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Double blind Study – Use of Gelronate Gel vs. Aloevera in Preventing / Minimizing Radiation-Induced Dermatitis in Breast Cancer Patients

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Study Number: 5652-18-SMC

Aim: To evaluate the effect of Gelronate® gel, NaHA based product (medical device for topical application) vs. Aloevera Jell, in preventing or minimizing of radiation induced skin reaction in breast cancer patients.

End Points:

1. Primary – Development and degree of any skin reaction.
   a. Grading according to RTOG skin toxicity score (appendix1).
   b. Assessment of skin reaction by scoring of weekly digital photographs.
   c. Patient comfort assessed by weekly administrated questionnaire.

2. Secondary – Skin reaction requiring conventional topical therapy (e.g. steroid cream etc.) as evaluated by clinical judgment of radiotherapy nurse/ radiation oncologist at OTV (on treatment view visits).

Background

One of the dose-limiting effect of radiotherapy is the acute reaction that ionizing radiation induces in normal tissues, i.e. skin. The severity of this acute reaction may link to different parameters, patient associated (BMI, diabetes) and radiation associated (dose per fraction and total dose).

Hyaluronic acid (HA) is linear polysaccharide formed from repetitions of a disaccharide unit composed of one aminosugar and one uronic acid residue ([D-glucuronic acid (1-β-3) N-acetyl-D-glucosamine (1-β-4)]$_n$) (Figure 1).

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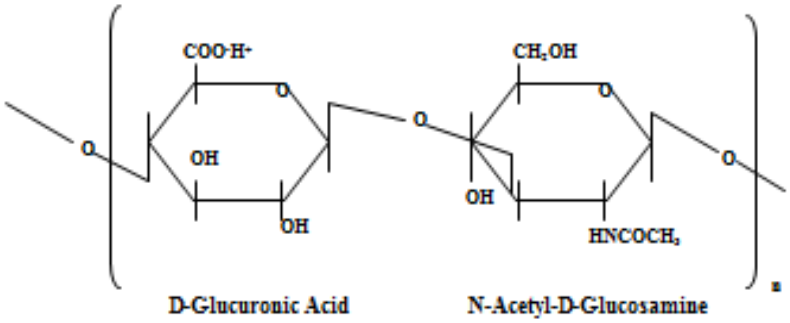
Fig, 1. Disaccharide repeating unit of hyaluronic acid.



The biopolymer is widespread in soft tissues (vitreous humour of the eye, joints, synovial fluid, skin and more). In vertebrates, HA has a wide variety of functions including maintenance of tissue hydration in the skin, sustaining tissue physical properties and induce rate changes in cell proliferation, cell migration and angiogenesis.

There are two industrial methods for the production of HA: from rooster combs or from bacterial fermentation. Bio-Technology General (Israel) Ltd. developed and manufacture HA for ophthalmology and orthopedics purposes. BioLon and BioLon Prime are two products for operations in the interior chamber of the eye (cataract surgeries, cornea implantation etc.) and Euflexxa (Arthrease) syringes are for pain relief in patients suffers from osteoarthritis (OA).

Due to its characteristics and biological properties including wound healing (Primavera et al. 2006, Moore et al 2005, Hanci et al 2015), HA may eliminate or reduce adverse events (AEs) like skin dermatitis. The purpose of this study is to evaluate the capability of 1% HA solution to eliminate or reduce skin reaction during radiation i.e. dermatitis.

The tested product, Gelronate®, is gel composed of 1% high molecular weight pharmaceutical grade sodium hyaluronate and two types of commercial preservatives (Germal 115 and Phanochem/Salinip/Phenonip) dissolved in pharmaceutical grade purified water. Gelronate® supply in an airless pump bottle contain ~30ml gel. The aloe Vera 99.9% product is made by ESI, Israel, with no artificial coloring, in the same package with no identification.

Study Plan

120 female patients planned to receive whole breast radiation (+/- lymphatic drainage) in the radiotherapy unit at Sheba, who give written consent for participation, will be entered into the study and randomized. Based on statistical evaluation, 65 will receive the aloe Vera and 55 will receive the HA Gelronate® in blinded packages.

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Patients will undergo CT simulation with 3D treatment planning (as routinely done) and will receive 42.4 Gy in daily fraction of 2.65 Gy, five times per week to the whole breast according to the standard department protocol, with or without concomitant or subsequent lumpectomy cavity boost. Patient data including demographics, staging, systemic therapy, radiation details, other medications will be recorded in the attached forms (Appendix A, pages 7-9 below).

BTG will provide sets of bottles sufficient for treatment of at least 120 patients, plus any extra gel bottles as needed for the participants to complete accrual and full treatment for 120 patients.

The study nurses will provide each patient with the bottle and will ensure that the patient understands how to apply according to protocol. The gel will be applied as a thin lotion twice a day, immediately after radiotherapy treatment and once more in the evening/morning. The therapy should continue for 10 days following the end of radiation therapy.

