

RESEARCH ARTICLE

Lack of Prophylactic Effects of *Aloe Vera* Gel on Radiation Induced Dermatitis in Breast Cancer Patients

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Abstract

Purpose: Radiotherapy induced dermatitis is a common and sometimes serious side effect. We conducted a randomized study to understand whether the adjunctive use of aloe vera gel might reduce the prevalence and/or severity of radiotherapy induced dermatitis. **Methods:** One hundred patients with newly diagnosed breast cancer were randomized to receive aloe vera gel or nothing during adjuvant radiotherapy consisting of conventional external beam radiation using 6 MV mega voltage linear accelerator photons. The radiation portals were composed of breast fields in all patients and supraclavicular and posterior axillary fields in node positive cases. The total dose was 50 Gy with a daily fraction of 2 Gy, five fractions per week. **Results:** Dermatitis was first found among patients of both groups after week 2. In the aloe vera and control groups, 2/8 patients and 5/12 patients had dermatitis grade 1 after weeks 2 (P value = 0.240) and 3 (P value = 0.317). After the 4th week, the numbers were 18 and, 23 for dermatitis grade 1 and only 1 for grade 3 dermatitis (P value = 0.328). After the 5th week, 31, 12 and 2 patients in the aloe vera group and 36, 6 and 5 of the controls had grades 1, 2 and 3 dermatitis, respectively (P value = 0.488). **Conclusion:** Aloe vera exerted no positive effect on prevalence or severity of radiation dermatitis in this study.

Keywords: Breast cancer- radiation dermatitis- *Aloe vera*- prevention

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Introduction

About two thirds of those patients diagnosed with cancer receive radiotherapy (Haddad et al., 2013). In patients with breast cancer, radiotherapy may be an essential part of treatment (Ansari et al., 2013). Acute reactions to radiotherapy occurs in hours to weeks after starting radiotherapy while late reactions may occur years later (Ryan, 2012). Unfortunately, radiation induced dermatitis occurs in 95% of those patients who receive radiotherapy (Ryan, 2012). Dermatitis can cause severe pain and discomfort. Occasionally, treatment is interrupted and cure is hampered (Ryan, 2012; Ansari et al., 2013). Newer techniques and machines have not eliminated dermatitis (Ryan, 2012). Fortunately, skin reaction in palliative radiotherapy is seen less commonly than with standard radiotherapy doses (Bolderston et al., 2006). There is no effective prophylactic or therapeutic agent for this serious side effect (Ryan, 2012; Haddad et al., 2013). Although this subject is a matter of debate, creams, lotions, and in more severe cases antibiotics and dressings, are prescribed by the attending staff (Bolderston et al., 2006).

Aloe vera is a juicy plant species of the genus *Aloe*. It usually grows as a wild plant in tropical climates around the world and is cultivated for agricultural and medicinal uses. It belongs to the Liliaceae family and the best-known type of aloe plant (Vogler and Ernst, 1999). *Aloe vera* provides two diverse products: yellow latex, which is known as aloe juice, and leaf pulp, which is the inner most part of the leaf for storage of food and nutrients that contain the *Aloe vera* gel. The raw pulp contains about 98.5% water with the remaining 1.5% containing a range of compounds including water-soluble and fat-soluble vitamins, minerals, enzymes, polysaccharides, phenolic compounds and organic acids (Hamman, 2008). *Aloe vera* is used as a treatment for eczema, skin burn, frost bite and other dermatologic diseases for many years (Loewenthal, 1949; Williams et al., 1996; Heggie et al., 2002). *Aloe vera* has been used for skin burn for centuries (Williams et al., 1996). It has also shown some benefits on RT induced dermatitis in previous studies (Olsen et al., 2001).

