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Effect of topical vitamin E on radiation-induced skin alteration in head and neck cancer patients

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Purpose : *This study was initiated to evaluate the effect of topical vitamin E on the reduction of ionizing radiation-induced skin reaction in head and neck cancer patients compared to placebo and the reliability of the application in clinical practice.*

Setting : *Division of Radiation Oncology, Department of Radiology, King Chulalongkorn Memorial Hospital.*

Research design : *Prospective randomized controlled trial.*

Patients and methods : *The study was from December 1, 2002 to July 31, 2003. There were 29 eligible patients. The applications of vitamin E cream and placebo were done in the same patients on each side of the face and neck areas that were irradiated, left / right. The applications of both creams were randomized and without naming the drugs on the tubes, colored tape were used to suggest the drug applications in order to prevent any bias. The drug applications have been done from the 1st week of the initiation of radiation: applied everyday, 2 times per day until the radiation dose reached 50 Gy.*

The skin was evaluated by the same person in the 1st week of radiation and then weekly during the irradiation period until the dose of radiation reached 50 Gy.

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Results : *The results show no significant statistical difference of the skin reaction to ionizing radiation of irradiated areas that were applied with topical vitamin E compared to placebo, evaluated under the same clinical criteria (CTC version 2.0) (p = 1.00).*

Conclusion : *From the data, it cannot be concluded whether or not the anti-free radical effect of vitamin E can reduce tissue injury from ionizing radiation. However, from the clinical criteria, it may be initially concluded that the topical vitamin E cream does not make any difference of skin alteration caused by ionizing radiation when compared to placebo; hence, there is no benefit of topical vitamin E applications in clinical practice.*

Keywords : *Radiation, Vitamin E*

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นพดล อัศวเมธา, ฐิตารีย์ สุวรรณาลัย, พรทิพย์ ภูวบัณฑิตสิน, จิตต์ธิดา ชูแสงเลิศวิจิตร. ผลของวิตามิน อี ชนิดทาภายนอกต่อการเปลี่ยนแปลงของผิวหนังที่เกิดจากการฉายรังสีในผู้ป่วยโรคมะเร็งบริเวณศีรษะและลำคอ (กรณีศึกษา). จุฬาลงกรณ์เวชสาร 2547 พ.ค;48 (5): 275 – 87

วัตถุประสงค์ : *การศึกษานี้ทำเพื่อเปรียบเทียบประสิทธิภาพของวิตามินอีชนิดทาภายนอกเทียบกับยาหลอก (placebo) ในการลดปฏิกิริยาของผิวหนังที่เกิดจากการฉายรังสี (ionizing radiation) ในกลุ่มผู้ป่วยโรคมะเร็งบริเวณศีรษะและลำคอ และประโยชน์ของการนำไปใช้ในทางคลินิก*

สถานที่ที่ทำการศึกษา : *หน่วยรังสีรักษา ภาควิชารังสีวิทยา โรงพยาบาลจุฬาลงกรณ์*

รูปแบบการวิจัย : *การศึกษาเชิงทดลอง*

วิธีการศึกษา : *ทำการศึกษาตั้งแต่ 1 ธันวาคม 2545 ถึง 31 กรกฎาคม 2546 มีผู้ป่วยที่ได้รับการประเมินทั้งหมด 29 คน ศึกษาโดยเปรียบเทียบประสิทธิภาพของวิตามินอีชนิดทาภายนอก กับ ยาที่ไม่มีวิตามินอี (ยาหลอก) ในผู้ป่วยคนเดียวกัน แบ่งการทายาบริเวณใบหน้าและลำคอ ส่วนที่ได้รับการฉายรังสี ออกเป็น 2 ข้าง ซ้าย – ขวา โดยทำการสุ่มเลือก ฉะนั้นแพทย์และผู้ป่วยจะไม่ทราบชนิดของยาที่ทา ให้ผู้ป่วยเริ่มทายาทั้งสองชนิดภายในสัปดาห์แรกของการฉายรังสี ทาทุกวัน 2 ครั้ง ต่อวัน จนกระทั่งฉายรังสีไปได้ 50 Gy การประเมินสภาพผิวหนังใช้เกณฑ์การประเมินทางคลินิก (CTC version 2.0) โดยผู้ประเมินคนเดียวกันทำการประเมินตั้งแต่สัปดาห์แรกของการฉายรังสีและทุกสัปดาห์ในระหว่างการฉายรังสีจนกระทั่งฉายรังสี ถึง 50 Gy (ประมาณ 5 สัปดาห์)*

