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Comparison of prophylactic topical application of *Cryptomphalus aspersa* secretion versus betamethasone for telecobalt radiation-induced skin reactions in locally advanced head and neck carcinoma patients

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ABSTRACT

Background: External beam radiation therapy (EBRT) with or without concurrent chemotherapy is practiced as backbone of treatment across sites and subsites of head and neck cancer (HNC) when the intent is definitive. Radiation-induced acute skin reaction is of major concern during and after definitive course of radiotherapy. Prevention and treatment of these reactions play an important role in the completion of the prescribed course of EBRT within stipulated time period while maintaining the quality of life. **Aims and Objectives:** The aim of the study was to compare results of topical *Cryptomphalus aspersa* secretion versus betamethasone cream for radiation-induced acute skin reactions in locally advanced head and neck carcinoma patients undergoing definitive irradiation from telecobalt and concurrent chemotherapy. **Materials and Methods:** A prospective randomized study was conducted to compare the topical application of *C. aspersa* secretion 4% cream (Study Group) versus betamethasone 0.1% ointment (Control Group) for the management of radiation-induced skin reactions in locally advanced head and neck carcinoma treated with concomitant chemoradiation. Thirty patients in each of the two groups were treated with radical EBRT 66 Gy/33 fractions/6.5 weeks (5 fractions/week) concomitant with Cisplatin 100 mg/m^2 every 3 weeks. **Results:** Grade 3 skin reactions were observed in 11 (36.67%) and 12 (40%) patients in the Control Group at the 6th week and at completion of treatment, respectively. There were no Grade 3 skin reactions in the Study Group. The difference in the development of skin reactions observed was statistically significant at 6th week, at completion of treatment as well as at the 1st month of follow-up (grade-1) between the two groups ($P<0.001$). **Conclusion:** Prophylactic application of topical *C. aspersa* secretion delays the emergence of skin reactions of HNC patients during telecobalt radiation treatment, prevents appearance of Grade 3 or higher skin reactions, and also repairs them faster as compared to betamethasone topical preparation.

Key words: Grade 3 acute skin toxicity; Head and neck cancer; Telecobalt; External beam radiation therapy; Acute radiodermatitis; Treatment; Prevention; Betamethasone; *Cryptomphalus aspersa* secretion

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INTRODUCTION

Head and neck carcinoma encompasses malignancies arising from lips anteriorly to thoracic inlet inferiorly, comprising oral cavity, oropharynx, hypopharynx, nasopharynx, larynx, and less commonly salivary glands, nose, and paranasal sinuses. Globally, the incidence of head and neck cancers (HNCs) when all these subsites

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are added together comes as the 6th most common cancer, and in India, they make the highest number of cases as per Global Cancer Observatory 2022 data.[1] More than 90% of head and neck carcinoma are squamous cell carcinoma, the other uncommon types include lymphoma, adenoid cystic carcinoma, and melanoma. Not only smoking but also tobacco chewing is associated with an increased risk of the commonly seen HNC, especially in the Indian context. The relationship between Human Papillomavirus and some HNC is increasingly recognized.[2]

Radiation-induced acute skin reactions

Despite improved imaging modalities and integration of them with newer radiation therapy techniques to minimize the damage to healthy cells, patients still develop several complications. One of the most important side effects is radiodermatitis (RD), a cutaneous reaction to the inflicted cellular injury caused by therapeutic ionizing radiation. Radiation-induced skin injuries are deterministic in nature, which implies that they occur once the deposited skin dose has exceeded the threshold level of radiation tolerance. The severity and progression of the skin reactions vary widely between patients depending on both treatment-related and patient-related risk factors. RD can occur as an acute (early) effect, developing within the first few hours to weeks after radiation exposure, or as a late effect (chronic), occurring months or years after the intervention. Radiation-induced skin reactions are most common in patients treated for breast, head and neck, anal, and vulva cancer. This higher incidence is due to the fact that irradiation target into these anatomical regions are closer to the skin and therefore the overlying skin receives a high radiation therapy dose. The radiation-induced skin reactions are graded as per guidelines laid down by the radiation therapy oncology group (RTOG) system.[3]

