Efficacy of Topical Hyaluronic acid during adjuvant Breast Cancer Radiotherapy for radiation dermatitis prophylaxis

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Abstract: Purpose: To determine the efficacy of an emulsion containing hyaluronic acid to reduce the development of grade II or higher radiation dermatitis after adjuvant breast irradiation. **Patients and methods:** Two hundred and nine female patients with breast cancer who conducted to receive adjuvant breast irradiation distributed into two groups, Group I, the control group (n=80 patients) and Group II, the treated group (n=129 patients) with application of hyaluronic acid-based gel topical agent (Ialugen ® plus) 2weeks before treatment course and then all- through radiation therapy period twice a day. All patients were followed during radiotherapy course and then 3 months later for the primary end point radio-dermatitis GII or higher according to (RTOG/EORTC Scale) and for the secondary end points pain, quality of life &treatment interruption. Univariate and multivariate analysis (ordered logistic regression) were considered. **Results:** Two hundred and nine female breast cancer patients aging 27-71years, distributed into two groups, Group I (control group) n=80patients (mean age= 48.7 SD= 10.845) and Group II (treated group) n=129 patients (mean age=50.95, SD= 10.369). Patients' characteristics were matched for both groups except for Body mass index (BMI), Quality of life (QOL) and treatment Interruption with significant differences in expense of control group. For radio-dermatitis, over all incidence of skin toxicity was 61,7%, with more than 2\3 reduction in radio- dermatitis with treated group, radio -dermatitis grade II and higher was 41.3%, n=33 patients in control arm versus 10.1%,n=13 patients in treated group, p=<0.001. No patients presented with severe skin reaction (GIII&IV) in treated group. More than 10 times reduction in pain scores in treated versus control groups. Our data consolidated with spearman rho correlation coefficient test for radiation dermatitis and pain scores during radiotherapy course and 3 months later. Multivariate analysis as regard skin radiation toxicity at week 3 of radiation dermatitis showed that the only effective risk factors were interrupted treatment, p =0.00, OR=0.02, 95%CI (0.002-0.176), QOL, p =0.02,OR=11.82,95%CI (1.411-97.027), radiation dose, p =0.00, OR=0.78,95%CI (0.306-1.995) and boost dose, p =0.00,OR=0.27,95%CI (0.134-0.541). **Conclusion:** Application of hyaluronic acid-based gel (Ialugen ® plus) during adjuvant breast cancer radiotherapy has favorable impact on radio-dermatitis GII or higher, skin welfare, tolerability and treatment effectiveness.

[Nehal Mohamed Elmashad, Fatma Zakaria Hussen and Rania Ahmed Eltatawy. **Efficacy of Topical Hyaluronic acid during adjuvant Breast Cancer Radiotherapy for radiation dermatitis prophylaxis.** *Life Sci J* 2015;12(6):42-53]. (ISSN:1097-8135). http://www.lifesciencesite.com. 5

Key words: hyaluronic acid, Breast cancer, adjuvant radiotherapy, radio-dermatitis, quality of life.

1. Introduction

Radiation dermatitis is one of the most common side effects of radiotherapy for cancer, affecting approximately 95 percent of all patients receiving radiotherapy [(1-3)]. Acute injury, which occurs within hours to weeks after radiation exposure, results from immediate structural tissue damage, generation of short-lived free radicals, irreversible double-stranded breaks in nuclear and mitochondrial DNA, and initiation of an inflammatory response in the epidermis and dermis [(4-6)].

The skin is susceptible to radiation damage, because it is a continuously renewing organ, which contains rapidly proliferating and maturing cells, with basal keratinocytes, hair follicle stem cells and melanocytes being very radiosensitive [(6)].The most sensitive skin areas are the anterior of the neck, extremities, chest, abdomen and face, along with the hair follicles on the scalp and breast tissue [(4)]. Radiation dermatitis has a negative impact on the quality of a patient's life [(7-9)] as acute skin reaction can lead to pain/discomfort, itching, poor aesthetic appearance [(10, 11)] and may even require changes to the person's radiation schedule (if severe) [(12)].In the long term, skin wounds can reappear due to abnormal pathological changes, such as excessive fibrosis that can occur during the initial phases of the healing process [(13)].

Therefore, managing skin reactions is an important priority in caring for those who undergo radiation treatment [(14)]. Therefore, a number of inconsistencies exist across radiation treatment centers globally with regard to the practice and recommendations given by health professionals to both prevent and manage this often painful side-effect of radiation treatment [(15- 17)].At present, topical

products with active agents are commonly used to palliate the effects on the skin, alleviate patient discomfort and avoid treatment interruption [18].

Although researchers have assessed the effectiveness of various topical and oral agents for the prevention and treatment of radio-dermatitis for several years, no consensus has been reached on an ideal strategy. The topical products studied include creams or lotions containing corticoids, sucralfate, trolamine, calendula, aloe vera, camomile or hyaluronic acid [19]. The results for these agents are conflicting; not all of them are reported to reduce skin toxicity, although they are still used in clinical practice.

The aim of this study is to assess the effectiveness of an emulsion containing hyaluronic acid (Ialugen ® plus) for the prevention of acute radiation-induced dermatitis of grade II or higher during postoperative radiotherapy for breast cancer, compared with best supportive care. The secondary objectives were to assess pain, quality of life, treatment interruption as a result of skin reactions and patient satisfaction.