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Methods and Materials

This study is a prospective randomized controlled clinical trial that has been conducted in Namazi Hospital, Shiraz, Iran. The study was approved by the Clinical Research Ethics Committee of Shiraz University of Medical Sciences in accordance with the code of ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. One hundred breast cancer patients entered this non-blinded study. All patients underwent conserving breast surgery and received radiotherapy 3-4 weeks after the last cycle of adjuvant chemotherapy. Patients who were treated with mastectomy were excluded. Chemotherapy regimens were doxorubicin-based. Patients had no metastasis or systemic disease. History of radiotherapy, skin sensitivities and history of severe dermatologic reaction were the exclusion criteria. Patients were randomly assigned into two groups, each consisting of 50 patients. In the study group, aloe vera gel was applied throughout treatment and the other group received radiotherapy alone.

Irradiation was done upto 50 Gy by linac machine, 6 mv photon. Adjuvant radiotherapy consisted of conventional external beam radiation using 6 MV mega voltage linear accelerator photons. The radiation portals were composed of the breast fields in all patients and supraclavicular and posterior axillary fields in node positive cases. The patients received a total dose of 50 Gy with a daily fraction of 2 Gy, with five fractions per week. No patients received electron boost. Concurrent chemotherapy was not allowed. The lotion was made of Aloe vera and about 1% additive materials by Anamis Co, Tehran, Iran. Additive agents were pectin, vitamin C and Natamycin. Aloe vera gel was applied twice a day in at least six hour intervals with a thickness of 1-2 mm on the radiation therapy field. The patients were examined weekly by 2 physicians and dermatitis grade was registered. Dermatitis was graded according to Acute Radiation Morbidity Scoring Criteria (Table 1) (Huang et al., 2015). Examiners were a radiation oncologist and a resident who visited and examined the patients separately in each week. The patients who had grade 2 or more dermatitis received additional local or systemic treatment for dermatitis such as antibiotics, corticosteroid or analgesics. Data were analyzed using IBM SPSS statistics version 21 software.

Results

The trial enrolled 100 patients. Median age of the participants was 48 years. Mean age in the aloe vera arm was 48 (28-76) years and in the control arm it was 49.1 (25-75) years. No patient refused treatment with aloe vera and all patients had a good cooperation.

After the 1st week of treatment, no dermatitis was found among any of the patients in either group. After the 2nd week, in patients who received aloe vera, 2 patients had grade 1 dermatitis and 5 patients in the control group had grade 1 dermatitis (P value = 0.240). As the treatment continued, the number of cases with dermatitis increased. After the 3rd week, 8 patients who had used aloe vera and

12 patients in the control group had dermatitis grade 1 (P value = 0.317). Before the 4th week, no grade 2 or more was seen. After the 4th week, both number of patients and grade of dermatitis increased. Eighteen patients developed dermatitis despite using aloe vera gel and 24 patients in the control group had dermatitis. Although patients in the aloe vera group had grade 1 dermatitis, 1 patient had grade 3 dermatitis (P value = 0.328). After the 5th week, 31, 12 and 2 patients in the aloe vera group and 36, 6 and 5 patients in the control had grades 1, 2 and 3 dermatitis, respectively. After the 2-4th weeks, dermatitis was more frequent in the control group (P value = 0.488). After the last week, the patients with dermatitis were more frequently seen in the aloe vera group (Table 2). The differences among the 2 groups were not significant in any week.

Discussion

Skin changes, consisting of swelling, changes in color and at last ulceration, are the usually seen in radiotherapy sites (Chan et al., 2014). The mechanism of injury is so different; therefore, radiation-induced lesions could not be treated like thermal injuries. It is important to note that radiation injuries are resistant to narcotics (Ryan, 2012).

Radiation interferes with cell division and consequently cells are lost (Chan et al., 2014). Skin injury is due to cell death. First, cells that are damaged are basal keratinocytes and hair follicles. These cells are continuously dividing and regenerating the skin (Ryan, 2012). Basal layer of the epidermis contains the cells whose damage leads to reactions that we see during radiotherapy. These cells are

