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ORIGINAL RESEARCH

Aloe vera for Prevention of Acute Radiation Proctitis in Colorectal Cancer a Preliminary Randomized, Placebo-Controlled Clinical Trial

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Abstract

Objective To examine the preventive effects of *Aloe vera* in colorectal cancer patients undergoing radiotherapy.

Material and Method Twenty colorectal cancer patients, who received radiation, were randomized to receive *Aloe vera* 3% or placebo ointment, 1 g twice daily for 6 weeks. At weekly visits, acute radiation proctitis (ARP) was evaluated by Radiation Therapy Oncology Group and clinical presentation criteria as the primary endpoint. We also evaluated secondary endpoints of quality of life, psychosocial status, by applying Hospital Anxiety-Depression (HAD) Scale and laboratory measures of quantitative measurement of C-reactive protein (CRP) as a marker for systemic inflammation.

Results There was a significant improvement in the symptom index (before treatment vs. after treatment with *Aloe vera*) for diarrhea ($p = 0.029$, median score: 0.5 vs. 0.001). The overall primary and secondary outcomes favored *Aloe* group, while the measures of toxicity did not achieve a statistical significant difference. The lifestyle score improved significantly with *A. vera* ($p = 004$), and they also had a lower depression score in HAD scale ($p = 0.008$). Furthermore, quantitative CRP decreased significantly during the course of treatment with *Aloe vera*.

Conclusion The use of topical formulation of *Aloe vera* 3% diminishes the severity of ARP in colorectal cancer patients.

Keywords Acute proctitis · *Aloe vera* · Colorectal cancer · Radiotherapy · Topical formulation

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Introduction

Aloe vera is an herbal remedy with a well-established history for its therapeutic effects in various disorders. Among its well-known biological activities are anti-oxidant, anti-inflammatory, analgesic, antiproliferative, anticarcinogenic, and antiaging properties. *Aloe vera* has also been used in radiation-induced skin reactions and proctitis treatment owing to its anti-inflammatory, anti-oxidant and analgesic properties [1–3]. Our understanding on the mechanism of action for the wound healing effects of *A. vera* is limited, but some suggest the critical role of suppression of cyclooxygenase-2 [4].

Acute radiation proctitis (ARP) is a common complication of pelvic radiotherapy (RT) in malignant diseases of lower abdomen and pelvis. ARP presents as rectal bleeding and pain, diarrhea, and fecal urgency, with negative impact on quality of life [5–7]. The molecular mechanism of ARP is due to an enhanced production of reactive oxygen species [5, 8].

Colorectal cancer is one of the leading causes of death worldwide which has a survival rate of less than 50% after 5 years [9]. Interestingly, the most common symptoms associated with colon cancer are similar to radiation including abdominal pain (44%), change in bowel habits (43%), and hematochezia or melena (40%) [10]. Preoperative RT is used as an adjuvant modality for rectal cancer, and a systematic review of 28 clinical trials have shown its effectiveness in reducing risk of local recurrence and death from rectal cancer [11]. Therefore, local treatment by means of pelvic RT may cause subsequent anorectal injury which may have a great deal of overlap between the symptoms of cancer and ARP [12].

Different modalities for prevention of ARP are available. A lot of efforts have been made to shield the rectum during radiation, but it is generally inapplicable or hard [13]. Hence, the risk of damage to the rectum during RT is high. Other less available modalities include precise dose-planning and new radiation techniques such as the use of contemporary conformal radiation therapy techniques (e.g., intensity modulated radiation therapy, intensity guided radiation therapy) which minimize the dose of radiation to the rectum while maximizing dose to the tumor [14, 15]. Medical therapy (e.g., amifostine) was associated with only a minimal effect and is not widely used [16, 17].

Evaluation of *A. vera* in a randomized trial against placebo in patients suffering from colorectal cancer is debatable, since the best current practice for prevention of ARP is yet to be established. Especially in this population, scientific studies remain infrequent and rare. Considering the molecular mechanism of *A. vera*, the underlying pathophysiology of ARP, disturbing symptoms associated with colorectal cancer, and also the uncertainties about a widely accepted prophylactic treatment for radiation proctitis, we decided to examine the issue in a preliminary prospective randomized, double-blind, placebo-controlled clinical trial in patients undergoing RT to the pelvis.