2. Material and Methods

2.1. Patients:

This prospective study include 209 female patients attended at Tanta University Clinical Oncology Department From December 2012 to June 2014 with T1-3, N0-2, M0 histologically confirmed carcinoma of the breast who underwent either breast conservation surgery with negative surgical margins or modified radical mastectomy were eligible. Upon confirmation of patients' eligibility, a medical history was obtained and demographic data collected, including breast size and body mass index. Breast size was defined as small (bra sizes 32A or 32B, 34A or 34B, and 36A), medium (bra sizes 32C, 34C, 36B or 36C, and 38A, 38B, or 38C), or large (larger bra sizes) [20]. For inclusion, the women in our study aged from 27 to 71 years of age with a non-metastatic breast adenocarcinoma treated by lumpectomy or modified radical mastectomy (MRM) with adjuvant postoperative chemotherapy. No concomitant chemotherapy was allowed. Women with bilateral or in situ breast cancer, patients who were allergic to the agents, pregnant women, use of a tissue-equivalent bolus, the presence of rashes or unhealed wounds in the radiation field, stage T4 breast cancer, planned receipt of concurrent chemotherapy with radiation and systemic lupus erythematosus or scleroderma were excluded. Written informed consent was mandatory for each patient.

2.1.1. Ethics approval

Ethical and record linkage approvals were obtained from the Human Research Ethics Committee at the University of Tanta. Each patient will have a code number and all data will be for scientific use only. The protocol was approved by an ethical committee code 1020/02/2012.

2.1.2. Methods:

Our study population were divided into two groups, control group (80 patients) and treated group (129 patients) with application of hyaluronic acid-based topical agent (Ialugen® plus) 2 weeks before treatment course and then all through radiation therapy period twice a day until completion of their radiotherapy courses. Standard irradiation fractionation (2 Gy per session, five sessions per week) was used. Each woman underwent a computed tomography scan if necessary wedge filters were used to optimize the dosimetry and to conform to the recommendations of the International Commission on Radiation Units and Measurements. Women who had undergone lumpectomy or MRM received 50 Gy or more from two tangential fields to the whole breast on a 6-MV Linear accelerator. A 10-Gy boost was delivered with electrons to the tumor bed. If relevant, internal mammary and supraclavicular nodes were irradiated with mixed beams (6-MV x-rays and electrons).

The allocated agents were delivered directly to the patients. No other prophylactic creams, lotions, or gels were allowed.

2.2. Study Outcomes

Each patient attended to dermatologic consultation with once a week, during which acute dermal toxicity was evaluated according to the Radiation Therapy Oncology Group (RTOG/EORTC Scale) scale [21] Patients rated pain, itching, reddening, desquamation and impact on skin welfare (quality of life) using visual analogue scales (VAS, 0 to 10) at each irradiated volume: breast or chest wall and peripheral lymphatics, if relevant, submammary fold, armpit, internal mammary nodes, and supraclavicular nodes [22]. Pain was assessed each week on a 10-cm visual analog scale (VAS). The relationship between numerical ratings of pain severity and interference with daily functions for cancer patients, and the reliability of VAS to assess acute toxicity, has been demonstrated previously [22-24].The occurrence, duration, and reasons for interruption of radiotherapy or of allocated cream application were registered, as well allergic reactions until the completion of radiotherapy. At the end of the study, the patients were asked to complete a questionnaire to assess their satisfaction with respect to ease of application, pain, and dermatitis relief for 3 months after the end of radiotherapy course [9].

2.3. Statistical analysis

Statistical presentation and analysis of the present study was conducted, using Number and percentage for qualitative and tested by chi-square test

by SPSS for Windows version 18.0 software package (SPSS Inc, Chicago, IL) and *P*-value < 0.05 was considered as statistically significant.

The qualitative measures were compared by the $\chi 2$ test or Fisher's exact test, as appropriate. For quantitative measures, the Student's t test or Wilcoxon-Mann-Whitney tests were used. All of the P values are two sided. Spearman rank-order correlations were used in comparative analysis of acute skin reaction to breast radiotherapy course.

Univariate analysis (ordered logistic regression) was performed to identify risk related factors associated with increased skin toxicity using the $\chi 2$ test. An association was considered significant at the 5% level of significance. A multivariate analysis (ordered logistic regression) for skin toxicity, which tested the type of ointment applied fitted on potential prognostic factors, also was performed. The first logistic regression model was applied to all patients.

3. Results

3.1. Sample size and patients characteristics':

Two hundred and nine breast cancer patients demographic characters in both control and treated with hyalouronic acid cream groups were ***balanced for*** age, breast size and site, total radiation dose, dose / fraction, boost dose, tumor grade, pathological subtypes and menopausal status "Table 1".

Fifty two (24.9%) patients presented with overweight in treated group versus 12(5.7%) in control group, 58(27.8%) patients had obesity class 1 in treated group versus 42(20.1%) in control group. Body Mass Index (BMI) showed statistically significant association between two groups higher in treated group by Chi-square X2 19.652, *P* value (<0.001) and by Mann-Whitney test was statistically significantly U = 3426.0, *P* value (<0.0001).

Quality of life (QOL) was statistically significant positive with treated group patients by Chi-square X^2 89.19, *P* value (<0.01) and by Mann-Whitney test U = 1482.5, *P* value (<0.0001).

As regards ***interruption of treatment***, 165/209 (78.9%) patients continue whole radiotherapy period without gap.115/129 (89.2%) patients with prophylaxis hyalouronic acid cream versus 50/80 (62.5%) patients in control group achieved continuous radiotherapy treatment without interruption with statistically significant difference by Chi-square X^2 21.09, *P* value (<0.01) and by Mann-Whitney test U = 3785.0, *P* value (<0.0001).

