical assessing and testing the effect of various conditions on this tissue heat transfer is not an appropriate option. Numerical simulation is an efficient solution to overcome this limitation. Through measuring the evapotranspiration and the transported heat inside the head tissues and their synergic impact in creating free convection in the vicinity of scalp, under controlled environmental conditions; then, applying the desired conditions in the model, it is possible to examine different effective conditions in this heat transfer.

Clark et al. [12] in a pure empirical measurement determined free convection around the head. The study conducted by Xu et al. [13] involved mathematical modeling of brain cooling with constant temperature boundary conditions. For the first time, Murakami et al. [14] numerically studied heat regulation induced by respiration in their model. They proposed a method for simulation composed of airflow, thermal radiation, and moisture transport to predict heat release from a human body. Vanleeuwen et al. [15] applied a temperature as low as 10°C on an infant head. Their results showed that only surface areas of the brain are cooled down to 34°C. They observed no significant temperature change in the deeper areas. Denis et al. [16] proposed some temperature distribution model of an adult human under cold therapy by putting ice on the scalp. Applying the convection and radiation heat transfer on body surface in 3D state, Sorenson and Voight [17] modeled the body heat with constant skin temperature condition using computational fluid dynamics. Sukstanskii et al. [18] used the analytical method to investigate the effect of various factors on the brain temperature and reported input blood flow and temperature to tissue as the only effective parameters in brain temperature. Johnson et al. [19] studied the relationship between scalp temperature and blood flow during the cooling process using a 1D modeling. In another work, Johnson et al. [20] empirically measured scalp temperature and blood flow in a laboratory through the scalp cooling using cooling cap.

Considering the 3D structure and complex geometry of the human brain, it is essential to use 3D modeling for higher accuracy and

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efficiency in simulating scalp heat transfer. The present study provides a 3D human head model and a cooling cap to examine the heat transfer between the coolant and the skull, scalp and meningeal layers.

Geometry and Boundary Conditions

The basic geometry of our FE model is based on Horgan and Gilchrist's [21] model, from the BEL repository managed by the Istituto Ortopedici Rizzoli, Bologna, Italy. The point clouds are extracted from the model to form the boundary layers of skull, subarachnoid space and the brain. Since the outer layer of the skull and meningeal layers are important in this study, the model was further modified utilizing new studies on the geometry and thickness of meningeal layers to add more details [22]. Finally, the model was constructed consisting of skull, arachnoid mater, subarachnoid space, pia mater, tentorium, falx, and the brain as shown in Figure 1. The study conducted the numerical simulation of scalp cooling in two steps. In the first step (Step I), the temperature fields are computed in the head assuming constant heat flux due to perfusion and metabolism without cooling cap. In the second step (Step II), the cooling cap is added to the model and the transient unsteady state solution is computed. The results of the first step are set as the initial conditions for temperature distribution in the second step. In the 3D simulation of heat transfer between human head and surrounding head, the fluid (air) and head are initially modeled inside a rectangular cubic area. Figure 2c illustrates human head model and the applied boundary conditions. The fluid speed in the periphery is considered zero (no slip boundary condition). At the bottom wall (marked with blue color) the inlet pressure with constant temperature of 300 K is set as boundary conditions. At the top wall (shown in red color) the boundary condition is set to be a pressure outlet. These conditions allow air flows to the model from lower boundary and exit from upper boundary. Due to the low height difference (1 m), the hydrostatic pressure difference induced by the height difference is neglected at its lower and upper surfaces. GAMBIT software is used as preprocessor for mesh generation and for simulation and post-processing FLUENT software is employed. Continuum, momentum, and energy equations are solved to solve heat transfer. The momentum and energy equations are discretized through second order upwind scheme; whereas the pressure and velocity correlation are solved using the Simple Algorithm. The joining area of neck and head are assumed insulated; hence, the heat transfer effect of the lower body parts is eliminated in this model.