Materials and Methods

Over a period of 12 months, 20 patients who met the inclusion criteria for the study were consecutively allocated to intervention or control group in the radiotherapy department of Imam Hospital, which is university affiliated. The eligible participants were evaluated for protective effects of *A. vera* rectal ointment in ARP associated with colorectal cancer. The trial profile is shown in Fig. 1. Patients were interviewed and given written informed consent. Individuals at the age of 18 years and over who were undergoing radiation for colorectal cancer were

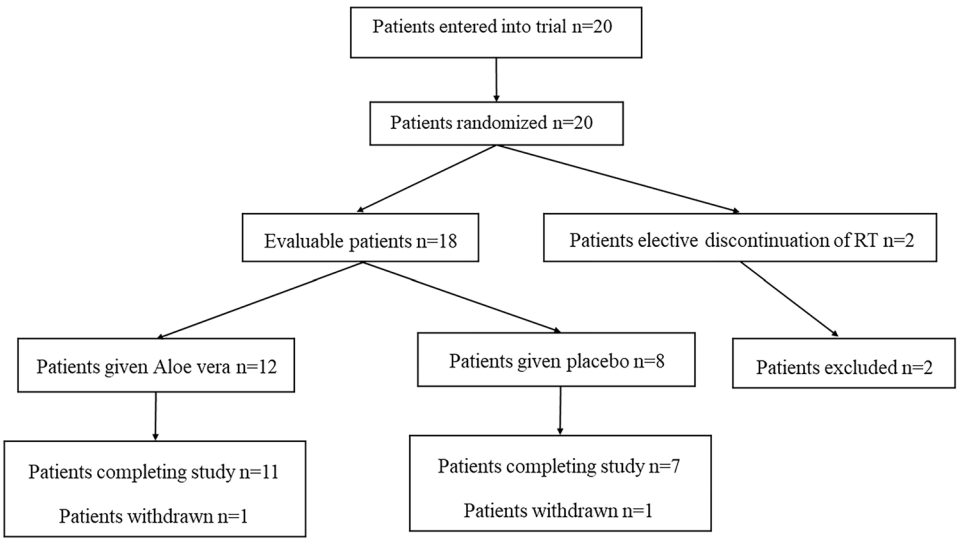

Fig. 1 Flowchart of the study

considered for this trial. They must not have had evidence of active infection; evidence of other sources of hematochezia including inflammatory bowel disease, and hemorrhoids; anal incontinence, anorectal fistula, and anorectal stenosis; pregnancy or breast feeding and female of child-bearing age not taking adequate contraception; known allergy to any ingredients of the ointment; and concomitant use of antibiotics or steroids.

For preparation and formulation of *A. vera* ointment, pure spray-dried *A. vera* powder was applied (Giah salamat nasim faraz, Fars, Iran). The inner gel of the plant was formulated in the ointment base as described previously [2].

The patients were randomized in a double-blind manner to receive either an *A. vera* 3% ointment or placebo. The study medication (*A. vera* or placebo) was to be applied rectally with an applicator. The dose used was 1 g twice a day starting from the first day of radiation initiation and then during 6 weeks of radiotherapy. The patients were assessed by completing questionnaires at study initiation and weekly until 6 weeks following initiation of radiation therapy.

The ointment tubes were exactly indistinguishable. Patients, clinician, and the investigator were not aware of the intervention or placebo arms. Trial allocation was according to Random Number Table, using permuted randomization blocks of four. Compliance assessment was determined by asking the participants to bring their tubes for weekly visits. At each weekly visit, ARP symptoms were evaluated by Radiation Therapy Oncology Group (RTOG) and clinical presentation criteria [2]. Four signs of rectal pain and bleeding, bowel movement, and fecal urgency were reported. For each sign, a scale from 0 (not present) to 4 (most symptomatic) was used. The maximum overall score was 16 [2, 5]. The primary outcome measures were prevention of proctitis development (defined as lower scores of RTOG Criteria and Clinical Presentation Criteria). All the scores were assessed by the same investigator of clinical responses, blind to the treatment given.