3.2. Global efficacy evaluation:

The primary end point of this study was to determine if a hyaluronic acid-based topical agent was effective than best supportive care in reducing the incidence of radiation dermatitis Grade II or higher. As regard radiation, dermatitis scores from week 1 till 3 months follow up in both groups, by the end of 1st week, in terms of the grade 0 of radiation dermatitis experienced, 115/129 (55%) patients in treated group versus 35/80 (16.7%) in the control group and only 13(6.2%) patients suffered from Grade 1 dermatitis versus 44(21.1%) patients in the control group. Dermatitis score grade II at week 2 was 28/80 (35%) versus 7/129 (5.4%) in treated group with Pearson chi-square X^2 =50.832 (*P.* value <0.001). For all 209 patients in the both groups during whole treatment and follow up period, *P values were* <0.001; indicating that irradiated skin treated with hyaluronic acid had less radiation dermatitis grade than control one **(Table 2).**

3.2.1. The second end points were pain, quality of life &treatment interruption.

Pain score in all patients were well tolerated but with statistically significantly better profile in treated group patients during whole period of radiation and 3 months later *P values were* <0.001 as shown in ***Table 3***.

3.3. Comparative analysis of acute skin reaction to breast radiotherapy:

A series of Spearman rank-order correlations were conducted in order to determine if there were any relationships between radiation dermatitis score from week 1 till 3 months follow up in both groups with different risk factors including radiation dose, QOL, Interrupted treatment, type of fractionation and boost dose.

During weeks 1-3, no difference in scores were seen in both groups. However, during week 4, the patients in control group was scored statistically significantly worse "***Quality of life***" (*P value*= (<0.0001). As regards ***Body Mass Index***, Patients with Obesity class 1 "58(27.8%) " or overweight 52(24.9%) tolerate well breast radiation therapy especially from the fourth week till three months follow up (*P value* = <0.001) as shown in table 4. A two-tailed test of significance indicated that there was a significant positive relationship between the BMI and grades of pain ρ = 0.465 (*P* value≤0.001) for control and (ρ=0.176, *P* ≤0.05) for treated group as shown in ***table 5.***

3.3.1. Univariate analysis for radiation dermatitis:

The *univariate analysis* with ordered Logistic regression performed at 3rd week of radiation therapy course to identify risk factors that may be associated with increased skin toxicity presented in table 6. No associations were found between the severity of the radiation dermatitis and age, menopausal status, Pathological subtypes, breast size, site, or grade ; on the other hand, patients with positive lymph nodes, interrupted treatment, worse quality of life, Overweight, obesity class 1, hypofractioation

radiotherapy, boost dose suffered from increase skin toxicity.

Table (1): Patients demographics and base line characteristics

Patients characteristics		Study arms						Chi-square		Mann-Whitney
		Control N= 80		Treated N= 129		Total		X^2	*P*	U and P value
		No	%	No.	%	No.	%			
Age	≤45	30	14.4	47	22.5	77	36.8	0.024	0.877	---------
	>45	50	23.9	82	39.2	132	63.2			
Breast Size	Small	4	1.9	18	8.6	22	10.5	4.369	0.113	----------
	Medium	52	24.9	79	37.8	131	62.7			
	Large	24	11.5	32	15.3	56	26.8			
Breast Site	Right	38	18.2	64	30.6	102	48.8	0.088	0778	----------
	Left	42	20.1	65	31.1	107	51.2			
Total radiation dose	50gy	59	28.2	86	41.1	145	69.4	1.166	0.354	----------
	>50gy	21	10.0	43	20.6	64	30.6			
Dose fraction	Conventional	50	23.9	79	37.8	129	61.7	0.033	0884	----------
	Hypo fractionation	30	14.4	50	23.9	80	36.3			
Boos t/dose	No	59	28.2	86	41.1	145	69.4	1.166	0.354	---------
	Yes	21	10.0	43	20.6	64	30.6			
BMI	Normal weight	0	0.0	1	0.5	1	0.5	19.652	**0.001**	**3426.0 (<0.0001)**
	Over weight	12	5.7	52	24.9	64	30.6			
	Obesity class 1	42	20.1	58	27.8	100	47.8			
	Obesity class 2	21	10.0	15	7.2	36	17.2			
	Morbid obesity	5	2.4	3	1.4	8	3.8			
QOL	Very dissatisfied	6	2.9	0	0.0	6	2.9	89.19	**<0.001**	**1482.5 (<0.0001)**
	Moderate dissatisfied	18	8.6	1	0.5	19	9.1			
	Slightly dissatisfied	25	12.0	7	3.3	32	15.3			
	Slightly satisfied	29	13.9	64	30.6	93	44.5			
	Moderate satisfied	2	1.0	57	27.3	59	28.2			
Pathological subtypes	Ductal	77	36.8	122	58.4	199	95.2	0.305	0.745	--------
	Lobular	3	1.4	7	3.3	10	4.8			
Menopausal status	Pre	38	18.2	51	24.4	89	42.6	1.281	0.314	----------
	Post	42	20.1	78	37.3	120	57.4			
T	T1	29	13.9	6	2.9	35	16.7	39.8	**<0.01**	**3879.0 (<0.0001)**
	T2	42	20.1	115	55.0	157	75.1			
	T3	9	4.3	8	3.8	17	8.1			
Grade	II	62	29.7	88	42.1	150	71.8	2.1	0.158	---------
	III	18	8.6	41	19.6	59	28.2			
Interrupted treatment	No	50	23.9	115	55.0	165	78.9	21.09	**<0.01**	**3785.0 (<0.0001)**
	Yes	30	14.4	14	6.7	44	21.0			
Chemotherapy protocols	FEC	62	29.7	88	42.1	150	71.8	2.1	0.158	
	FEC/T	18	8.6	41	19.6	59	28.2			