ผลการศึกษา : *การเปลี่ยนแปลงของผิวหนัง ในบริเวณที่รักษาด้วยการฉายรังสี (ionizing radiation) ซึ่งทาด้วยวิตามินอีชนิดทาภายนอก และยาหลอกเมื่อประเมินโดยใช้เกณฑ์ทางคลินิก (CTC version 2.0) พบว่าไม่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ ($p = 1.00$)*

สรุป : *จากผลการศึกษาดังกล่าว ไม่สามารถสรุปได้ว่าโดยแท้จริงแล้วคุณสมบัติในการเป็นสารต้านอนุมูลอิสระ (antioxidant) ของวิตามินอี สามารถลดการบาดเจ็บของเนื้อเยื่อผิวหนังที่เกิดจากการฉายรังสี ชนิด ionizing radiation ได้หรือไม่ แต่จากการประเมินโดยใช้เกณฑ์ทางคลินิกอาจสรุปเบื้องต้นได้เพียงว่าวิตามินอีชนิดทาภายนอกไม่สามารถทำให้เกิดการเปลี่ยนแปลงของผิวหนังจาก ionizing radiation ได้แตกต่างจากยาหลอกและไม่สามารถนำมาใช้ให้เกิดประโยชน์กับผู้ป่วยในทางคลินิกได้*

คำสำคัญ : *การฉายรังสี, วิตามิน อี*

The collected data show that from the year 1998 to 2002, there was a rise in number of cancer patients treated at the Division of Radiation Oncology, Department of Radiology, King Chulalongkorn Memorial Hospital. It is estimated that 250 to 400 new cases of head and neck cancer were diagnosed in each year from 1988 to 2002 with an increasing annual trend.

Recently, there are many therapeutic options for cancer treatment such as surgery, radiation, chemotherapy or combined modalities of treatments. For head and neck cancer, we use the high radiation dose to control the disease in the curative condition. However, the higher the radiation dose is used, the more radiation side effects occur.

From basic radiation biology, we know that water is the most abundant substance in irradiated tissue. And water is the substance with which an ejected electron is most likely to interact. The interaction causes the formation of reactive oxygen species such as superoxide radical ($O2^-$), hydroxyl radical (HO^-), hydrogen peroxide (H_2O_2) etc. These molecules carry an unpaired orbital electron in the outer shell and they are therefore highly reactive. These free radicals cause tissue damage especially for rapid dividing tissue such as the skin more than slowly dividing tissue.[1]

When the skin is irradiated, the ionizing radiation injures and kills actively proliferating cells in the basal cell layer of the epidermis. These differentiated basal cells are no longer dividing and the remaining basal cells undergo cornification and shed at an increased rate. The non-proliferating basal cells are stimulated and their cell cycles are shortened. Subsequence peeling of the skin is defined as dry desquamation. If the basal layer has been repaired prior to desquamation, the skin surface remains dry and the patients may experience dry, flaking skin and pruritus in the treated area. If new cell proliferation does not occur and the basal cell does not recover, moist desquamation with exposed dermis and oozing of serum occurs.[1] This side effect increases the risk of infection, discomfort, and pain. Without proper management, the complication possibly necessitates the interruption of treatment plan to allow further healing. This can compromise the final outcome of cancer therapy.