In addition to our primary end point, we evaluated secondary end points of quality of life (QOL), psychosocial status using Hospital Anxiety-Depression Scale (HAD), and also changes in laboratory measures of inflammation (quantitative measurement of C—reactive protein (CRP)). Possible adverse effects of the trial medications were also recorded.

Quantitative CRP was measured by obtaining serum samples at baseline, week 2, and week 6. CRP-Latex Bionik slide agglutination kit with a specificity of 95.6% and specificity of 96.2% was applied. According to our previous study, psychosocial status of patients was assessed by HAD Scale. At each visit, patients were requested to fill out quality of life and HAD form by themselves [2].

For statistical analyses, we used the Shapiro-Wilk test to test whether data were normally distributed. Descriptive baseline characteristics for study group comparisons were tabulated as mean ± SD, median (inter-quartile range), or as percentages. Categorical data were statistically analyzed using chi-square or Fisher-exact test, and continuous data were analyzed using *t* test or Mann-Whitney *U* test. The method of analysis was intention-to-treat. We used a generalized estimating equation (GEE) model to estimate the differences in values of endpoints at each time point between the two groups (between group effects). Within-group effects were assessed with the Friedman test. A *p* value of 0.05 or less was considered statistically significant, and between 0.05 and 0.1 was considered marginally statistically significant. Data were analyzed using IBM SPSS statistics version 16 and stata version 10.

Ethical Approval

The study protocol was approved by the Ethics Committee of Mazandaran University of Medical Sciences (IR.MAZUMS.REC.94-1196) and registered in the Iranian Registry of Clinical Trials (IRCT201606042027N6).

Results

Over a period of 12 months, 20 patients completed a cycle of external-beam radiation therapy to the pelvis. They were randomly assigned to receive *Aloe* ointment ($n = 12$) or placebo ointment ($n = 8$). Demographic and baseline clinical

Table 1 Baseline characteristics of patients

Characteristics	Aloe ($n = 12$)	Placebo ($n = 8$)	*P* value
Age, median (IQR) (year(	62.5 (51–70.5)	49.5 (37–61)	0.18
Male gender, No. (%)	9 (75%)	5 (62.5%)	0.64
BMI, median (IQR) (kg/m^2)	22.4 (21–25)	26.6 (22–30)	0.06
Dose of radiotherapy in each session, median (IQR) (cGy)	180 (180–195)	180 (180–195)	0.99
Total dose of radiotherapy received, median (IQR) (cGy)	5040 (5010–5040)	5040 (5000–5040)	0.68

BMI body–mass index

characteristics of enrolled patients were presented in Table 1. All patients were followed-up regularly. However, two patients (one on each arm) withdrew from the study, because of elective discontinuation of RT. Average patient age was 55.3 years, with no significant difference between groups. The rectal ointments were well tolerated in all patients. No patient in either group experienced any adverse effects. Our patients were objectively monitored with a patient diary. Compliance was good as assessed by comparing the actual and estimated volumes of residual ointment. As illustrated, both intervention and placebo groups were well balanced with respect to baseline patient characteristics in terms of age, gender ratio, body mass index, dose of radiotherapy in each session, concomitant medication, and comorbidities (Table 1). Flow diagram of the study population selection is displayed in Fig. 1.

Symptom Scores

Effect of *Aloe vera* Rectal Ointment on Symptoms

Table 2 ; Figs. 2 and 3 describe the median and IQR values of the symptom scores and show the effect of *A. vera* rectal ointment on prevention of individual proctitis symptoms during the 6-week course of radiation treatment. As shown in Table 2, there was a statistically significant downward time trend (within-subject differences or time effect) for rectal bleeding, rectal pain, total clinical symptoms, proctitis, RTOG total ($p < 0.05$), and marginally statistically significant time trend for diarrhea and fecal urgency ($p = 0.08$) in *A. Vera* group. In placebo group, there was not no statistically significant time trend for overall and each symptom scores, proctitis, cystitis, and RTOG total ($p > 0.05$). The values of diarrhea score and RTOG total in *A. vera* group were lower than placebo group, and these differences were statistically significant (between-subject differences or group effect) ($p < 0.05$).