As stated above the cap was added to the model in Step II. In this analysis the followings were determined: 1) the interior temperature distribution, 2) the heat transfer (cooling effect) of the head due to blood circulation, 3) the forced heat exchange between scalp and cooling cap, and 4) the generated heat by the intracellular metabolism. Therefore, the model covers the entire simulation of the heat transfer from the

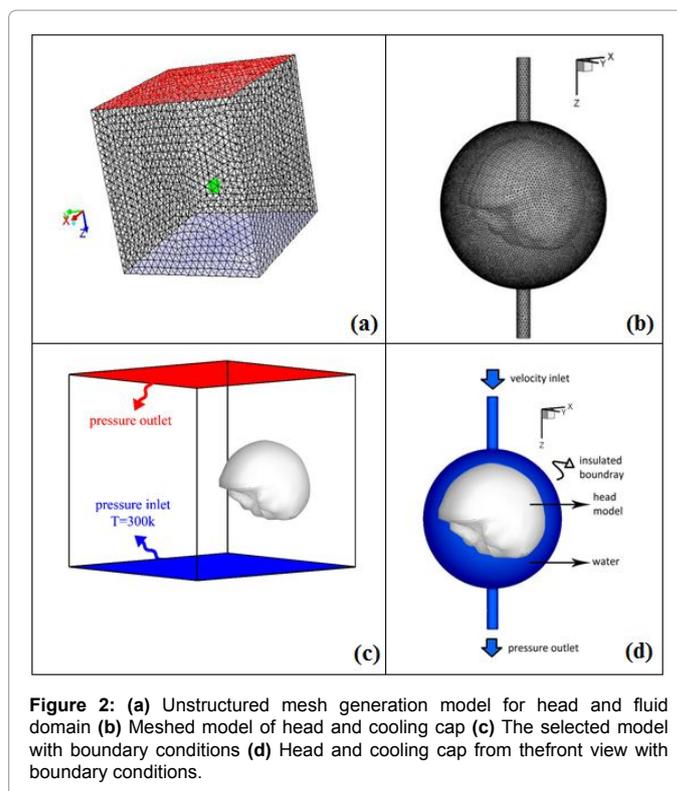
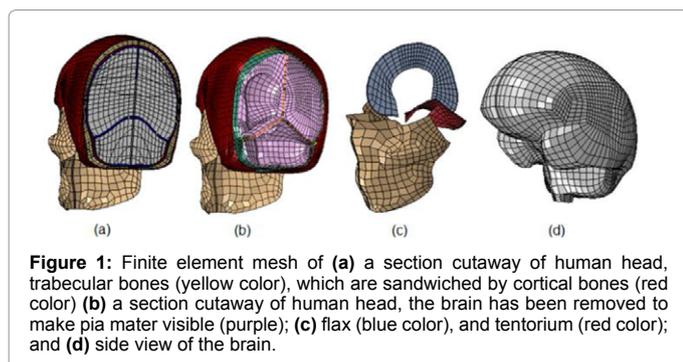


Figure 2: (a) Unstructured mesh generation model for head and fluid domain (b) Meshed model of head and cooling cap (c) The selected model with boundary conditions (d) Head and cooling cap from the front view with boundary conditions.

head (and its interiors) to the fluid circulating inside the cooling cap. Figure 2d illustrates the model setting inside the cooling cap in Step II. The cooling cap completely covers the head with no air gap. In this model, the hair effects and the cap layer thickness between the coolant and scalp are neglected. Water is selected as circulating fluid inside the cooling cap that enters from the upper boundary and exits from the lower boundary. The model incorporates convection heat transfer between the cap and the head (through the water medium), and conduction heat transfer through various layers of the head that are in contact with one another. The inlet temperature is set at 0°C with a constant flow rate of 0.04 kg/s. The outlet gauge pressure is set to be 0 atm. All other external boundaries of the cap were assumed insulated with no heat flux. In this analysis, the unsteady method using first order implicit algorithm with time step of 15 seconds is used.