BMI= body mass index, T=tumor status, QOL= quality of life

Table (2): Distribution of skin reaction (Dermatitis scores) over the monitoring period

Groups	Grade	Week 1	Week 2	Week3	Week4	Week 5	1st Month	2nd Month	3rd Month
Control Group	**0**	35	13	4	2	5	36	59	72
	I	44	39	43	52	63	39	20	8
	II	1	28	17	18	9	4	1	0
	III	0	0	16	7	3	1	0	0
	IV	0	0	0	1	0	0	0	0
Treated Group	**0**	115	80	18	6	4	120	129	129
	I	13	42	98	119	125	9	0	0
	II	1	7	13	4	0	0	0	0
	III	0	0	0	0	0	0	0	0
	IV	0	0	0	0	0	0	0	0
Pearson chi-square X^2		50.832	52.371	37.468	35.631	22.295	85.946	37.645	13.413
***P*-Values**		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Table (3): Distribution of (pain scores) over the monitoring period

Treatment groups	Score	Week 1	Week 2	Week3	Week4	Week 5	1st Month	2nd Month	3rd Month
Control group	0	10	6	19	0	0	13	21	58
	1	31	21	34	22	31	59	59	22
	2	35	26	13	35	42	8	0	0
	3	4	19	14	18	7	0	0	0
	4	0	8	0	5	0	0	0	0
Treated group	0	95	23	66	1	1	110	120	128
	1	31	94	55	110	112	19	9	1
	2	3	5	8	17	16	0	0	0
	3	0	7	0	0	0	0	0	0
	4	0	0	0	1	0	0	0	0
Pearson chi-square X^2		93.403	76.802	36.661	79.443	57.192	98.960	100.300	36.009
P-Values		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001

Spearman's rho Correlation Coefficient

Factor	Radiation Dose		Quality of life		Body Mass Index		Interrupted treatment		Fractionation		Boost Dose	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated
Dermatitis Week 1	0..543	0.383	-0.478	0-.455	0.435	0.321	0.634	0.752	0.535	0.332	0.543	0.383
	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)
Dermatitis Week 2	0.619	0.313	0-.557	0-.477	0.405	0.228	0.799	0.625	0.649	0.275	0.619	0.313
	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(0.009)	(<0.0001)	(<0.0001)	(<0.0001)	(0.002)	(<0.0001)	(<0.0001)
Dermatitis Week 3	0.664	0.258	0-.608	0-.477	0.378	0.203	0.811	0.589	0.661	0.356	0.664	0.258
	(<0.0001)	(0.003)	(<0.0001)	(<0.0001)	(0.001)	(0.021)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(<0.0001)	(0.003)
Dermatitis Week 4	0.437	0.158	0-.466	0-.101	0.352	0.091	0.653	0.288	0.513	0.102	0.437	0.158
	(<0.0001)	0.074	(<0.0001)	(0.255)	(0.001)	(0.304)	(<0.0001)	(0.001)	(<0.0001)	(0.252)	(<0.0001)	(0.074)
Dermatitis Week 5	0.121	-0.063	0-.303	0.035	0.105	-0.001	0.290	0.062	0.197	0.051	0.121	0-.063
	(0.284)	(0.476)	(0.006)	(0.693)	(0.356)	(0.988)	(0.009)	(0.482)	(0.079)	(0.570)	(0.284)	(0.476)
Dermatitis First Month	0.172	*	0-.430	-0.195	0.179	0.030	0.373	0.253	0.252	0.111	0.172	0.125
	(0.127)		(<0.0001)	(0.027)	(0.113)	(0.738)	(0.001)	(0.004)	(0.024)	(0.021)	(0.127)	(0.158)
Dermatitis Second Month	0.253	*	0-.367	*	0.230	*	0.368	*	0.259	*	0.253	*
	(0.023)		(0.001)		(0.040)		(0.001)		.020		(0.023)	
Dermatitis Third Month	-0.009	*	0-.222	*	0.059	*	0.086	*	0.000	*	0-.009	*
	(0.934)		(.047)		(0.604)		(0.448)		1.000		(0.934)	

* Cannot be computed because at least one of the variables is constant.

Table 4: Results of Side-by-Side Radiation Dermatitis Comparisons in weekly, then monthly Evaluations

Spearman's rho Correlation Coefficient

Factor	Radiation Dose		Quality of life		Body Mass Index		Interrupted treatment		Fractionation		Boost Dose	
	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated
Pain Week 1	0.419	0.179	-0.032	-0.300	0.465	0.176	0.566	0.497	0.381	0.292	0.419	0.179
	(0.000)	(0.042)	(0.781)	(0.001)	(0.000)	(0.046)	(0.000)	(0.000)	(0.000)	(0.001)	(0.000)	(0.042)
Pain Week 2	0.630	0.264	-0.328	-0.196	0.522	0.217	0.828	0.520	0.611	0.275	0.630	0.264
	(0.000)	(0.002)	(0.003)	(0.026)	(0.000)	(0.013)	(0.000)	(0.000)	(0.000)	(0.002)	(0.000)	(0.002)
Pain Week 3	0.597	0.204	0-.358	-0.309	0.567	0.154	0.829	0.496	0.624	0.208	0.597	0.204
	(0.000)	(0.020)	(0.001)	(0.000)	(0.000)	(0.082)	(0.000)	(0.000)	(0.000)	(0.018)	(0.000)	(0.020)
Pain Week 4	0.549	0.337	-0.250	-0.324	0.639	0.285	0.741	0.641	0.548	0.329	0.549	0.337
	(0.000)	(0.000)	(0.025)	(0.000)	(0.000)	(0.001)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.000)
Pain Week 5	0.315	0.191	-0.106	-0.254	0.396	0.264	0.437	0.465	0.300	0.193	0.315	0.191
	(0.004)	(0.030)	(0.351)	(0.004)	(0.000)	(0.003)	(0.000)	(0.000)	(0.007)	(0.028)	(0.004)	(0.030)
Pain First Month	0.244	0.356	0.076	-0.227	0.266	0.288	0.352	0.629	0.303	0.298	0.244	0.356
	(0.029)	(0.000)	(0.503)	(0.010)	(0.017)	(0.001)	(0.001)	(0.000)	(0.006)	(0.001)	(0.029)	(0.000)
Pain Second Month	0.291	0.258	0.025	-0.170	0.241	0.221	0.403	0.491	0.345	0.157	0.291	0.258
	(0.009)	(0.003)	(0.825)	(0.054)	(0.031)	(0.012)	(0.000)	(0.000)	(0.002)	(0.076)	(0.009)	(0.003)
Pain Third Month	0.205	-0.063	-0.137	0.096	0.260	0.045	0.390	-0.031	0.332	-0.070	0.205	-0.063
	(0.068)	(0.482)	(0.227)	(0.279)	(0.020)	(0.610)	(0.000)	(0.729)	(0.003)	(0.428)	(0.068)	(0.482)