Secondary End Points

Quality of life (QOL), depression and anxiety for assessment of psychosocial status of patients, and quantitative CRP were evaluated as secondary endpoints.

As shown in Table 2, the QOL and anxiety in HAD scale during RT score getting increased and there is

Table 2 Change trends of clinical presentation in *Aloe vera* and placebo during 6 weeks of follow-up

		Week		Effect	
		1 Median (Q1,Q3)*	6 Median (Q1,Q3)*	Within group	Between group
Rectal bleeding	*Aloe vera*	1.5 (< 0.01– 2)	< 0.01 (< 0.01–< 0.01)	< 0.001	0.46
	Placebo	1 (1–1)	1 (< 0.01–1)	0.24	
Rectal pain	*Aloe vera*	1 (0.25–2)	1 (< 0.01–1)	0.01	0.69
	Placebo	1 (< 0.01–1)	1 (1–2)	0.5	
Diarrhea	*Aloe vera*	< 0.01 (< 0.01–1)	< 0.01 (<–0.01–< 0.01)	0.08	0.04
	Placebo	< 0.001 (< 0.001–1)	1 (< 0.01–2)	0.69	
Fecal urgency	*Aloe vera*	0.5 (< 0.01–1.75)	< 0.01 (< 0.01–< 0.01)	0.08	0.78
	Placebo	0.5 (< 0.01–1)	1 (< 0.01–1)	0.55	
Total clinical symptoms	*Aloe vera*	4 (0.25–5.75)	1 (< 0.01–1)	< 0.001	0.62
	Placebo	3 (1–4.75)	4 (0.5–4)	0.94	
Proctitis	*Aloe vera*	2 (< 0.01–3)	< 0.01 (< 0.01–< 0.01)	< 0.001	0.42
	Placebo	1.5 (1–2)	1 (1–2)	0.76	
Cystitis	*Aloe vera*	< 0.01 (< 0.01–< 0.01)	< 0.01 (< 0.01–1)	0.04	0.32
	Placebo	< 0.01 (< 0.01–0.75)	< 0.01 (< 0.01–1)	0.89	
RTOG total	*Aloe vera*	3 (< 0.01–4)	< 0.01 (< 0.01–1)	< 0.001	0.02
	Placebo	2 (1–4)	3 (2–3)	0.97	
QOL	*Aloe vera*	2 (< 0.01–2)	< 0.01 (< 0.01–< 0.01)	< 0.001	0.9
	Placebo	0.5 (< 0.01–2)	1 (1–2)	0.93	
CRP	*Aloe vera*	2 (1–2)	1 (1–2)	0.47	0.01
	Placebo	1 (1–1)	1.5 (1–2)	0.1	
Depression	*Aloe vera*	4 (1.25–6.5)	2 (< 0.01–4)	0.28	0.52
	Placebo	4 (2–7.5)	9 (4–11)	0.51	
Anxiety	*Aloe vera*	4.5 (2.5–6.75)	3 (2–3)	0.01	0.52
	Placebo	5 (1.75–7.75)	3 (2–6)	0.28	