- Grade-0 skin reactions are characterized by no change over baseline.
- Grade-1 skin reactions start as red rash, dry desquamation, decreased sweating, skin atrophy, pigmentation change, and some hair loss.
- Grade-2 skin reactions are characterized by a bright erythema, patchy moist desquamation, moderate edema, patchy atrophy, moderate telangiectasia, and total hair loss.
- Grade-3 skin reactions are characterized by confluent, moist desquamation other skin fold, pitting edema, marked atrophy, and gross telangiectasia.
- Grade-4 skin reactions are characterized by ulceration, hemorrhage, and necrosis. Management of radiation-induced acute skin reactions.

RD depending on severity may be distressing and painful for the patients, which in turn affect their general well-being as well as delivery of tumoricidal radiation dose. Therefore, adequate management of RD is a necessary component of a radiation delivery program to improve the patient's quality of life. Prevention and treatment of radiation-induced skin reactions comprises:[4] (1) Gentian violet dressing which can significantly reduce RD. (2) Steroidal topical application of betamethasone, and mometasone. More recent trials show more consistent results in favor of reduced acute RD with the use of topical corticosteroids. In double-blinded randomized study of 49 patients with topical mometasone, a potent corticosteroid cream can significantly reduce acute radiodermatitis as compared to emollient. (3) Oral systemic therapies-proteolytic enzymes containing papain, trypsin, or chymotrypsin. However, one small unblinded trial of 74 participants reported that the use of oral systemic therapies was ineffective for preventing the development of radiation-induced skin reactions.[5] Usually, no cream, ointment, gel, or foam are used in radiotherapy protocols due to possible secondary effects regarding greater penetration of radiation, however, no alteration has been seen with *Cryptomphalus aspersa* secretion.

C. aspersa is a gastropod (Snail). It is secretion contains antioxidant superoxide dismutase and glutathione-s-transferase. In addition, it stimulates fibroblast proliferation and rearrangement of the actin cytoskeleton. It also stimulates extracellular matrix assembly and regulation of metalloproteinase activity. Together, these effects provide an array of molecular mechanisms underlying *C. aspersa* secretion which induces cellular regeneration and postulates its use in the regeneration of wounded tissue.[6] Betamethasone, a topical corticosteroid known for its anti-inflammatory effect, is helpful in many skin disorders including RD. Topical corticosteroids inhibit up-regulation of interleukin (IL)-6 in response to the ionizing radiation.[7]

Aims and objectives

Comparison of prophylactic topical application of cryptomphalus aspersa secretion versus betamethasone for telecobalt radiation induced skin reactions in locally advanced head and neck carcinoma patients.

MATERIALS AND METHODS

Pre-treatment evaluation

The pre-treatment evaluation in all patients included complete history, general physical examination, and systemic examination. The assessment of general condition was done using Karnofsky performance status (KPS). Hematological assessment was done by complete hemogram including hemoglobin, total leukocyte count, differential leukocyte count, platelet count, and peripheral

blood film. Biochemical assessment to assess the kidney and liver functions was done by the estimation of blood urea, serum creatinine, serum glutamic-oxaloacetic transaminase, and serum glutamic-pyruvic transaminase levels. Radiological assessment including chest X-ray, ultrasonography of the abdomen and pelvis, and contrast-enhanced computerized tomography face and neck were done in all patients. The patients were staged according to American Joint Committee on Cancer 2017 staging and end result reporting system.

Eligibility criteria

Based on the above assessment, the patients with following eligibility criteria were included in the study (Table 1).