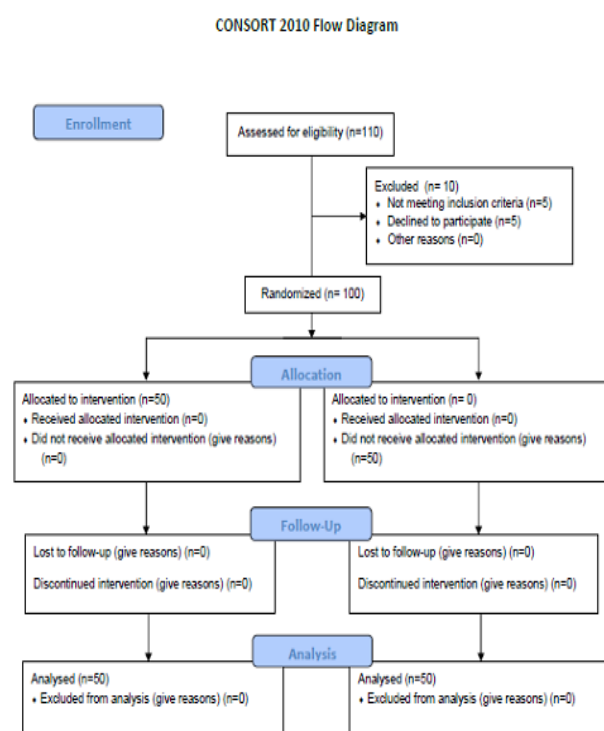


Diagram 1. CONSORT 2010 Flow Diagram

Table 1. Grading of Radiation Induced Dermatitis

grade	color	Desquamation and edema	ulceration
1	slight erythema	Dry desquamation and no edema	no
2	Moderate erythema	Moist desquamation in skin folds, Moderate edema	no
3	any	moist desquamation \geq 1.5 cm diameter outside of skin folds, pitting edema	no
4	any	any	Full thickness ulceration

Table 2. Dermatitis During Radiotherapy in the Aloe Vera and Control Groups

Week	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
1					
Aloe vera	50 (100)	0	0	0	0
Control	50 (100)	0	0	0	0
2					
Aloe vera	48 (96)	2 (4)	0	0	0
Control	45 (90)	5 (10)	0	0	0
3					
Aloe vera	42 (84)	8 (16)	0	0	0
Control	38 (76)	12 (24)	0	0	0
4					
Aloe vera	32 (64)	18 (36)	0	0	0
Control	26 (52)	23 (46)	0	1 (2)	0
5					
Aloe vera	5 (10)	31 (62)	12 (24)	2 (4)	0
Control	3 (6)	36 (72)	6 (12)	5 (10)	0

continuously dividing. It is estimated that 10% of them go through mitosis daily. Besides these change, inflammation starts and increases the damage. Additionally, other cells are injured and other side effects are seen. Hair follicles are damaged and hair loss occurs. Detrimental effects of radiotherapy on the sweat glands are seen after 30 Gy. The result is dryness and pruritis sensation (McQuestion, 2006).

Radiation induced skin reaction is dose dependently (Bey et al., 2010). Although damage to the cells start from the 1st dose, observable skin lesion starts in a dose of 20-25 Gy. In practice, dermatitis occurs from weeks 2-3. Skin injury increases during radiotherapy and may last for 2-4 weeks after radiotherapy. In this article, we are discussing the acute reactions. Radiotherapy induced reactions may start years later (Richardson et al., 2005; Ryan, 2012; Chan et al., 2014). As we showed in our study, skin reaction usually starts after 20 Gy. In our study, the patients received 2 Gy every day, five days per week. After the 2nd week, dermatitis started (Bolderston et al., 2006). Extension and severity of dermatitis depend on multiple factors including sex, age, genetic susceptibility, location, total dose and dose per fraction of radiotherapy (Ryan, 2012). Obesity and smoking are also effective in dermatitis severity (Richardson et al., 2005). Additionally, concurrent chemotherapy increases radiotherapy related skin reactions (Richardson et al., 2005).

There is no standard management for radiation

induced dermatitis (Bolderston et al., 2006; Merchant et al., 2007). Multiple agents and intervention such as washing with water and soap, amifostine, dressing, creams, corticosteroids, calendula, Henna and sucralfate have been tested in trials (Bolderston et al., 2006; Merchant et al., 2007; Omidvari et al., 2007; Ansari et al., 2013). But for each therapeutic agent few studies are reported (Chan et al., 2014).