Table 5: Results of Side-by-Side Radiation Pain Comparisons in weekly, then monthly Evaluations

Table (6): Results of the proportional odds model according to dermatitis at week 3 (ordered Logistic regression) in both groups

Covariate	Univariate analysis			
	Logistic coefficient	Standard error	P_{value}	Odds Ratio
Age **<=45** **>45**	-0.271	0.302	0.369	0.76
Menopausal status **Pre** **Post**	-0.123 ----	0.293 ---	0.675	0.88
Breast Site **Right** **Left**	-0.06	0.289	0.83	0.94
Brest size **Small** **Medium** **Large**	-0.114 -0.177 ----	0.524 0.332	0.82 0.59	0.89 0.84
Pathology **Ductal** **Lobular**	-1.95 ----	0.667	0.771	0.142
T **T1** **T2** **T3**	0.217 -0.282 -----	0.606 0.529	0.72 0.59	1.24 0.76
Grade **II** **III**	0.023	0.321	0.94	1.02
Involved Node **Node negative** **Node positive**	-4.04 -----	0.486	**0.00**	56.826
Interrupted treatment **No** **Yes**	-5.27 ---	0.611	**0.00**	0.005
Quality of life **Very Dissatisfied** **Moderate Dissatisfied** **Slightly Dissatisfied** **Slightly Satisfied** **Moderate Satisfied**	5.221 4.447 3.096 0.689 ---	0.946 0.643 0.548 0.413	**0.00** **0.00** **0.00** 0.09	0.005 0.012 0.045 0.502
Body Mass Index **Normal Weight** **Over weight** **Obesity(class 1)** **Obesity(class 2)** **Morbid Obesity**	-2.354 -2.498 -2.207 -0.308 -----	2.35 0.737 0.704 0.720 -------	0.316 0.001 0.002 0.669 -------	0.094 0.082 0.11 1.361 ------
Radiation Dose **Dose 50 Gy** **Dose > 50 Gy**	-1.781 -----	0.336	**0.00**	0.168
Fractionation **Conventional 2Gy/F** **HypoFractionation 265cGy/F**	-2.272 ---	0.369	**0.00**	0.103
Boost Dose **No** **Yes**	-1.781 ---	0.336	**0.00**	0.168

3.3.2. Multivariate analysis for radiation dermatitis:

Multivariate analysis for significant risk factors in univariate analysis with ordered Logistic regression performed at 3rd week showed in ***table 7*** denote that only *interrupted treatment* with *P* value <0.001; Odds Ratio 0.02; CI (0.002 - 0.176), *worse quality of life* with *P* value <0.02; Odds Ratio 11.82; CI (1.411 – 97.027) and *boost dose P* <0.001; Odds Ratio 0.27; CI

(0.134 - 0.541) were associated with increased skin toxicity.

The proportional odds ratios with the 95% confidence intervals for the ordered logistic model given in Table7 indicate that interrupted treatment, worse quality of life and boost dose above 50Gy for all patients treated with radiation therapy expressed positive odds of skin reaction than others.

3.4. Case presentation:

3.4.1. Case number 1:

Female patients aged 55 years old presented with left IDC grade II Breast cancer after conservative breast surgery treated with conventional external beam radiotherapy treated with application of hyaluronic acid-based topical agent (Ialugen ® plus) 2 weeks before treatment radiation therapy course and then all through the period **(Treated group).** Pre radiation therapy **(Figure 1)** shows normal skin. Two week later Grade I dry desquamation appears through whole irradiated breast area especially left breast fold **(Figure 2).** Four weeks later, Grade II Patchy moist dermatitis, moderate edema with tender erythema skin folds **(Figure 3).** One month post radiation therapy **(Figure 4)** shows healed skin with no evidence of radiation dermatitis.