Regarding the skin care during the radiation treatment, various topical agents were used to reduce skin reaction such as aloe vera, corn starch, steroid cream, etc. [2-10] But there was no definite conclusion concerning which agents should be used as the standard of care for reducing skin damage from ionizing radiation. This study is performed with the purpose to find topical agent that can solve the problem.

Vitamin E acts as a free radical scavengers that prevents tissue damage from excessive free radical molecules.[11] In the past, many studies tried to evaluate this effect of topical vitamin E and its efficacy in reducing skin hyperpigmentation from sunlight (ultraviolet radiation). The results suggested that topical vitamin E can reduce hyperpigmentation of the skin from ultraviolet radiation. [12-15] Up to the present, there is no study about the effect of this agent in related to ionizing radiation. However, from basic radiation biology, both the ultraviolet and ionizing radiations can cause free-radical formations, so this study hypothesized that topical vitamin E may reduce tissue injury from ionizing radiation as it acted in the

ultraviolet trials.

Concerning the safety dose of vitamin E, the Academy of Sciences reported that, the daily tolerable upper intake level for adult is 1,000 mg of vitamin E (1,500 IU of natural vitamin E or 1,000 IU of synthetic vitamin E). However, no information about the upper most concentration of topical vitamin E is suggested. [16] But the collected data from the topical vitamin E in the ultraviolet trials, illustrates that 5 % tocopheral acetate is effective and causes no serious side effects. [17,18]

The reported side effect of topical vitamin E preparation is contact dermatitis which may be directly from vitamin E or other ingredients in the cream base, for example moisturizer or preservative agents. [19]

Populations and methods:

From December 1, 2002 to July 31, 2003 we recruited 32 head and neck cancer patients who were treated at the Division of Radiation Oncology, Department of Radiology, King Chulalongkorn Memorial Hospital who met the inclusion criteria. These patients had been proved to have cancer by biopsy without previous surgical treatment on the head and neck regions. Also, the patients were planning to be treated with radiation, with or without mask. The radiation therapy was given alone or in combination with chemotherapy. The total radiation dose must be at least 50 Gy. Further, the patients had to have good performance status (EGOG 0, 1 or 2). There must be no skin rash or ulcer at the irradiated areas. The cancer had no involvement of the skin on the irradiated regions. The patients were mature and were able decide to enter the study by themselves. Their informed-consents were completely written. The exclusion criteria were that the patients who had cancer other than head and neck region. The patients who had inflammatory or connective tissue disorder of the skin or the ones with complicated medical disease were excluded. Patients with mental incompetence or psychological disorder were all excluded.

Radiation therapy equipment : The radiation machine used was Linear Accelerator with 6 &10 MV photon energy or Cobalt-60 machine. Electron beam therapy may be used for posterior aspect of the treatment field to limit the dose to the spinal cord. Selection of appropriate electron energy will depend on the thickness of the neck and the depth of the disease. Brachytherapy was not permitted in the study. Treatment distance minimum 80 cm. SSD/SAD was allowed. Immobilization devices such as plastic mask could be used. Simulations of the initial field and any planned boost fields were required. Appropriate immobilization devices should be used. Conventional fractionation was used. Radiation treatment was continued until the dose reached 50 Gy

Drug therapy : The drugs used in this study were produced in cream base form: vitamin E cream and placebo. Both of them contained almost the same ingredients which were moisturizers that protect skin hydration and reduce transepidermal water loss, except vitamin E that was not contained in the placebo. The production of the drug was controlled by a pharmacist of the Drug Production Division, Department of Pharmacy, King Chulalongkorn Memorial Hospital.

Treatment : The applications of vitamin E cream and

placebo were done on the same patients by divided their face and neck areas that were irradiated into 2 sides, left / right. The drug applications were done during the 1st week of the initiation of radiation, they were applied every day, 2 times per day until the radiation dose reached 50 Gy. The application of both creams were randomized without naming the drugs on the tubes. Colored tapes were used to suggest the drug applications for preventing bias. Regarding the out-patients, the drugs were applied by the patients themselves. For the admitted cases, the nurses at the radiation oncology ward applied the drugs for them. The patients and the nurses were told to wash their hands after finished one drug application to prevent the 2 drugs from contaminating. Both groups of the patients were randomized with the same blinding technique.