All the patients after they had given written informed consent for the study were divided randomly in two groups of 30 patients each using internet-based computer software (website https://www.random.org/lists).[8] All patients were treated with Telecobalt (Gamma rays of average energy 1.25 Mega electron volt) to a radiation dose of 66 Gy/33 fractions/5 fractions/week over 6.5 weeks to head and neck region along with concomitant Cisplatin 100 mg/m^2 3 weekly, for three cycles. Antiemetic drugs were given and forced diuresis was maintained to prevent drug toxicity. All patients in the Study Group were given topical application of *C. aspersa* secretion (4%) cream over radiation field site, once a day starting from the 1st day of radiation therapy and continued till 3 weeks after completion of radiation therapy. Every patient in the control arm was given a topical application of betamethasone ointment (0.1% w/w) over the radiation field site, once a day starting from 1st day of radiation therapy and continued till 3 weeks after completion of radiation therapy.

Table 1: Inclusion and exclusion criteria

Inclusion	Exclusion
Histologically proven squamous cell carcinoma of head and neck region AJCC (8th Ed.) Stage III/IVA/IVB	Distant metastasis
Complete hemogram with Hb ≥10 gm/dL; TLC ≥4000/mm^3; ANC ≥2000/mm^3, Platelet count ≥100,000/mm^3	Prior radiation, surgery, or chemotherapy for the disease
Renal function tests with Blood urea <40 mg/dL and Serum creatinine <1.3 mg/dL	Pregnant or lactating patient
Liver function tests with SGOT <40 IU/L and SGPT <0 IU/L	Associated medical conditions which make the patient unsuitable for the proposed courses of radiotherapy
Karnofsky performance status (KPS) ≥70	Karnofsky performance status (KPS) <70

AJCC: American Joint Committee on Cancer 8th edition, Hb: Hemoglobin, TLC: Total leukocyte count, ANC: Absolute neutrophil count, SGOT: Serum glutamic-oxaloacetic transaminase, SGPT: Serum glutamate pyruvate transaminase

Radiotherapy technique

All the patients were treated in supine position. The patients were treated by parallel opposed fields and the dose was prescribed at the midplane of the head and neck region. The shrinking field technique was used after a dose of 45 Gy to respect the dose limit of the spinal cord. Radiotherapy was delivered by Cobalt-60 tele-therapy machine using the field generated as per requirement. Patients in both groups were delivered five fractions of radiation per week, a tumor dose of 66 Gy in 33 fractions (2 Gy per fraction) in an overall period of 6.5 weeks. There was not any difference in planning or target coverage between the two groups.

Evaluation during treatment and follow-up

All the patients were evaluated every week for radiation-induced acute skin reactions during treatment, at the completion of treatment, and monthly for 6 months during follow-up. Tumor control was assessed at the completion of treatment and monthly for 6 months during follow-up. Radiation reactions were assessed using RTOG acute and late scoring criteria.

Ethics

The study was conducted after clearance from Institutional Ethical Committee on 60 previously untreated, histopathologically proven patients of locally advanced squamous cell carcinoma of head and neck region, attending the Department of Radiation Oncology, Pt. B. D. Sharma Postgraduate Institute of Medical Sciences, Rohtak, India in accordance to declaration of Helsinki and following the norms of good clinical practices. Informed consent from all subjects for both study participation and publication of identifying information/images in online open-access medium was obtained.

RESULTS

Statistical analysis

The data, thus obtained, were used to compare results of topical *C. aspersa* secretion versus betamethasone for radiation-induced skin reactions in locally advanced head and neck carcinoma using Statistical Package for the Social Sciences version 20. The Chi-square test was used to analyze categorical variables. Student's t-test was performed for continuous variables. Level of significance was kept below 0.05.

Baseline characteristics

The patients were randomized keeping several aspects of patient and tumor characteristics in context. Patient-related factors such as age, gender, performance status, smoking status, alcohol intake, KPS, and tumor-related factors such as primary site, tumor node metastasis (TNM) stage,

tumor differentiation, and hemoglobin level were equally distributed in both arms (Table 2).