3.4.2. Case number 2:

Female patients aged 41 years old underwent conservative breast surgery presented with left IDC grade II Breast cancer treated with conventional external beam radiotherapy **(Control group).** One week later Grade I dry desquamation appears through whole irradiated breast area especially left breast fold and left axillary fold **(Figures 5,6).** Two weeks later, Grade II Patchy moist dermatitis, moderate edema with tender erythema left breast and axillary skin folds **(Figures 7,8).** After another week, Grade III severe radiation dermatitis (moist desquamation with pitting oedema **(Figure 9).**

Table (7): Results of the proportional odds model according to dermatitis at week 3 (ordered Logistic regression)

Covariate	Multivariate analysis				
	Logistic coefficient	Standard Error	P_{value}	Odds Ratio	95% CI for Odds ratio
Involved Node **Node negative** **Node positive**	-0.941	0.846	0.26	0.39	0.074 - 2.050
Interrupted treatment **No** **Yes**	-3.96	1.13	**0.00***	**0.02**	0.002 - 0.176
Quality of life **Very Dissatisfied** **Moderate Dissatisfied** **Slightly Dissatisfied** **Slightly Satisfied** **Moderate Satisfied**	 2.47 3.72 0.799 0.54	 1.07 0.814 0.713 0.455	 **0.02*** **0.00*** 0.26 0.23	 11.82 41.26 2.22 1.72	 1.411 – 97.027 8.158 - 198.503 0.550 - 8.990 0.704 - 4.184
Body Mass Index **Normal Weight** **Over weight** **Obesity(class 1)** **Obesity(class 2)** **Morbid Obesity**	 1.439 0.392 -0.389 -0.326	 3.36 0.984 0.903 0.892	 0.66 0.69 0.67 0.71	 4.22 1.48 0.68 0.72	 0.006 - 30.560 0.215 - 10.186 0.116 - 4.000 0.126 - 4.147
Radiation Dose **Dose 50 gy** **Dose > 50 gy**	-0.246	0.476	**0.00***	0.78	0.306 - 1.995
Fractionation **Conventional 2Gy/F** **Hypo Fractionation 265cGy/F**	-0.419	0.497	0.40	0.66	0.248 - 1.743
Boost Dose **No** **Yes**	-1.31	0.355	**0.00***	0.27	0.134 - 0.541

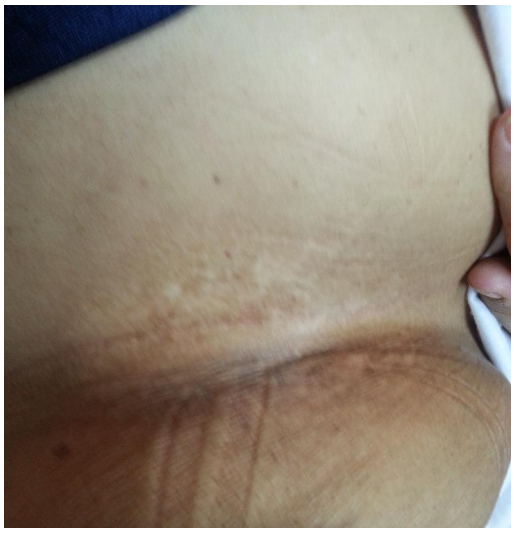

Figure 1: Pre radiation therapy normal skin (Grade 0 radiation dermatitis) in left side cancer breast female patient in treated group.

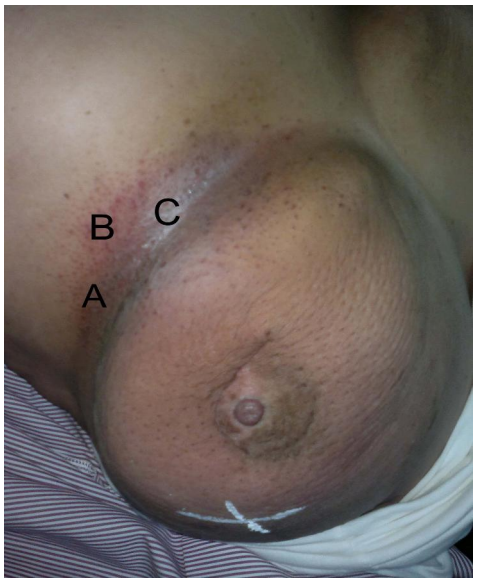

Figure 2 Two week later (Treated group) Radiation dermatitis seen (A) Area depicting hyperpigmentation, (B) dry desquamation, and (C) Grade I dry desquamation over left breast fold (Grade I radiation Dermatitis).

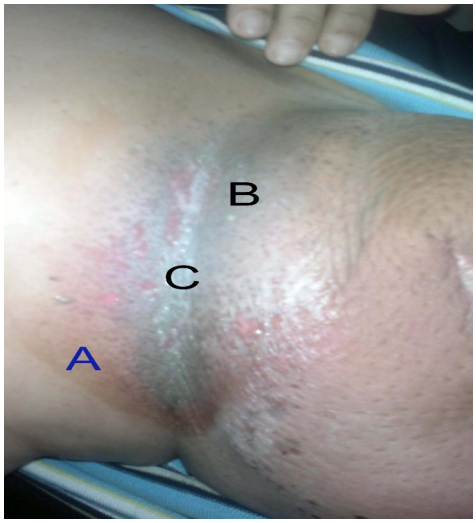

Figure 3: At 4th week (Treated group), Radiation dermatitis (A) Area depicting hyperpigmentation, (B) dry desquamation, and (C) confluent moist desquamation Grade II Patchy moist dermatitis, moderate edema with tender erythema skin folds (Grade II radiation dermatitis).

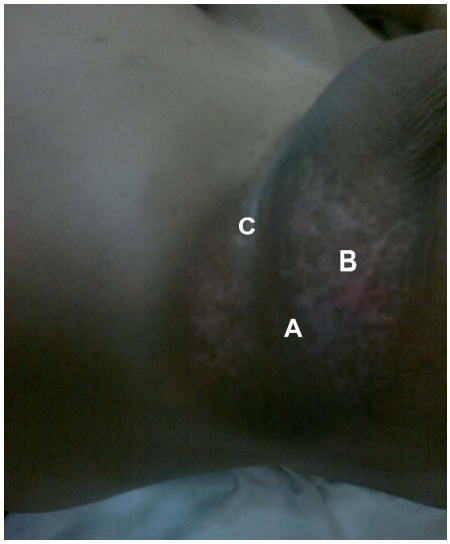

Figure 4: One month post radiation therapy, (A) Area depicting hyperpigmentation, healed skin (B), (C) with no evidence of radiation dermatitis (Grade 0 radiation dermatitis) "treated group".