Governing Equation

To model the heat transfer induced by the blood diffusion in the live tissue, Pennes Bioheat Equation with the effect of surface evaporation (q_s) was employed. The material properties used for this model are the physical and physiological homogeneous properties from Dennis et al. [16] (Table 1). In the absence of radiation and convection, heat transfer equation is expressed as [23]:

$$\rho c \frac{\partial T}{\partial t} = \nabla \cdot (k \nabla T) + q_b + q_m + q_s \quad (1)$$

Where, k is thermal conductivity, ρ is density, c is specific heat, T is the local tissue temperature, q_s is heat transfer due to surface evaporation, q_b is the heat generation source in form of rate of heat transfer per unit volume due to perfusion, and q_m is the heat generation source in form of metabolic heat production in the tissue.

Thermo-physical Properties	Perfusion (kgs/m ³) ω_b	Metabolic rate (W/m ³) q_m	Density (kg/m ³) ρ	Specific heat (J/kg/K) C	Conductivity (W/m/K) k
Scalp	0.43	33	1480	2495	0.34
Skull	0.066	5	1600	1500	1.16
Brian	8.6	525	1000	3680	0.52

Table 1: The physical and physiological homogeneous properties of scalp, skull and brain under normal conditions [16].

Thermo-physical Properties	Dynamic viscosity (kg/s/m) μ	Thermal expansion (1/K) β	Density (kg/m ³) ρ	Thermal capacity (J/kg/K) C	Thermal conductivity (w/m/K) k
Air	0.0000178	0.0033	1.225	1006.43	0.0242

Table 2: Physical properties of air at 300 K temperature.

Note that, q_b is the energy generation or output in the tissue volume unit which is controlled by blood flow to maintain the tissue central temperature at its biological balance. According to the Pennes [23], the energy exchange between blood vessels and the surrounding tissue mainly occurs at the level of the capillaries. Therefore, the thermal contribution of blood can be modeled by a so-called heat sink. This energy depends on the temperature gradient between the local tissue and the artery. It is also dependent on the blood diffusion in the given tissue. So, the perfusion heat transfer can be expressed as [23]:

$$q_b = \omega_b c_b (T_{art} - T) \quad (2)$$

Where,

ω_b is the volumetric perfusion rate, c_b is the specific heat of blood (3825 J/kg/K), T_{art} is the temperature of the arterial blood (37°C), and T is the local tissue temperature.

One of the main points of interest in this study is the relationship between scalp temperature and perfusion during cooling. The following equation indicates the blood flow variations with respect to temperature [24]:

$$\frac{\omega_b}{\omega_{b,0}} = Q_{10}^{\left(\frac{T-T_0}{10}\right)} \quad (3)$$

In which, $\omega_{b,0}$ is the blood flow in the tissue at natural temperature, Q_{10} is the perfusion coefficient, and T_0 is the tissue temperature at initial condition which was calculated from the Step I simulation.

This equation indicates that by decreasing 10°C in the tissue temperature, the blood flow correspondingly decreases with blood flow coefficient (Q_{10}). According to Denis et al., Q_{10} varies in the range of 2 to 3 [16]. Besides, q_m is the heat generation potential in volume unit induced by the metabolic activities of the cells in the entire tissue, which is considered as homogenous because of the slight temperature variations in the brain. In the present study, the constant value of 2.5 is used for the head standard model [19].

Perspiration helps maintaining stable body temperature. The water placed in the interface provides the heat needed for evaporation through convection and conduction heat transfer from the lower surfaces. Evaporation rate is controlled by many factors such as water temperature at the water-air interface, atmospheric moisture, surface area of the water-air interface, and water temperature [25]. To model the heat transferred from skin surface by perspiration, a thermal sink was added to the skin outermost layer in the heat reflection manner. As previously mentioned, for the sake of simplification, this heat reflection was assumed constant and equal to the discharged mean heat induced by evapotranspiration under human welfare conditions. Murakami

et al. [14] obtained the heat transferred from skin surface induced by evapotranspiration as 24.2 W/m². To use this amount in the present study, heat waste should be expressed in volume unit. Assuming constant skin thickness of 3.9 mm, q_s is therefore obtained as -6208 W/m³.