Radiation induced skin reactions observed during treatment

Radiation-induced skin reactions were observed weekly during the treatment (Table 3) and at the completion of treatment and graded as per RTOG criteria. There were no skin reactions observed during the 1st and 2nd weeks in both groups. In the 3rd week, no skin reactions were observed in the Study Group, and in the Control Group, only two (6.67%) patients had Grade 1 skin reactions. In the 4th week, only Grade 1 skin reactions were observed in 5 (16.67 %) patients in the Study Group, while in the Control Group, 11 (36.67%) had Grade 1, and 1 (3.33%) patients had Grade 2 skin reactions. In the 5th week (Figure 1), Grade 1 skin reactions were observed in twelve (53.33%) patients in Study Group and eighteen (60%) patients in Control Group. Grade 2 skin reactions

Table 2: Baseline characteristics

Factors	Study (%)	Control (%)	Statistical significance
Age			
≤50 years	6 (20)	9 (30)	0.37
>50 years	24(80)	21 (70)	
Gender			
Male (%)	29 (96.67)	28 (93.33)	1.000
Female (%)	01 (3.33)	02(6.67)	
Background			
Rural	24 (80)	27 (90)	0.472
Urban	6 (20)	3 (10)	
Smoking status			
Smoker	29 (96.67)	30 (100)	1.000
Non-smoker	01 (3.33)	00 (0)	
Alcohol intake			
Alcoholic	08 (26.67)	09 (30)	0.775
Non-alcoholic	22 (73.33)	21 (70)	
Performance status			
Karnofsky 90	20 (66.67)	17(56.67)	0.426
Karnofsky 80	10 (33.33)	13 (43.33)	
Primary site			
Oral cavity	1 (3.33)	2 (6.67)	1.000
Oropharynx	23 (76.67)	21 (70)	0.559
Hypopharynx	4 (13.33)	0 (0)	0.112
Larynx	2 (6.67)	7 (23.33)	0.146
TNM stage			
T3/T4a	16(53.3)	20(66.6)	0.81
N1	7(23.3)	9(30)	
N2	11(36.6)	10(33.3)	
Stage III	19 (63.33)	18 (60)	0.791
Stage IV	11 (36.67)	12 (40)	
Grade			
WDSCC	2 (6.67)	0	0.492
MDSCC	26 (86.67)	30 (100)	0.112
PDSCC	2 (6.67)	0	0.492
Hemoglobin			
<13 g/dL	6 (20)	4 (13.3)	0.48
≥13.0	24 (80)	26 (86.66)	

KPS: Karnofsky performance score, TNM: Tumor node metastasis, WDSCC: Well differentiated squamous cell carcinoma, MDSCC: Moderately differentiated squamous cell carcinoma, PDSCC: Poorly differentiated squamous cell carcinoma

Table 3: Radiation-induced skin reactions observed during treatment (RTOG criteria) in 60 patients of head and neck carcinoma RTOG-radiotherapy oncology group

Timeline	Study group (n=30) number of patients (%)					Control group (n=30) number of patients (%)					P-value
	Grade 0 (%)	Grade1	Grade 2 (%)	Grade 3	Grade 4	Grade 0 (%)	Grade 1 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4	
1st week	30 (100)	0	0	0	0	30 (100)	0	0	0	0	
2nd week	30 (100)	0	0	0	0	30 (100)	0	0	0	0	
3rd week	30 (100)	0	0	0	0	28 (93.33)	2 (6.66)	0	0	0	0.492
4th week	25 (83.3)	5 (16.65)	0	0	0	18 (60)	11 (36.63)	1 (3.33)	1 (3.33)	0	0.111
5th week	16 (53.3)	12 (40)	2 (6.67)	0	0	1 (3.33)	18 (60)	11 (36.63)	0	0	<0.001
6th week	0	19 (63.3)	11 (36.63)	0	0	0	5 (16.65)	14 (46.62)	11 (36.63)	0	<0.001
At completion	0	19 (63.3)	11 (36.63)	0	0	0	4 (13.32)	14 (46.62)	12 (40)	0	<0.001