The skin evaluation was done by the same person from the 1st week of treatment and then weekly until the 5th week of irradiation (total dose 50 Gy). The skin was evaluated using the common toxicity criteria version 2.0, the standard criteria for evaluation of the side effects caused by radiation treatment.

The final outcome was analyzed: the degree of skin change between the irradiated skin that was applied with vitamin E cream versus the area applied by placebo. The comparison was done at each week to demonstrate the difference of each drug efficacy in the reduction of radiation induced skin change. The comparison of the difference of skin change on each side between the 1st week to the 5th week was also done. Because, if the degree of difference was increased continuously from the 1st week to the 5th week, it could demonstrate the obvious difference of each drug efficacy in the reduction of radiation induced skin change.

The treatment was stopped when the patients wanted to withdraw or stop radiation due to any cause such as severe medical or surgical demands. If the patients had an allergy to the topical drugs (vitamin E cream or placebo) they were not allowed to continue using the drugs and were subsequently given proper treatment.

Common toxicity criteria version 2.0

Grade 0	Normal skin
Grade 1	Faint erythema or dry desquamation
Grade 2	Moderate to brisk erythema or patchy moist desquamation, mostly confined to skin folds and skin crease, moderate edema
Grade 3	Confluent moist desquamation, 1.5 cm. diameter; not confined to skin folds, pitting edema
Grade 4	Skin necrosis or ulceration of full thickness dermis; may include bleeding not induced by minor trauma

Results

1. Characteristics of the patients: 32 patients were recruited ; three withdrew from the study (Two subjects left the trial out of their own preference, they refused to continue radiation and sought for other modality of treatment, The other subject ,however, had drug allergy that appeared on both areas of the two drug applications, probably due to other ingredients of the drug, not the vitamin E) (Table 1 and Figure 1). The remaining 29 patients received complete treatment; 8 were admitted and 11 were out patients. (Table 2)

Table 1. The number of head and neck cancer patients recruited in the study.

Treatment	Number of the H&N cancer patients
Complete treatment	29
Withdraw	3
Total	32

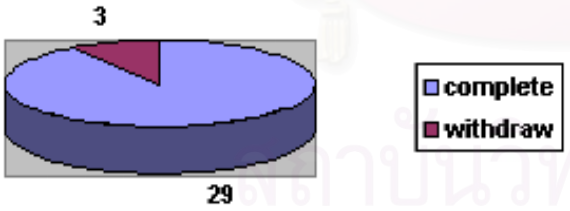

Figure 1. The number of head and neck cancer patients recruited in the study.

Table 2. The number of head and neck cancer patients who received complete treatment.

Patients	Number of patients
Admitted cases	18
OPD cases	11

2. Characteristics of the head and neck cancer patients who received complete treatment:

21 male and 8 female patients were recruited; their age ranged from 20 to 80 years. The patients had good performance status. Most patients were in stage 3 and 4 of the disease. Their most common histology was squamous cell carcinoma.

Table 3. ECOG performance of the patients.

ECOG	Number of patients
0	0
1	7
2	22
3	0
4	0
Total	29

Table 4. Stage of the head and neck cancer patients who received complete treatment.

Stage	Number of patients	Percentage (%)
1	3	10.35
2	3	10.35
3	11	37.29
4	12	41.38
Total	29	100.00

Table 5. Histology of cancer.

Histology	Number of patients	Percentage (%)
SCCA		
: well diff.	6	20.96
: moderate diff	5	17.24
: poorly diff.	2	6.90
: not specific	4	13.79
Undifferentiated	10	34.48
Lymphoma	1	3.45
Sarcoma	1	3.45
Total	29	100.00

Clinical evaluation of radiation dermatitis and statistical analysis

Comparison in each week : there was no difference of skin alterations between the irradiated skin that applied with vitamin E cream *versus* those applied with placebo (Table 6). The data were analyzed by Non-parametric test (Wilcoxon Signed Rank Test) p = 1.00

Table 6. Grading of skin alteration from ionizing radiation in each week.