The more recent models of live tissue heat transfer involve the impact of vascular system in heat transfer phenomenon inside the body. Since the majority of the tissues do not have any vascular system in this model (except a wide net of capillary systems in the brain), only Pennes Bio heat Equation was performed in this study. Free convection exists in the human body due to temperature gradient between the body and surroundings. This includes the convection in the vicinity of the head where it creates an upward air flow due to the air temperature increase in the head area. In Equation 1, energy conservation equation inside the tissue is linked to the continuum and momentum equations and also the energy inside the fluid around the head. To study the free convection flow, Boussinesq approximation is used. In this method the density is considered as a function of temperature in momentum and energy equations. Therefore, the governing equations in free convection are interrelated because of the temperature changes. As shown in Equations 5 and 6, density change contributes as the main cause of generating volumetric force in the momentum equation. So, the governing equations on fluid around the head (air) are expressed as follows:

$$\nabla \cdot v = 0 \quad (4)$$

$$\rho v \cdot \nabla v = -\nabla p + \mu \nabla^2 v + \rho g \beta (T - T_a) \quad (5)$$

$$\rho c_p v \cdot \nabla T = k \nabla^2 T \quad (6)$$

Where, v is velocity, p is pressure, ρ is density, β is the thermal expansion coefficient, g is gravity, k is thermal expansion coefficient, T_a is reference temperature in calculating fluid density, μ is dynamic viscosity and C_p is the fluid thermal capacity.

Table 2 presents physical properties for air at 300 K temperature, which is considered as the environment temperature in this study. Equation 4 is the continuity equation for incompressible flow. Equation 5 represents the momentum equation for incompressible flow with volumetric force term added (the last term in Equation 5) to apply the temperature change. Equation 6 presents equilibrium of convection heat transfer and diffusion in head.

Mesh Generation

To make the model ready for simulation, unstructured mesh structure was utilized to model the fluid domain; head and fluid interface are discretized using finer mesh size. Figure 2a presents mesh structure of the head and the head periphery for Step I and Figure 2b

illustrates mesh generation for the head and cooling cap employed for Step II. To demonstrate mesh size in dependence, three different mesh sizes including coarse (138429 elements), medium (250364 elements), and fine (500283 elements) are investigated. Mean temperature distribution was assessed on the scalp, shown in Figure 3. As indicated, the results remain almost constant with increasing the mesh density. Therefore, the incremental grid size was not necessary and the coarse mesh was sufficiently fine for the analysis.

Validation

The model was validated against Johnson et al. [19]. Their results indicated that during 50 minutes of cooling, the temperature of scalp drops from the maximum amount of 34.4°C to minimum level of 18.3°C. Thus, relative perfusion inside the skin reaches to its minimum level of 25%. These results are obtained given 4 mm hair layer thickness in the head modeling. For a more accurate heat transfer between the head and cap, they considered hair thickness as 1 mm in the next step. In this case, the results showed that the minimum skin temperature reaches 10.05°C and the perfusion inside the skin decreases down to 13% as compared to their natural value. In the present study the scalp temperature dropped from 34.3°C to 9.68°C. Consequently, the perfusion decreased down to 12% of its natural amount. As shown in Table 3, the response of the model of the present study matched relatively well with Johnson et al. 8% However, this difference can be attributed to the fact that presence of hair was neglected in the present research.

Results and Discussion

Step I results

Mid-sagittal plane of the brain is chosen to record the results. Figure 4 shows the temperature distribution obtained by solving the fluid field and head tissues in the control model. Temperature distribution of the head shows the appropriate thermal convection of this organ