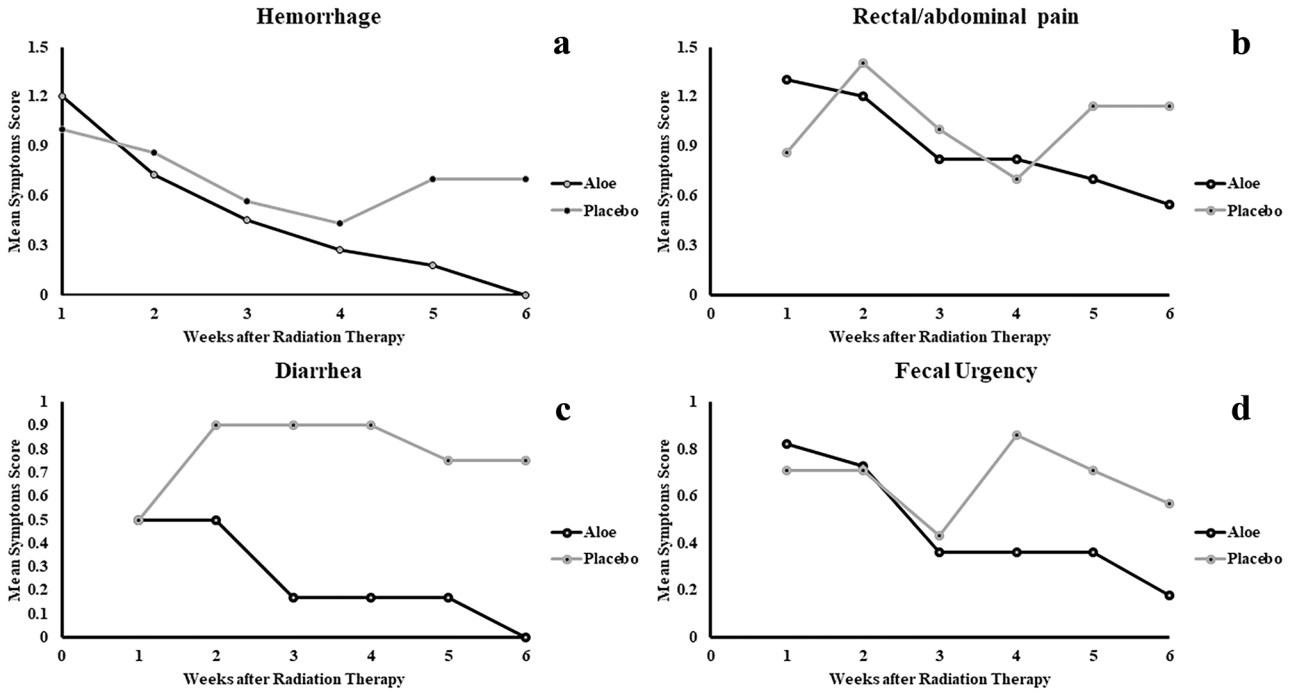

Fig. 2 The median and IQR values of the symptom scores for hemorrhage, rectal/abdominal pain, diarrhea, and fecal urgency during the 6-week course of radiation treatment

a statistically significant time trend (within-subject differences or time effect) ($p < 0.05$) in placebo ointment group. Quantitative measurement of C-reactive protein (CRP) score getting decreased, and there is a statistically significant time trend (within-subject differences or time effect) ($p < 0.05$) in *Aloe vera* ointment group (Fig. 4). Quality of life and CRP scores in *Aloe vera* group was better than placebo group, and there were statistically significant differences between groups (between-subject differences or group effect) ($p < 0.05$).

Discussion

The present study is the first randomized, double-blind, placebo-controlled clinical trial evaluating the effectiveness of topical *A. vera* 3% ointment at a dose of 1 g/twice a day in the prevention of ARP in colorectal cancer patients receiving RT. The results from this study show that *A. vera* gel is superior to the placebo in the prevention of the incidence of ARP and related symptoms in some assessment criteria.

Numerous risk factors play an important role in radiation-induced skin damage. Continuous free radical production potentiates the intracellular inflammatory response. The main mechanism of RT-induced proctitis is DNA damage and cell death which trigger the inflammatory responses following exposure to radiation [18]. Previous studies indicated that anti-inflammatory agents can decrease the severity of ARP partly through reduction of inflammation [19, 20].

Previous studies have demonstrated the healing effects of *A. vera* in radiation-induced oral mucositis possibly through free radical scavenging mechanism. It is interesting to note that radiation-induced-mucositis has a similar pathophysiology to that of ARP. In both conditions, reactive oxygen species probably have a significant influence on initiation and progression of inflammatory lesions. Although the preventive effects of *A. vera* in ARP has not been investigated earlier, our findings herein give us a clue regarding the beneficial effects of this herbal medicine [20]. Different modalities for ARP prevention, including shielding the rectum during radiation, precise dose-planning, new radiation techniques, and medical therapy (i.e., amifostine), have indicated some degrees of improvements in several clinical trials. Clinically significant results with reduction of ARP symptoms, however, have not been achieved in most studies. Thus, alternative therapeutic options for this bothersome condition are needed [14–17].