Patients' number	Grading of RT dermatitis									
	week 1		Week 2		Week 3		Week 4		Week 5	
	L	R	L	R	L	R	L	R	L	R
1	0	0	0	0	1	1	1	1	2	2
2	0	0	0	0	1	1	1	1	2	2
3	0	0	0	0	1	1	1	1	2	2
4	0	0	0	0	0	0	1	1	2	2
5	0	0	1	1	1	1	2	2	2	2
6	0	0	0	0	1	1	1	1	2	2
7	0	0	0	0	1	1	1	1	2	2
8	0	0	0	0	0	0	1	1	2	2
9	0	0	0	0	1	1	2	2	2	2
10	0	0	0	0	1	1	1	1	2	2
11	0	0	0	0	1	1	1	1	2	2
12	0	0	0	0	1	1	2	2	2	2
13	0	0	0	0	1	1	2	2	2	2
14	0	0	0	0	1	1	1	1	2	2
15	0	0	0	0	1	1	1	1	2	2
16	0	0	0	0	1	1	1	1	2	2
17	0	0	0	0	1	1	2	2	3	3
18	0	0	0	0	1	1	1	1	2	2
19	0	0	1	1	1	1	2	2	2	2
20	0	0	1	1	1	1	2	2	2	2
21	0	0	0	0	1	1	1	1	2	2
22	0	0	1	1	1	1	1	1	2	2
23	0	0	0	0	1	1	1	1	2	2
24	0	0	0	0	1	1	1	1	2	2
25	0	0	0	0	1	1	1	1	2	2
26	0	0	0	0	1	1	1	1	2	2
27	0	0	0	0	1	1	1	1	2	2
28	0	0	1	1	1	1	1	1	2	2
29	0	0	0	0	1	1	2	2	3	3

Comparison between 1st week to 5th week : there was no difference of skin alterations between the irradiated skin that applied with vitamin E cream *versus* those applied with placebo (Table 7). The data were analyzed by Non-parametric test (Friedman Test) p = 1.00

Table 7. The difference of grading of skin alteration from ionizing radiation between 1st to 5th weeks.

H & N cancer Patient	Difference of grading of radiation dermatitis				
	week 1	week 2	week 3	week 4	week 5
1	0	0	0	0	0
2	0	0	0	0	0
3	0	0	0	0	0
4	0	0	0	0	0
5	0	0	0	0	0
6	0	0	0	0	0
7	0	0	0	0	0
8	0	0	0	0	0
9	0	0	0	0	0
10	0	0	0	0	0
11	0	0	0	0	0
12	0	0	0	0	0
13	0	0	0	0	0
14	0	0	0	0	0
15	0	0	0	0	0
16	0	0	0	0	0
17	0	0	0	0	0
18	0	0	0	0	0
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29	0	0	0	0	0

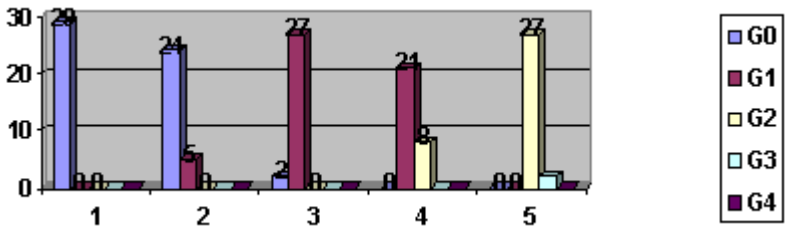

Figure 2. Grading of skin alteration from ionizing radiation in each week.

Complication of drug applications : There was no serious complication from the applications of vitamin E cream and placebo in the study. There was only 1 patient who had mild skin rash which improved when the drug application was stopped.