In animal studies, aloe vera improved wound healing. Aloe vera is effective on platelets and leucocytes and also inhibits vasoconstriction. Aloe vera is also known as an anti-inflammatory and antibacterial agent (Heggie et al., 2002).

Haddad et al. compared aloe vera with no treatment in 60 patients with different cancers. Their patients used aloe vera in half of the radiotherapy field during radiotherapy. The other half of the radiotherapy field received no local therapy. Their patients were not similar in treatment site, field size or radiotherapy dose. In addition, 20 patients received concurrent chemotherapy. Male/female ratio was 0.49 and mean age was 52 years. Most primary sites were the breast (38%), pelvis (32%), head and neck (22%). Aloe vera significantly reduced dermatitis during and after radiotherapy. Dermatitis decreased in week 4 to 6 and 2-3 weeks after radiotherapy in locations that had received aloe vera (Haddad et al., 2013). The site of RT and dose of radiation have known impact on the development of dermatitis, while the severity of dermatitis

is higher in female patients (Ryan, 2012). Haddad's study was the only study which showed aloe vera was successful in reducing dermatitis.

Another simple and practical modality that has been tested in several studies is washing. Washing with soap was effective in reducing dermatitis severity and incidence. Washing with soap is better than no washing or washing with water alone (Chan et al., 2014). Olsen et al. in a retrospective study on 73 patients compared washing the skin with soap alone and washing with soap and aloe vera gel. Patients had different cancers; they were both male and female with high variation in dose of radiation. Aloe vera gel was used liberally by patients. Despite the challenges imposed by this heterogeneous population, their study was able to draw an interesting finding: aloe vera was more effective in higher radiotherapy doses (Olsen et al., 2001).

Despite the above mentioned studies, there are some studies that report no effect by aloe vera. Heggie et al. in a study on 225 patients with breast cancer compared aqueous cream (101 patients) and aloe vera (107 patients). Aqueous cream was better than aloe vera to control dry desquamation and pain. No difference was seen in moist desquamation, itching and erythema. Improvement in pain and dry desquamation was not associated with a strong superiority. Grade 2/3 pain was improved, not grades 1 and 3. Considering desquamation, they measured $\geq 1\%$, 25% and 50%. Only those patients with $\geq 1\%$ dry desquamation had better results. In their study, breast size was directly related to dermatitis (Heggie et al., 2002).

Aloe vera is used in both pediatric cases and adult patients. Merchant compared aloe vera and anionic polar phospholipid (APP)-based cream in 45 pediatric patients with a mean age of 11 (3–19) years (Merchant et al., 2007). In their study, anionic polar phospholipid (APP)-based cream and aloe vera were used in the same field. APP-based cream was significantly better than aloe vera. Their patients had different diseases (Hodgkin disease, CNS tumor, sarcoma and neuroblastoma) in other parts of the body. The radiotherapy dose was 34.3 (25.5–67) Gy (Merchant et al., 2007). In their study, both objective and subjective aspects were evaluated. They measured 15 subjective and 15 objective variables. Compared with anionic polar phospholipid (APP)-based cream, Aloe vera gel was not successful in reducing the severity and treating dermatitis (Merchant et al., 2007).

Williams et al. in a prospective randomized double blind study on 194 patients compared aloe vera with inert gel. They found no difference between inert gel and aloe vera gel. The authors think about superiority of both groups to other patients who were not under the study. In the next step, they compared aloe vera with no treatment. A non-blinded study was designed to compare aloe vera gel to no treatment in 108 patients. In a later study, no benefit was reported with aloe vera in maximum and mean dermatitis (Williams et al., 1996).

Among these studies, although measurement, patients, and site of treatment were so different in these studies, aloe vera was not a successful agent in treatment of radiation induced dermatitis. As our best knowledge, this the first randomized controlled clinical trial investigating the

efficacy and safety of aloe Vera gel in preventing radiation dermatitis in breast cancer patients.

Conflict of interest

All authors disclose any actual or potential conflict of interest including any financial, personal, or otherwise.

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