Aloe vera contains multiple antioxidant and anti-inflammatory compounds which have including superoxide dismutase and vitamins C and E [20]. Previous studies showed that *A. vera* has been widely used to

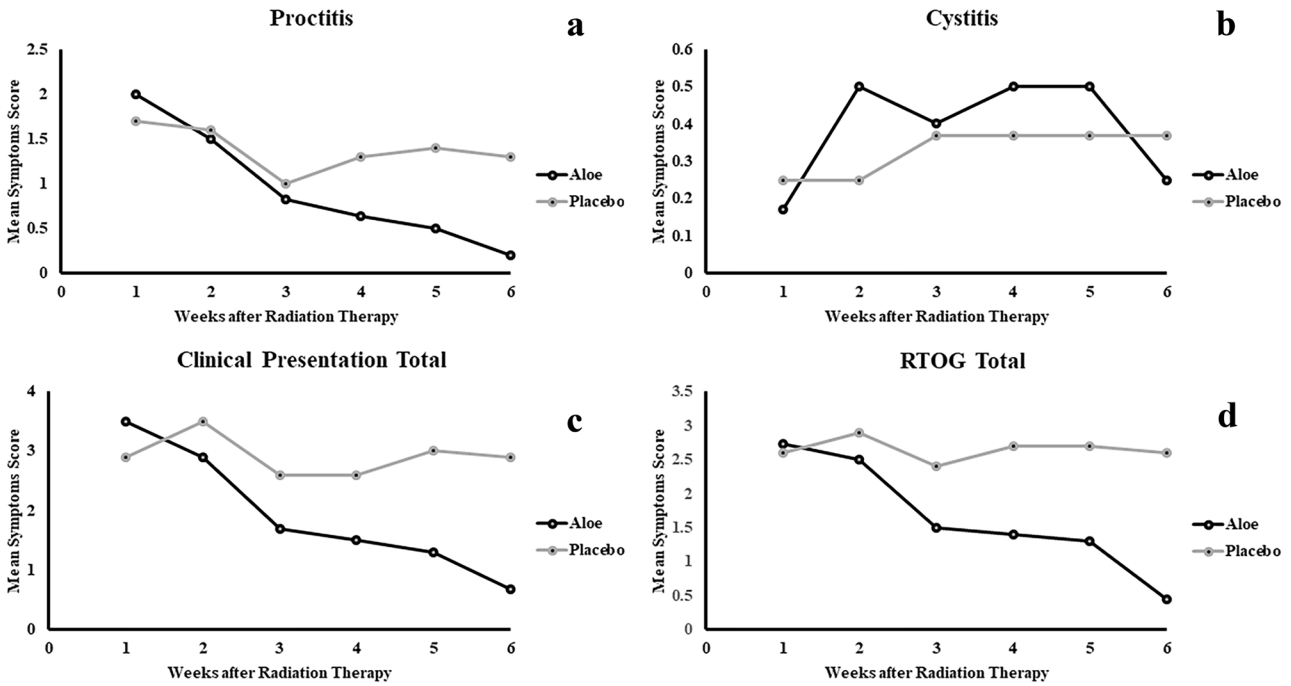

Fig. 3 The median and IQR values of the symptom scores for proctitis, cystitis, clinical presentation total, and RTOG total during the 6-week course of radiation treatment

treat various conditions such as burn wound, radiation-related dermatitis, mucositis, esophagitis, acne vulgaris, and psoriasis vulgaris [1, 21–23]. However, but studies investigating the effect of this dry and warm weather plant in ARP are not available.