Discussion

The severity of skin alteration from ionizing radiation depends on many factors such as total dose of ionizing radiation, condition of skin of individual patients, the surgical treatment that disrupts the blood supply of the irradiated skin or combination chemotherapy etc. If the skin damage is severe, it increases the risk of infection, discomfort, and pain to the patient and possibly necessitates the interruption of treatment plan to allow further healing. This can compromise the final outcome of cancer therapy. Therefore, the most effective treatment with the least complication is the mainstay of treatment. So this study was launched to find out the effective topical agent that can reduce the severity of skin damage from ionizing radiation, the common complication of radiation treatment, especially in the head and neck cancer that requires high radiation dose to control the disease for curative aim.

The comparison of the irradiated areas in the same patient lets the homogeneity of the studied regions and decreases factors that may affect the skin reaction to radiation. So, any difference that occurs should be the true difference and reliable.

The study used the clinical criteria (CTC version 2.0) for evaluation of the severity of skin change. These clinical criteria are the standard criteria, accepted among the radiation oncologist to evaluate the skin complication from ionizing radiation. The criteria are graded into 5 levels, 0 to 4, depending on the findings. The evaluation was made by looking and touching. We, however, did not use a colorimeter, the equipment that is used by dermatologists to evaluate skin color. Technically, a colorimeter reports the level of skin color in number. So the difference can be sensitively demonstrated and may detect the difference that cannot be demonstrated by the use of clinical criteria. The reason that we did not use the equipment is, if the difference was detected by the colorimeter it did not make any clinical difference, since it has no clinical importance and made no difference for treatment. Therefore, in clinical practice, a radiation oncologist uses clinical criteria which are easy, convenient and provide accurate information for evaluating the skin complication that is caused from radiation treatment.

The results of this study show that the skin reaction, evaluated by clinical criteria (CTC version

2.0) comparing the areas applied with vitamin E cream *vs*. placebo, had no statistical significant difference by Non parametric test (Wilcoxon Sign Rank Test and Friedman Test), p = 1.00.

From the data, it cannot be concluded whether or not the anti-free radical effect of vitamin E can reduce tissue injury from ionizing radiation. But from the clinical criteria, it may be initially concluded that there is no evidence to support the clinical benefit of topical vitamin E applications in the radiation induced skin reaction.

Limitation of the study : This study excluded patients who were previously treated by surgical treatment to prepare the most homogeneity of the study area. Because the blood supply of surgical regions would be disrupted, causing the difference of the skin at this area from the normal skin that might cause the false positive result. So, the number of recruited patients was small when compared with the incidence of the head and neck cancer patients. This small number of cases might have prevented the difference to be demonstrated.

The one factor that affected the reliability of this study is the choice of drug application. We tried to control this factor in the admitted cases that the nurse would apply the drug for the patients and the close observation could be done. But for the OPD cases, the reliability mainly depended on the compliance of the patients and we tried to control the reliability by close follow-up.

The follow-ups were made until the radiation dose reached 50 Gy. Higher radiation dose might demonstrate the clearer differences, but at the radiation level higher than 50 Gy different radiation technique was used because of the difference in disease extension. This would make the difference in the study area. Therefore, this study was limited the skin evaluation at the radiation dose of 50 Gy.

Suggestion for further work : Although this study cannot demonstrate the difference of skin alteration from ionizing radiation between the areas applied by vitamin E cream versus placebo, we observed that the degree of skin change was not severe. Most of the skin changes were grade 1 and 2. Few cases had grade 3 skin complication. No serious complication was demonstrated. From the data, we hypothesized that moisturizing agent which was the ingredients of cream base of both drugs might decrease the severity of skin damage, probably by reducing the transepidermal water loss or from other mechanism. Therefore, the study compared the application of this moisturizer versus no topical treatment on the irradiated skin could prove this hypothesis. If the hypothesis is proved true, we can find the effective, cheap and easily produced topical agents that can be used in clinical practices.

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