were observed in 2 (6.67%) patients in Study Group and 11 (36.67%) patients (Figure 2) in Control Group. In the 6th week (Figure 1), Grade 1 skin reactions were observed in 19 (63.33%) patients in the Study Group (Figure 2) and 5 (16.67%) patients in the Control Group. Grade 2 skin reactions were observed in 11 (36.67%) patients in Study Group and 14 (46.67%) patients in Control Group. At the completion of treatment (Figure 1), Grade 1 skin reactions were observed in 19 (63.33%) patients in Study Group and 4 (13.33%) patients in Control Group. Grade 2 skin reactions were observed in 11 (36.67%) patients in Study Group and 14 (46.67%) patients in Control Group. Grade 3 skin reactions (Figure 2) were only observed in 11 (36.67%) and 12 (40%) patients in the Control Group at the 6th week and at completion of treatment, respectively. There were no Grade 3 skin reactions in the Study Group. Grade 4 skin reactions were not observed in any of the groups.

Radiation induced skin reactions during follow-up

Radiation-induced skin reactions were observed monthly for 6 months during follow-up and graded as per RTOG criteria. The radiation-induced skin reactions persisted in the Control Group during the 1st month of follow-up. There was no persistence of skin reactions in the Study Group. In the 1st month of follow-up (Figure 3), Grade 1 skin reactions were observed in 14 (46.67%) patients in the Control Group (Figure 2). The difference in distribution was statistically significant at the 1st month of follow-up between these two groups (P≤0.001). There were no skin reactions observed beyond the 1st month of follow-up in both groups.

The radiation-induced skin reactions were more severe in Control Group as compared to Study Group and also early to appear. The difference in the development of skin reactions observed was statistically significant at 5th week, 6th week, and at the completion of treatment between these two groups with P<0.001.

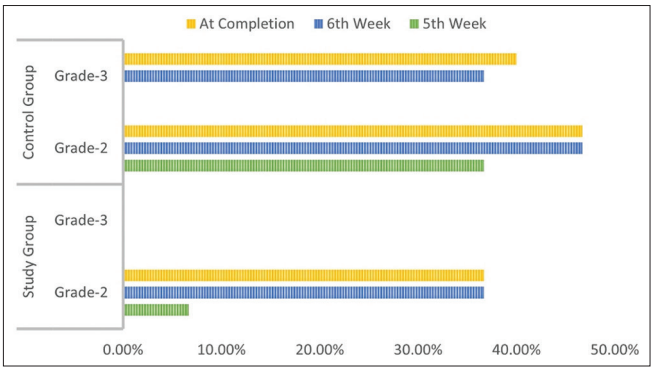

Figure 1: Radiation-induced skin reactions observed during treatment (radiotherapy oncology group criteria) in 60 patients of head and neck carcinoma

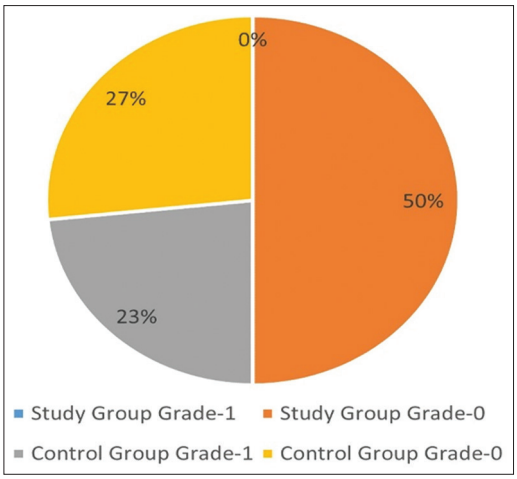

Figure 2: Radiation-induced skin reactions observed during 1st month of follow-up (radiotherapy oncology group criteria) in 60 patients of head and neck carcinoma radiotherapy oncology group

