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ORIGINAL ARTICLE

Protective Effect of *Punica granatum* Extract in Head and Neck Cancer Patients Undergoing Radiotherapy

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Abstract In India, head and neck cancers account for 30–40% cancers of all sites. Due to lack of screening program, wide variation in the availability of infrastructures and expertise, patients present at an advanced stage. The main stay of management of the head and neck tumours is surgery and chemoradiation. Radiation dermatitis and mucositis is one of the most common side effect encountered during the radiotherapy. Aim of our study was to study protective role of pomegranate extract on radiation induced dermatitis and mucositis in head and neck cancer patients. It was a prospective, clinical, double blind, case control study. 60 patients (30 active and controls) undergoing radiotherapy for head and neck cancer were studied for 12 months. Patients in study group were given whole fruit pomegranate extract. Each capsule contained 300 mg of whole fruit extract, each capsule contains 40% polyphenols and 27% punicalagin. Each patient were given 2 capsules every day for a period of 6–7 weeks. The skin and mucosal changes was graded according to the acute radiation morbidity scoring criteria (RTOG) for skin and mucous membrane. The results were statistically significant. Pomegranate extract proved to be radioprotective. Our study is one of the first study in humans to demonstrate the effectiveness of pomegranate extract in preventing radiation dermatitis and mucositis.

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Introduction

In India, head and neck cancers account for 30–40% cancers of all sites. Due to lack of screening program, wide variation in the availability of infrastructures and expertise, patients with head and neck cancer present at an advanced stage. The main stay of management of the head and neck tumours is surgery and chemoradiation. Radiation dermatitis and mucositis is one of the most common side effect encountered during the radiotherapy causing increased morbidity to the patient. Various in vitro studies have shown that pomegranate extracts are rich in anti oxidants particularly phenolic compounds.

Aim of the Study

To study the protective role of pomegranate juice in these radiation induced skin and mucosal changes.

Methodology

60 Inpatients undergoing chemoradiotherapy for head and neck cancer admitted at a tertiary hospital from June 2015 to June 2016, were randomised to two groups, study group and control group respectively (30 cases and 30 controls) who fulfilled the following criteria.

Patients suffering from other skin diseases, having food allergy were excluded from the study.

Table 1 Acute Radiation Scoring criteria

	(0)	(1)	(2)	(3)	(4)
Skin	No change over baseline	Follicular, faint or dull erythema/epilation/ decreased sweating	Tender or bright erythema, patchy moist desquamation/moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, haemorrhage, necrosis
Mucous membrane	No change over baseline	Injection, may experience mild pain not requiring analgesic	Patchy mucositis which may produce an inflammatory serosnaguinitis discharge/may experience moderate gain requiring analgesia	Confluent fibrosis mucositis/may include Severe pain requiring narcotic	Ulceration, haemorrhage, necrosis

All cases were subjected to complete history taking including risk factors, demographic data, clinical and treatment details were documented using a standardized proforma. Hematological examination.

Hb, TC, DC, ESR, RBS, LFT, RFT, electrolytes, the investigations were done at 0, 3 and 6 weeks

1. The study group was given whole fruit pomegranate extract, obtained from M/s Pharmanza (India) Ltd. Each capsule contained 300 mg of whole fruit extract, each capsule contains 40% polyphenols and 27% punicalagin. Each patient were be given 2 capsules every day for a period of 6–7 weeks. Human dose was determined based on the dosage used in mice studies done at our centre previously.
2. The skin and mucosal changes were graded according to the acute radiation morbidity scoring criteria (RTOG) for skin and mucous membrane.

All patients were closely observed at regular intervals for the skin and mucosal changes during their course of chemoradiotherapy/radiotherapy for 6–7 weeks.

Results

During the period of 1 year study, among the 60 inpatients who participated, 30 were randomly selected as study group and were given *Punica granatum* (pomegranate) extract tablets and 30 inpatients were included in the control group. Both groups had patients with similar age, built, nourishment, risk factors.

The average age in the study group was 47 years while that in the control group was 45 years.

Avearage BMI of the study group was 20.2 whereas that of the control group was 21.

Both the groups included patients of squamous cell carcinomas of larynx, oral cavity, pharynx.

Blood investigations were repeated at every weekend and all patients were carefully watched and evaluated.

Table 2 Distribution of study population based on the site involved

	Larynx	Oral cavity	Pharynx
Study group	7	15	8
Control group	8	17	5

Table 3 Results at 6 weeks of radiotherapy

Grade	Study group	Control group
Mucositis ($\chi^2 = 34.57$, $p < 0.0001$)		
0	01	00
1	11	0
2	15	05
3	03	20
4	00	05
Dermatitis ($\chi^2 = 33.71$, $p < 0.0001$)		
0	00	00
1	12	00
2	12	02
3	05	19
4	01	09

Mucositis and dermatitis were observed for 6 weeks in the study group and control group and graded at the end of every week in co ordination with the radiation oncologists.

The table below shows the results at the end of 6 weeks (Tables 1, 2, 3).

Results were determined using Chi square test and the comparative study was found to be statistically highly significant ($p < 0.0001$).

Majority of the patients in the study group had grade 1 and grade 2 mucositis, whereas grade 3 mucositis was observed in majority of the patients in control group.

Grade 1, 2 dermatitis was observed in 80% of the patients in the study group whereas grade 3, 4 dermatitis was observed in more than 90%.

Discussion

The overall objective of this study was to determine the radioprotective effect on head and neck cancer patients. p value was < 0.05, for both dermatitis and mucositis. It has shown to have a protective role. This study was carried out on humans with th basis of our previous study on swiss albino mice [1].

Bhandary et al. [1] did a study on ameliorative activity of *P. granatum* extracts and ellagic acid against radiation induced biochemical changes in swiss albino mice, which suggested that *P. granatum* ethanolic extracts and synthetic ellagic acid has a worthy protective efficacy against the damaging effects of electron beam radiation on hepatic antioxidants and antioxidative enzymes. They also concluded that the ameliorative activity of the extracts and synthetic compound against the radiation induced biochemical alterations in mice may be due to their free radical scavenging properties and their ability to induce antioxidant enzymes.

Pacheco-Palencia et al. [2] studied, protective effects of standardized pomegranate (*P. granatum* L.) polyphenolic extract in ultraviolet-irradiated human skin fibroblasts and the study demonstrated the protective effects of PE against UVA- and UVB-induced cell damage and the potential use of pomegranate polyphenolics in topical applications.

Dai et al. [3] These data suggest that PE, which is a proven and safe dietary supplement, has promise as an treatment against breast cancer by preventing proliferation of cancer stem cells.

Conclusion

Our study has proved that pomegranate extract has a role in preventing the severity of radiation induced mucositis and dermatitis.

No human studies have been carried in this regard due to the high price of the fruit and lack of awareness among public regarding the beneficial effects of pomegranate and its role as an anti oxidant.

The study will help us

1. To create awareness about the beneficial effect of pomegranate extract in preventing the radiation dermatitis and mucositis.
2. To identify the radioprotective phytochemicals in pomegranate and prepare a cost effective pharmaceutical product.

This study is a platform for future studies in this regard.

Compliance with Ethical Standards

Conflict of interest Amulya Manohar Thotambailu and B. Satheesh Kumar Bhandary declares that they have no conflict of interest.

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