The study nurses will examine each patient weekly during treatment and 7-10 days after completion of radiotherapy. At each visit skin reaction based on RTOG toxicity score will be recorded and the patient will complete a short questionnaire regarding subjective and objective skin reaction. The patient's skin will be photographed (no face in the picture) on fraction 10-11, 15-16 and at the follow-up visit, days 9-10 after the end of radiation. This will be done with a digital camera and the electronic image will be stored for later evaluation. The images will be stored anonymously except for the patient's study number.

Any patient developing moist desquamation or other grade 3 skin reaction during the radiation will stop treatment and will receive topical therapy as clinically indicated.

Eligibility:

Inclusion Criteria:

1. Female patients aged at least 18 years with unilateral breast cancer following lumpectomy +/- chemotherapy.
2. Planned to receive 42.4 Gy whole breast irradiation +/- boost to tumor bed.
3. ECOG performance status 0-2.
4. Capable of giving written informed consent.
5. No co-morbidities known to affect radiotherapy reactions.
6. No co-existing acute or chronic skin disease.
7. No evidence of infection or inflammation of breast to be treated.

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8. Not receiving chemotherapy during radiotherapy course. Biological therapy (e.g. Herceptin) or hormone therapy will be allowed during the study.

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Exclusion Criteria:

1. Chemotherapy within 4 weeks prior to planned start of radiation or chemotherapy planned during radiation.
2. Prior radiotherapy to the chest wall.
3. Collagen vascular disease.
4. Participation in other clinical study.

Statistical Considerations:

Based on published data and previous experience we expect around 90% of patients to develop some degree of skin reaction and about 20% would require medical intervention due to grade 2-3 skin reactions. (Ben-David et al 2016, Fenig et al., Kodiyan et al. 2015, Olsen et al 2001).

The relative large number of patients in the study was chosen in order to be able to have sufficient amount of data on large variety of patients (different age, BMI, skin color, origin, smokers/non-smokers etc.). Participation in this study will be offered and available to all radiation treated patient in the institute, therefore large variety of patients are expected to participate in this study. As a result, the data that will be obtained in the study may be used by any irradiation institute in the world.

In addition to the weekly nurse/patient evaluation of skin toxicity (see appendix A), at the completion of the study the patient photographs will be evaluated blindly by a panel of 3 radiotherapy staff. The digital photo with the worst reaction of each patient will be scored.

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APPENDIX A (Translated from Hebrew to English)

Gelronate Study, Weekly Data Collection

Number in study_____

Filling date_____

Number of given fractions _____ Dose Gy_____

Skin condition

Status according to RTOG_____ :

	0	1	2	3	4
Skin	No change over baseline	Follicular, faint or dull erythema/epilation/dry desquamation /decreased sweating	Tender or bright erythema, patchy moist desquamation /moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis

Clinical description

_____

_____

_____

_____

Photo taken Yes/No

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Dermatology Assessment

1. Nothing .2 A little .3 Frequent .4 Continuing

4	3	2	1	
				Dryness
				Erythema
				Suntan
				Swelling
				Rash
				Wound
				Peeling
				Bleeding
				"Wet" peeling
				"Dry" peeling
				Cellulitis
				Pigmentation changes

Treatment decision: Continue study/Stop the study

Inspected by:_____ Signature:_____ Date:_____

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Personal evaluation of status and filling in the skin

Study Number _____ **Date:_____**

Number of radiation until today:_____

Grade your fillings during last week on the treated breast-

1. **Nothing 2. Small parts of the breast 3. Most of breast area 4. All breast area**

4	3	2	1	
				Biting
				Hurt
				Burn
				Rough
				Prickly
				Soft
				Dry
				Wet
				Smooth
				Strange
				Tickling

Comments_____

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Patient's code_____

Data collection CRF

1. Birth date:_____
2. Clinical background: Blood pressure/Diabetes/Other _____
3. Full list of taken medicines_____
4. Detailed smoking habits_____
5. Weight
6. Hight Calculated BMI
7. Size of bra
8. Skin color
9. Origin
10. Right/left breast
11. Surgery date of the radiated breast_____
12. Histology_____
13. Stage in the disease: In surgery T N M:
    T N M before chemotherapy _____
14. T N M after chemotherapy (or without)_____
15. Tumor's location according to simulation? Upper external/upper internal/lower external/lower internal/ breast's center
16. SLNBX / ALND / NONE
17. Repeated surgery in the breast? Yes/No (date of repeated surgery_____)
18. Starting date of radiation_____
19. Boost? Yes/No (concomitant Yes/No)
20. Type of boost? P/E Dose in Gy_____
21. Radiation into supraclavicular? Yes/No
22. Radiation to intramammary? Yes/No
23. ɔTotal radiation to the breast in Gy (without boost)_____
24. SEPARATION
25. Received hormonal treatment? (anytime) Yes/No (What type? _____)

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