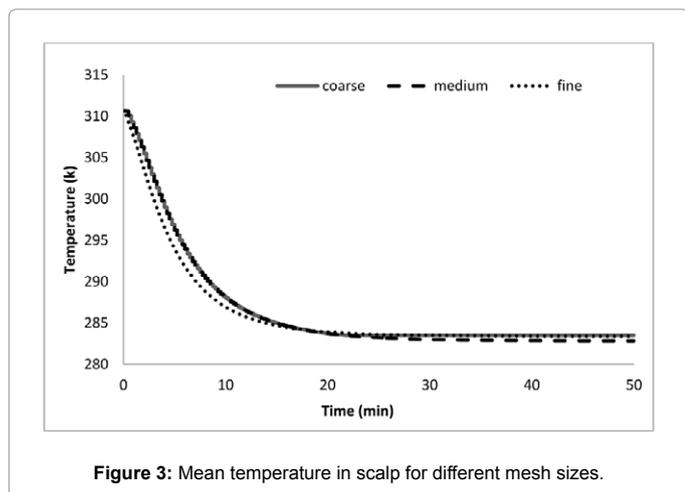


Figure 3: Mean temperature in scalp for different mesh sizes.

Model	Max. scalp temperature (°C)	Min. scalp temperature (°C)	Perfusion decrease (%)
Johnson et al. with 4 mm hair layer	34.4	18.3	25
Johnson et al. with 1 mm hair layer	34.4	10.05	13
Present study	34.3	9.68	12

Table 3: The model was validated against Johnson et al. As indicated the model matches well with the case with 1 mm hair layer.

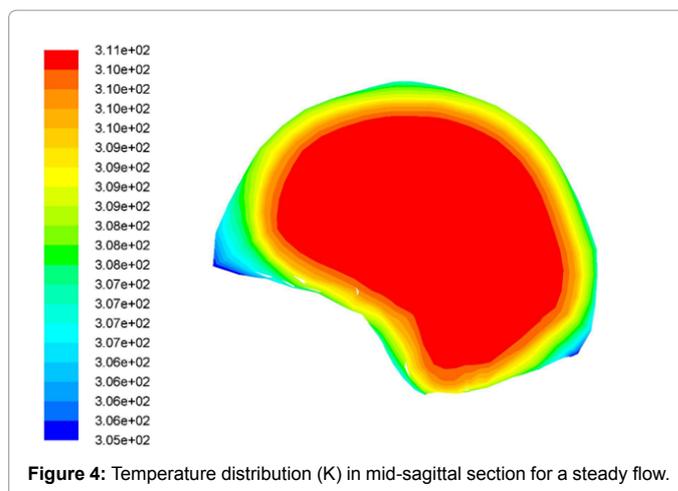


Figure 4: Temperature distribution (K) in mid-sagittal section for a steady flow.

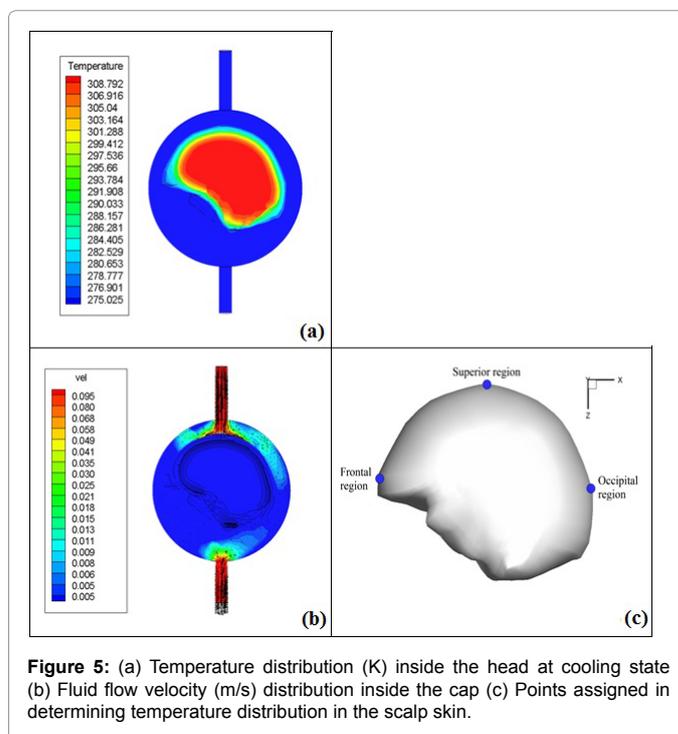


Figure 5: (a) Temperature distribution (K) inside the head at cooling state (b) Fluid flow velocity (m/s) distribution inside the cap (c) Points assigned in determining temperature distribution in the scalp skin.

with its environment. Considering the governing conditions, through decreasing the environment temperature and reducing the blood flow it is possible to develop the cool layers in the higher depths. Maximum temperature in this model was 37.4°C in the brain tissue. Moving towards the scalp, the temperature in other tissues gradually decreases to a minimum level at the surface. Because of the more contact area between the skin surface and air in the anterior and posterior regions, the temperature reached to its minimum value in these regions. In other words, the minimum temperature in these areas is attributed to the lack of heat generation in the surface vicinity and the wider contact area.