DISCUSSION

Literature suggests that the most frequently seen side effect of radiation therapy in patients with HNC is radiation dermatitis that occurs in approximately 90–95% of patients.[9,10] Majumder et al., observed Grade 3 skin reactions in 30% of patients with HNC treated with concomitant chemoradiation. Radiotherapy is an essential modality of management for definitive as well as palliative HNC due to the complex and close proximity of vital structures to tumor in this region.[11] Inflammatory response and oxidative stress are chiefly implicated in precipitating radiation-induced dermatitis both of which interact to complement and promote each other.[12,13] Many patients related intrinsic cues and treatment-related extrinsic factors influence the appearance and severity of RD. Increased age

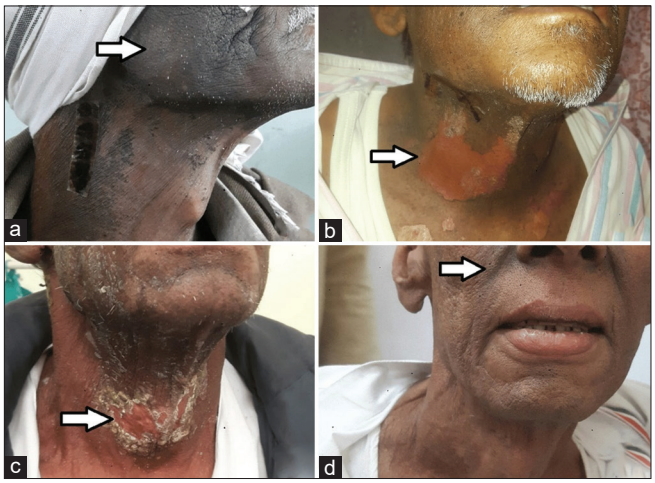

Figure 3: Radiation-induced acute skin reactions. (a) Grade 1 skin reaction (white solid arrow) study group at 6th week, (b) Grade 2 skin reactions (white solid arrow) 4th week control group, (c) Grade 3 skin reaction (white solid arrow) control group at 6th week, (d) Grade 1 skin reaction (white solid arrow) 1st month of follow-up control group

and higher TNM stage have been found to be related to occurrence of higher acute RD whereas association with gender, irradiated surface area, history of smoking, and diabetes have been dubious.[14] Presence of genetic defects such as mutation in ataxia telangiectasia gene especially increases sensitivity to ionizing radiation with predisposition to higher grades of RD. Among the extrinsic factors, total radiation dose, fractionation schedules, absorbed dose over a certain period of time (e.g. weekly accumulated dose), and volume of irradiated tissue are implicated in producing radiation-induced skin reactions.[15] Ionizing radiation when interacts with biological tissue incites inflammation through proinflammatory cytokines such as ILs (IL-1, IL-3, IL-5, IL-6, and tumor necrosis factor -a), chemokines (eotaxin and IL-8), receptor tyrosine kinase, and adhesions molecules (intercellular adhesion molecule 1, E-selectin, and vascular cell adhesion protein). These factors create an inflammatory response of eosinophils and neutrophils locally, leading to self-perpetuating tissue damage and hence radiation-induced dermatitis. Radiation-induced cell damage when not repaired leads to mitotic death and further propagates oxidative stress. Persistence of inflammation and oxidative stress leads to retarded healing and chronic radiation-induced skin toxicity. Acute RD not only affects the patient's quality of life during treatment but also threatens the continuity and compliance of treatment when the toxicity is of a higher grade. Interruption in treatment (due to pain, discomfort, esthetic changes in skin) predisposes the patient to an increased chance of treatment failure.