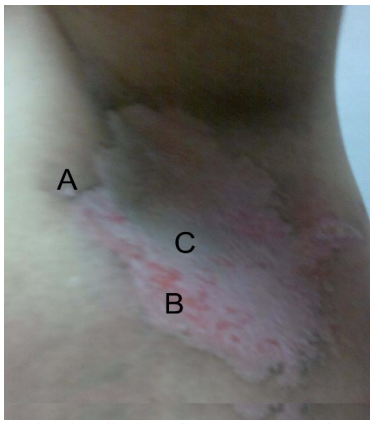

Figure 5: 1st week of radiation therapy (Control group) shows (A) area depicting hyperpigmentation, dry desquamation (B), (C) appears through whole irradiated left axillary fold **(Grade I radiation dermatitis)**

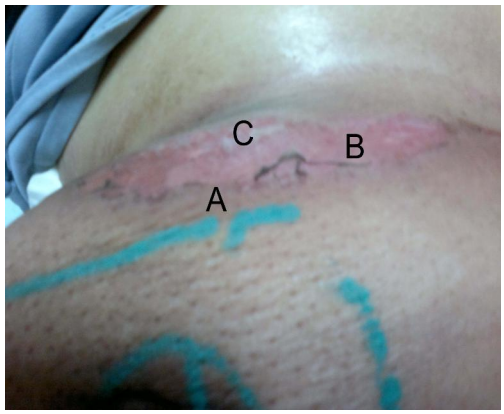

Figure 6: 1st week of radiation therapy (Control group)(A) area depicting hyperpigmentation, (B), (C) **dry** desquamation appears through whole irradiated left breast fold **(Grade I radiation dermatitis).**

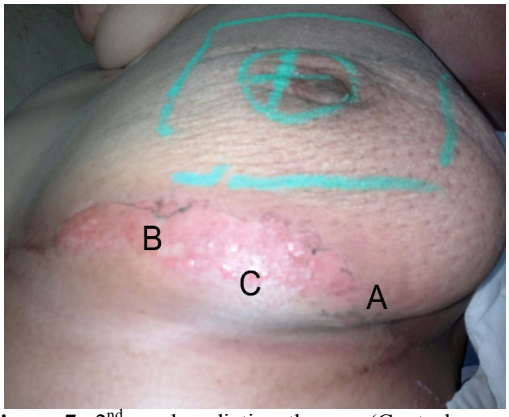

Figure 7: 2nd week radiation therapy (Control group) **Radiation dermatitis Grade II** (A) Area depicting hyperpigmentation, (b) dry desquamation, and (c) confluent moist desquamation Grade II Patchy moist dermatitis, moderate edema with tender erythema left breast skin folds.

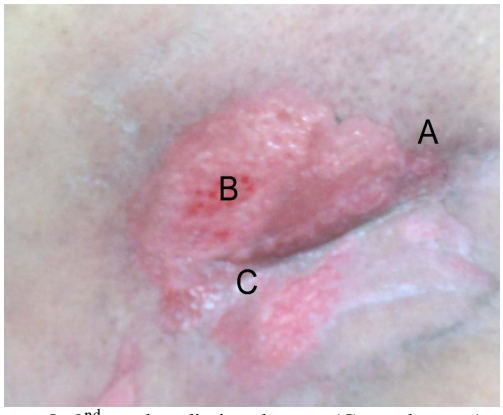

Figure 8: 2nd week radiation therapy (Control group) shows **Radiation dermatitis Grade II** (A) Area depicting hyperpigmentation, (B) dry desquamation, and (C) confluent moist desquamation Patchy moist dermatitis, moderate edema with tender erythema left axillary skin folds.

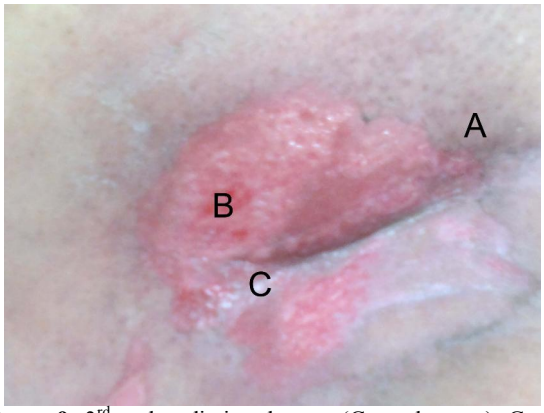

Figure 9: 3rdweek radiation therapy (Control group), Grade III severe radiation dermatitis (moist desquamation with pitting oedema **(Grade III radiation dermatitis)** (A) Area depicting hyperpigmentation, (B) moist desquamation with pitting oedema and (C) confluent moist desquamation

4. Discussion

Management of radiation dermatitis would improve the Therapeutic benefit of radiation therapy for cancer. Currently, there is no effective treatment to prevent or mitigate radiation skin injury [25].

Data compiled from Pommier *et al.,* 2004[26], Xiao *et al.,* 2006[27], Holler *et al.,* 2009 [28], Jensen *et al.,* 2011 [29] and Ryan *et al.,* 2011[30], reported that unfortunately, there is no gold standard exists for the measurement or management of radiation skin injury.