Step II results

In this step, the cap is added to the 3D human model to analyze human head cooling through its thermal exchange to the circulating fluid inside the cooling cap. Simulation procedure of the scalp cooling continued until the thermal steady state condition was obtained. Figure 5a

illustrates the temperature distribution at $t=3000$ s (50 minutes). Note that the dramatic temperature change occurred in scalp, skull and Meningeal layers and not in the brain which shows the efficacy and validity of temperature parameter in fluid domain. The maximum temperature change happens at 20 mm from scalp towards the brain. As predicted, the maximum temperature occurred at the center of the brain a region where heat generation is high and the distance for heat transfer between the cold cap and hot biological material is greatest. The velocity of the flow distribution remained constant during the 50-minute simulation, at 0.045 m/s as shown in Figure 5b. This flow enables the cold fluid to stay in motion and continuously removes the flux of heat from the head. The velocity remains highest at inflow where velocity is forced in and the area through which the coolant may flow is the smallest. However, as the fluid spreads out over the cap, it is flowing through a much larger area and therefore slows down dramatically. One of the main objectives of this simulation is to find the appropriate cooling temperature. In this regard, superior region, frontal region and occipital region on head scalp were selected to present temperature distribution inside the scalp tissue (Figure 5c). Figure 6 indicates temperature changes inside the scalp for the selected regions. Temperature is separately measured for each region; then, the average is calculated as the main temperature change in the transitional state. The average scalp temperature varying with time is shown in Figure 7. These variations allow detecting the appropriate temperature options in cooling process without making any injury to the scalp.

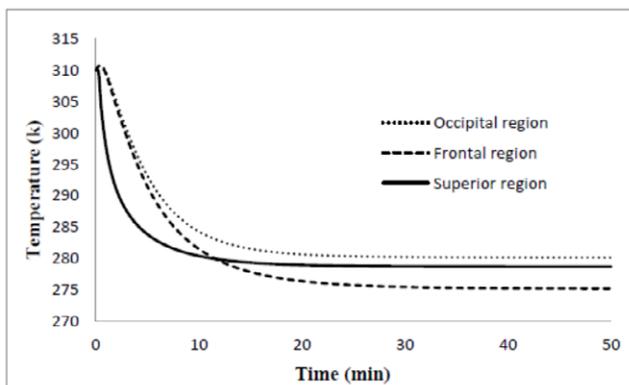


Figure 6: Steady state temperature (K) during the scalp cooling in subarachnoid space in occipital, frontal and superior regions. The maximum temperature drop happened in the frontal region.

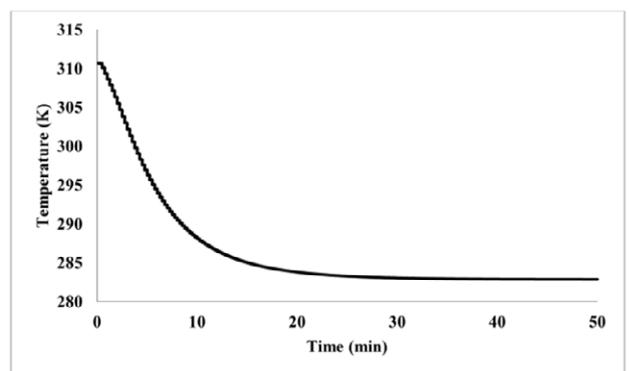


Figure 7: Mean temperature distribution in the scalp skin during the cooling process.