Although the overall primary and secondary outcomes of the *A.* group were better than the placebo group, with exception of diarrhea, all measures of clinical presentation toxicity did not achieve a statistically significant difference with *Aloe vera* ointment, when compared with the placebo arm. Results from this study have extended the findings of earlier researches and indicated that *Aloe vera* was at least beneficial in alleviating the bothersome symptoms of radiation-induced damages [24]. *Aloe vera* has shown promising effects in prevention of radiation-induced dermatitis in breast cancer patients receiving RT, through its anti-inflammatory and anti-oxidant properties, likewise to the results observed in the present study [25].

Quantitative-CRP is a non-specific, highly sensitive, acute-phase reactant because of the pronounced rise in concentration after tissue injury or inflammation [26]. DNA damage in ARP can increase inflammatory responses

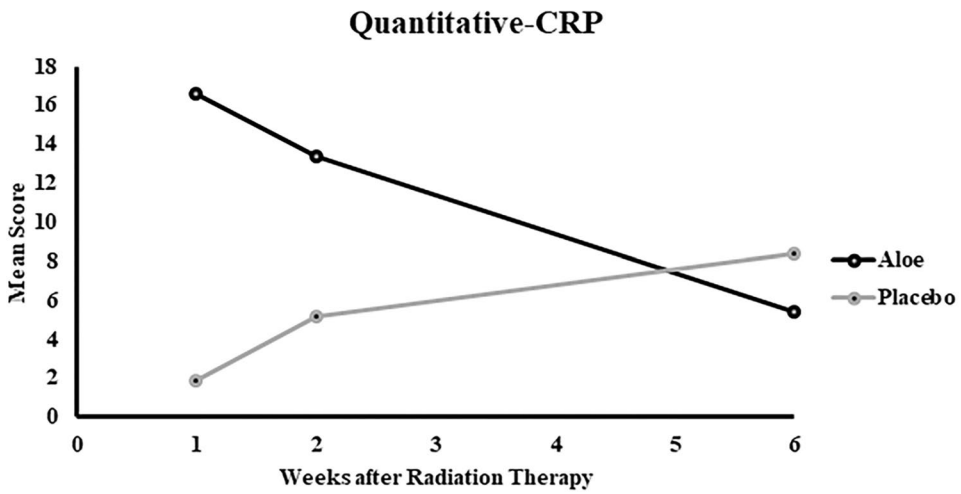

Fig. 4 Quantitative measurement of C-reactive protein (CRP) score and a statistically significant time trend in *Aloe vera* ointment group

and rise in CRP levels. In this study, quantitative CRP was measured during the course of RT, as a reflection of systemic inflammation. As the results of the present study illustrated, CRP serum levels had a descending trend after the treatment with *Aloe vera*, which was significantly lower in in comparison to the placebo group (Fig. 4).

Study Limitations

The main limitation is the small sample size. It should be pointed out that until now, the efficacy of *Aloe vera* in ARP prevention in rectal cancer has not been evaluated. Thus, this primary evaluation is the first trial of *Aloe vera* to gain an insight for future studies. Another limitation was the lack of measurement of chemical constituents of *Aloe vera* extract that possess antioxidant and anti-inflammatory effects. Although endoscopic evaluation of the rectosigmoid would be advantageous for response assessment, it has yielded inconsistent descriptions of the character of inflammation. Focal erythema, friability, and mechanical damage are commonly noted. This is the first preliminary clinical trial of treatment with *Aloe vera* and seeks further studies.

Conclusion

There is limited evidence on whether topical *Aloe vera* is effective in preventing radiation-induced proctitis in colorectal cancer patients. Further sufficiently powered research studies should be conducted to evaluate the effectiveness of currently used and novel therapies for the prevention, minimization, and management of radiation-induced skin reactions.

Author Contribution AS: collecting data, drafting the manuscript and submission. FS: Drafting manuscript, submission guidance. AGH: head of treatment team, the physician providing clinical visit, supervising on data records, and consulting on the incidence of acute-radiation proctitis. JA: Formulation of *Aloe vera* and placebo ointment, GMP quality control tests. AA: analysis and interpreting data. SH: English editing, interpreting data. MS: Conception and design of the study, submission guidance. HRG: design of the study. ES: the principal investigator and manager of the study, design and conduction the study.

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Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

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