Severe reactions (GIII and IV) are often observed during and after radiotherapy treatments has its negative impact on patients quality of life, the early onset of sever acute skin reactions during radiotherapy is often responsible for treatment interruption and for a reduced compliance to the planned schedule of irradiation leads to prolonged treatment time and

increase the risk of local recurrence as demonstrated in head and neck cancers [31, 32].

The application of skin creams with physicochemical properties of hyaluronic acid, which is found in relatively high physiologic concentration in the human body, lays its ability to retain more water than any other natural or synthetic polymer. An example of non-Newtonian liquid, this compound is also characterized by its rheological nature and a viscosity which dramatically increase even at relatively low concentrations [33].

In the present randomized study which involved 209 patients with breast cancer, 80 patients as a control group and 129 patients as a treated group were followed weekly during radiation course and then monthly for 3 months since radiotherapy courses according to (RTOG/EORTC Scale) [21, 34]. Both study groups were matched in all characteristics except for body mass index, quality of life and interruption of treatment with statistical significant differences, *p*-values =<0. 00l &0.0l & 0.0l respectively and Mann-Whitney test u = 3426.0 & 1482.5 &3785.0 respectively, according to line of skin treatment with or without hyaluronic acid-based topical agent (Ialugen ® plus) in harmony with Kumars S *et al.,* 2010 [35], Pinnix C *et al.,* 2012 [36], RJ Chan *et al.,* 2014[37], Hindley A *et al.,* 2014[38] and Reisman S *et al.,* 2014[39].

Radiation dermatitis usually manifests within one to four weeks after initiation of radiotherapy and persists until two to four weeks after completion of radiotherapy. Radiation dermatitis may cause pain, long term scaring and fibrosis that can disfigure and limit motion, and it often reduces the patient's overall quality of life [40]. In the present study in which the lotion was used twice daily, initiating two weeks prior to radiotherapy course, the over all incidence of skin toxicity was 61.7 % below the rates reported in the literature, Bolderston A *et al.,* 2006 (92%) [41], Cabeza *et al.,* 2008 (95%) [42], N Salvo *et al.,* 2010 (85%) [43].

Furthermore, the rate of radio -dermatitis in treated sample was significantly lower than the control sample of patients, where radio-dermatitis appeared between the 2nd and 4th week of radiotherapy course in the treated arm. The hydrating lotion in our study prevented more than 2\3 of patients to develop radiation dermatitis with significant reduction of grade II or higher skin toxicity 41.3% (n=33) versus 10.1% (n=13) in week 3 in control and treated arms respectively, *p*=<0.001, with delay in the development of grade II or higher skin dermatitis in treated arm by a week in harmony with Munoz JL *et al.,* 2008 [44].

Also, the incidence of skin toxicity in general and of skin toxicity Grade II or higher in particular and is associated with high tolerability indicated that hyaluronic acid also, accelerates healing of irradiated skin in harmony with Trabucchi E *et al.,* 1986[45], Leonardi MC *et al.,* 1985[46], Weigel PH *et al.,* 1986[47] and West DC etal,1985[48] where hyaluronic acid has been shown by various research teams to stimulate and accelerate healing mechanisms during the three main phases of this process (Chemo static phase, inflammatory phase and finally, the phase of granulation) [49-52]. As regard skin reactions higher than GII, No patients in treated group during radiotherapy course presented with sever skin reactions versus 27 patients (33.8%) in controlled arm. The incidence of radio-dermatitis with scores more than 1 decreased more rapidly in treated arm than control one indicated that hyaluronic acid also, accelerates healing of irradiated skin. Moreover, more than10 time's reduction in pain scores in treated group versus controls. Our data consolidated by spearman's rho correlation coefficient test for radiation dermatitis and pain scores during treatment period and 3 months after where there were negative significant correlation for quality of life and positive correlation with BMI and treatment interruption, in harmony with Primavera *et al.,* 2006[49] and Leonardi *et al.,* 2008 [50] where hyaluronic acid reduce dermatitis and improve compliance and quality of life. More-over, Univariate analysis according to dermatitis score at week 3 for whole study groups showed significant statistical correlation with involved nodes, interrupted treatment, quality of life, BMI,radiation dose 50Gy, > 50Gy, fractionation and Boost dose *P*=0.0,0.0,0.0,0.002,0.0 respectively which matched with Kumar *et al.,* 2010[35], Pinnix C *et al.,* 2012 [36],RJ Chan *et al.,* 2014[37], Hindley A *et al.,* 2014 [38], Reisman S *et al.,* 2014[39] and MacBride SK *et al.,* 2014 [40]. Multivariate analysis (ordered logistic registration) showed that interrupted treatment, *p* =0.00, OR= 0.02, 95 % CI(0.002 -0.176), quality of life, *p*= 0.02, OR= 11.82, 95 %CI) 1.411-97.027), radiation dose 50Gy& > 50Gy *P*=0.00,OR =0.78, 95% CI (0.306-1.995) and boost dose, *P*=0.00, OR=0.27, 95%CI (0.134-0.541) were statistical significantly for dermatitis at week 3 positive for interrupted treatment, Radiation dose& Boost dose and negative for quality of life in harmony with, De Langhe S and his colleague 2014[51] and Kong M *et al.,*,2014[52].

5. Conclusion:

To date, there has been no consensus on the gold- standard approach for prevention or minimization of radiation dermatitis in patients with breast cancer. The results of our study showed that (Ialugen ® plus) therapy can have a beneficial role in preventing radiation dermatitis in patients with breast cancer. To confirm the results of our study, well designed randomized studies with large sample sizes are required.

Conflict of interest: None declared.

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