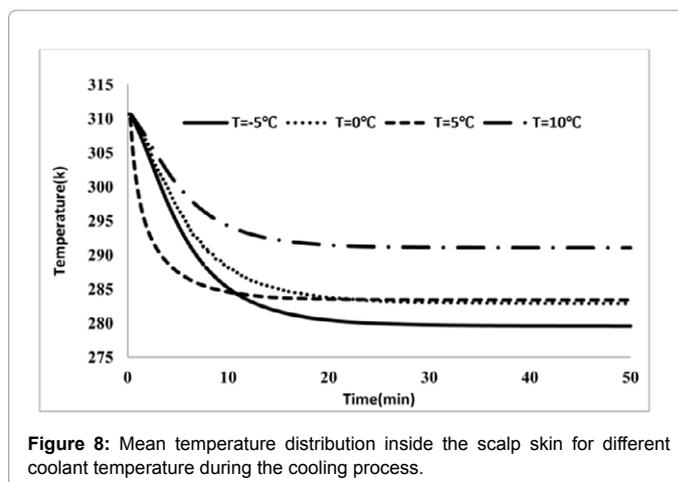


Figure 8: Mean temperature distribution inside the scalp skin for different coolant temperature during the cooling process.

Coolant temperature (°C)	Min. scalp temperature (°C)	Perfusion decrease
-5	6.4	10%
5	10.22	13%
10	17.68	21%

Table 4: Effect of changes in coolant temperature on minimum scalp temperature (T_{skin}) and relative perfusion during cooling.

The results indicated that the scalp temperature during the cooling process reached its minimum value (9.68°C) from its maximum (34.3°C). This temperature variation is obtained during 50 minutes followed by steady state condition. Also, the model showed that perfusion drops down to 12% of normal value when Equation 3 is used to calculate skin blood flow. Figure 8 presents mean temperature distribution over time in human scalp in various water temperatures entering the cooling cap.

Effect of changes in coolant temperature on minimum scalp temperature (T_{skin}) and relative perfusion are shown in Table 4.

The recent studies have shown that there is a relation between head tissues temperature and the protective effect of scalp cooling in preventing hair loss. The main objective of the current study was to investigate the suitable temperature range to minimize the hair loss. Based on this simulation results, cooling is effective only when the scalp temperature drops below 22°C. In contact temperature, most dropped temperature was seen in sub arachnoid space in the frontal region. Therefore, we considered frontal region as the critical region to compute the lowest possible temperature range. In other words, the frontal region of the brain should keep its normal metabolism during cooling process and the range of acceptable temperature is 35.7°C to 34.2°C. It's recommended to keep the coolant fluid temperature range between -5 to 1°C to get the most efficient results. According to the results, the coolant fluid temperature shouldn't be set below -5°C. This is done in an attempt to reduce the risk of tissue injury from lack of blood flow. The constant contact with cooling cap may affect head tissues, if the scalp temperature drops below 2°C. Therefore, this study proposes to keep the temperature at 5°C for all points of head tissues to prevent damaging tissues in patients under treatment. In summary, according to the results, if coolant temperature and mass flow rate are set to -5°C and 0.04 kg/s, respectively, the minimum scalp temperature (6.4°C) is achieved. This subsequently would have the maximum protective effect against hair loss.

Conclusion

This study was carried out to study site-dependent scalp cooling system in order to enhance reducing hair loss during chemotherapy. The results of this study are matching to those obtained in previous works. At cooling temperature of -5°C , the scalp temperature settles on a minimum of 6.4°C from the maximum temperature of 34.3°C and blood flow pressure reaches 10% of its natural amount. At the similar period and at 5°C , the scalp temperature reaches the minimum temperature 10.22°C from maximum 34.3°C level and blood flow pressure decreases to 13% of its natural amount. At 10°C , this temperature drops from 34.3°C to 17.86°C and blood flow pressure decreases to 21% of its natural amount.

Hair loss prevention can be achieved by cooling of the scalp without any further deep cooling of the brain. The recent studies have shown that there is a relation between head region temperature and the protective effect of scalp cooling in preventing hair loss.

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