The present study has been carried out on sixty patients of locally advanced (Stage III and Stage IV), histologically proven squamous cell carcinoma of the head and neck region. A prospective randomized study was conducted to compare topical application of *C. aspersa* secretion 4% cream (Study Group) versus betamethasone 0.1% ointment (Control Group) for management of radiation-induced skin reactions in locally advanced head and neck carcinoma treated with concomitant chemoradiation. Thirty patients were assigned to each of the two groups keeping in view equivalent distribution of patient, tumor, and treatment-related factors. Patients in both groups were treated with radical EBRT 66 Gy/33 fractions/6.5 weeks (5 fractions/week) concomitant with Cisplatin 100 mg/m^2 every 3 weeks. All patients were observed for radiation-induced skin reactions weekly during treatment and monthly thereafter for 6 months after completion of treatment.

The present study showed that radiation-induced skin reactions were more severe in the Control Group as compared to Study Group and also earlier to appear. Early onset of Grade 1 and Grade 2 reactions were more pronounced in the Control Group as compared to the Study Group. Grade 3 skin reactions were only observed in 11 (36.67%) and 12 (40%) patients in the Control Group at the 6th week and at completion of treatment respectively. There were no Grade 3 skin reactions in the Study Group. Grade 4 skin reactions were not observed in any of the groups. The difference in the development of skin reactions observed was statistically significant at 5th week, 6th week, and at completion of treatment between these two groups with P<0.001. Grade 1 skin reactions were observed in fourteen (46.67%) patients in the Control Group at the 1st month of follow-up. There were no skin reactions observed in the Study Group at the 1st month of follow-up. The difference in persistence of skin reactions was statistically significant at the 1st month of follow-up between these two groups with P<0.001. *C. aspersa* is a gastropod (Snail). It has been noted that snails perceive radiation, retract their orientation organs, and secrete large amounts of mucus substance and defensive response to protect themselves from harmful radiation. In addition,[6] the fact that snails never suffer from skin infection directed attention to explore the possibility of its secretion's use for skin-compromising disease. The secretion of *C. aspersa* is an alternative therapy for many patients diagnosed with malignant tumors which require radiotherapy, especially with good results in breast and neck RD. *C. aspersa* secretion has collagenase activity against Type 4 collagen which would facilitate remodeling of the basal membrane of skin (as the denatured collagen is more susceptible to collagenase action).[15] It also stimulates activity of fibroblast proliferation and would facilitate the presence of biochemical machinery that reconstitutes the skin. Ledo et al., studied treatment of acute RD with *C. aspersa* secretion. In the group treated with *C. aspersa* secretion, a statistically significant clinical improvement in erythema, itching, and burning pain was noted both at the 1st week and 1 month after starting treatment. These results opened a new way in the future treatment of acute RD.[16] Recently, due to its glutathione-s-transferase and superoxide-dismutase, antioxidant property of this substance has been identified. Addor studied topical effect of *C. aspersa* secretion associated with regenerative and antioxidant ingredients on aged skin.[17] Espeli et al., observed ≥Grade-3 skin toxicity in 37% of the patients, with concomitant chemo-radiation using 3 weekly cisplatin in patients with HNC.[18] Evaluation of patients reporting with itching, burning and irritation in the treated skin field at the end of radiation therapy shows strong effect of the potent local corticosteroid for amelioration of the subjective symptoms.[19] This effect was consistent, in both the conventional radiotherapy and hypofractionated radiotherapy group.

Limitations of the study

Acute RD arising from treatment using medical linear accelerator (LINAC) is lesser as compared to that using telecobalt. Wider availability of medical linear accelerator at present times has pushed usage of telecobalt to backseat. Higher energy of X-rays produced from LINAC has better skin-sparing penetrative property as compared to gamma rays of lesser energy from telecobalt. Trial with higher number of subjects could certainly have added more values to the findings. Furthermore, if a third arm of patients who did not receive prophylactic drugs could have been arranged then a wider comparison could have happened.

CONCLUSION

Prophylactic application of topical *C. aspersa* secretion slows down the emergence of skin reactions of HNC patients during telecobalt radiation treatment, prevents appearance of Grade 3 or higher acute RD, and also repairs the cutaneous reactions faster as compared to betamethasone topical preparation.

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