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RESEARCH ARTICLE
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# "A COMPARATIVE STUDY OF EFFICACY AND SAFETY OF TOPICAL CURCUMIN VERSUS 1% POVIDONE IODINE IN RADIOTHERAPY INDUCED ORAL MUCOSITIS PATIENTS WITH HEAD AND NECK CANCER AT A TERTIARY CARE HOSPITAL"

**Dr Gandham Ravi[1], Dr Vishnu K[2], Dr Kiran Warrier[3], Dr Shruti Ayyappanavar[4*]**

[1]Assistant Professor, Department of Pharmacology, NSMCH, Amhara, Bihta, Patna
[2]Assistant Professor, Department of Pharmacology, Shri Atal Bihari Vajpayee Medical college & Research Institute, Bangalore, Karnataka, India
[3]Medical advisor, Novo Nordisk India Pvt Ltd Bengaluru, Karnataka, India
[4*]Senior resident, Department of Pharmacology, ESIC-MC PGIMSR, Bangalore, Karnataka, India. Shriram sameeksha, 17th tower 401,Gangamma gudi police station road, Kuvempu nagar,East Jalahalli, 560013 Email: shrutiayyappanavar80@gmail.com, Contact No: 7019898101

***Corresponding Author**: Dr Shruti Ayyappanavar
*Senior resident, Department of Pharmacology, ESIC-MC PGIMSR, Bangalore, Karnataka, India. Shriram sameeksha, 17th tower 401,Gangamma gudi police station road, Kuvempu nagar,East Jalahalli, 560013 Email: shrutiayyappanavar80@gmail.com, Contact No: 7019898101

**Abstract**

**BACKGROUND**: Radiotherapy has been the most common modality for treating human cancers needed by 80% of cancer patients at some time or other, either for curative or palliative purposes. Damage to cells by radiotherapy is potentiated or mitigated by depending on several factors. Oral mucositis is a common complication and a dose limiting toxicity in up to 90% of head & neck cancer patients (HNCP) undergoing radio-chemotherapy. Several adjuvant agents like folic acid, Vit-E, antibiotic mouth rinse etc. have been tried without remarkable success. Curcumin is known to have antioxidant and free radical scavenging activity that had shown its radio protective potential in in vitro studies. The study objective is to evaluate the efficacy and safety of Curcumin versus Povidone Iodine among radiotherapy induced oral mucositis in head & neck cancer patients

**METHODS:** 60 patients with radiotherapy induced mucositis were equaly randomized into two groups of 30 each to receive either 10 ml Curcumin mouthwash TID or 1:100 diluted 1ml Povidone Iodine solution mouthwash TID for 12 weeks. Efficacy was measured by reduction in pain Numerical Rating score (NRS) and Radiation Therapy Oncology Group (RTOG) score at week 4, 8 and 12 from baseline. Safety was assessed by monitoring treatment emergent adverse effects. Data analysed by using repeated measure ANOVA test with repeated measure analysis and with Bonferroni corrections.

**RESULTS:** The baseline mean NRS ( $p = 0.90$) and RTOG score ( $p = 0.7$) score was comparable between the two groups. The mean NRS and RTOG score was 5.2 (2.75) and 2.9 (0.78) in Curcumin group, 5.5 (2.47) and 2.4 (0.85) in Povidone Iodine group. The mean NRS and RTOG score after 12 weeks of treatment was 0.6 (0.75) and 1.1 (0.30) in Curcumin group and 1.9 (0.80) and 1.5 (0.57) in

Povidone Iodine group. Curcumin and Povidone Iodine both groups effectively reduced NRS and RTOG score compared to baseline at the end of 12 weeks. No significant adverse effects were noted. **CONCLUSION:** Turmeric extract, Curcumin mouth wash significantly reduced NRS and RTOG score as compared to 1% Povidone Iodine with no significant adverse effects and thus can be favourable therapeutic option in patients with radiotherapy induced oral mucositis.

**KEY WORDS:** Radiotherapy ; oral mucositis ; Curcumin ; Povidone Iodine; Turmeric extract

**Introduction:** Oral mucosal inflammation is one of the most common and most troublesome complications of the cancer radio-chemotherapy among the patients undergoing radiotherapy for various cancers especially of head and neck[1]. Derangement of the function and integrity of the oral mucosa not only leads to poor quality of life but also causes prolongation of recovery. Currently available treatment options for this radiation induced adverse effect have their own drawbacks such as need for multiple interventions, no possibility for objective evaluation of efficacy etc[2].
For many years, Turmeric, Curcumin extract has been used for its antioxidant property, for topical application to prevent infections, ability to inhibit bacterial growth, acting aginst inflammation, ability to modulate immune system, pain relieving property[3]. It also has shown to have therapeutic benefits in clinical oncology such as chemo preventive, antitumoral, chemosensitizing and radio sensitizing properties against various cancers and the complications associated with their management[4].
In this study we have evaluated the safety and efficacy of topical curcumin and comapared the results with the 1% Povidone Iodine in preventing and alleviating the signs and symptoms of rqadiation induced oral mucositis among the individuals sufffering from and neck cancer.

**Materials and Methods:**
It was a Randomized, single blinded, Prospective, Comparative Study conducted in the Radiotherapy department at a tertiary care centre, Bengaluru after getting the approval of the Institutional Ethics Committee. Radiotherapy induced oral mucositis was diagnosed by the clinical evaluation .Research participants age group was ranging between 18 and 80 years of both male and female, diagnosed with head and neck cancer needing radiotherapy either before surgery or after surgery . [Table I] Patients who were already using prophylactic or therapeutic mouthwashes, those who were not able to tolerate curcumin mouth wash, those who previously were treated with radiotherapy or chemoradiotherapy for head and neck cancer, pregnant ladies, planning to become pregnant, breast feeding mothers and those who are using any other topical or oral preparations for mucositis were excluded.

**Table I Pain severity : Numerical Rating Scale[5]**

| Pain score | Grading |
|---|---|
| 0 | No pain |
| 1-3 | Mild |
| 4-6 | Moderate |
| 7-9 | Severe |
| 10 | Worst pain imaginable |

**Table II Oral mucosal changes due to the radiation were grouped according to the Radiation Therapy Oncology Group (RTOG) Scale5 as follows-**

| Grade | Description |
|---|---|
| 1 | Asymptomatic or mild symptoms; Interventions not needed |
| 2 | Moderate pain or ulcer that does not interfere with oral intake; Modified diet indicated |
| 3 | Severe pain; Interfering with oral intake |
| 4 | Life threatening consequences; Urgent interventions indicated |
| 5 | Death |

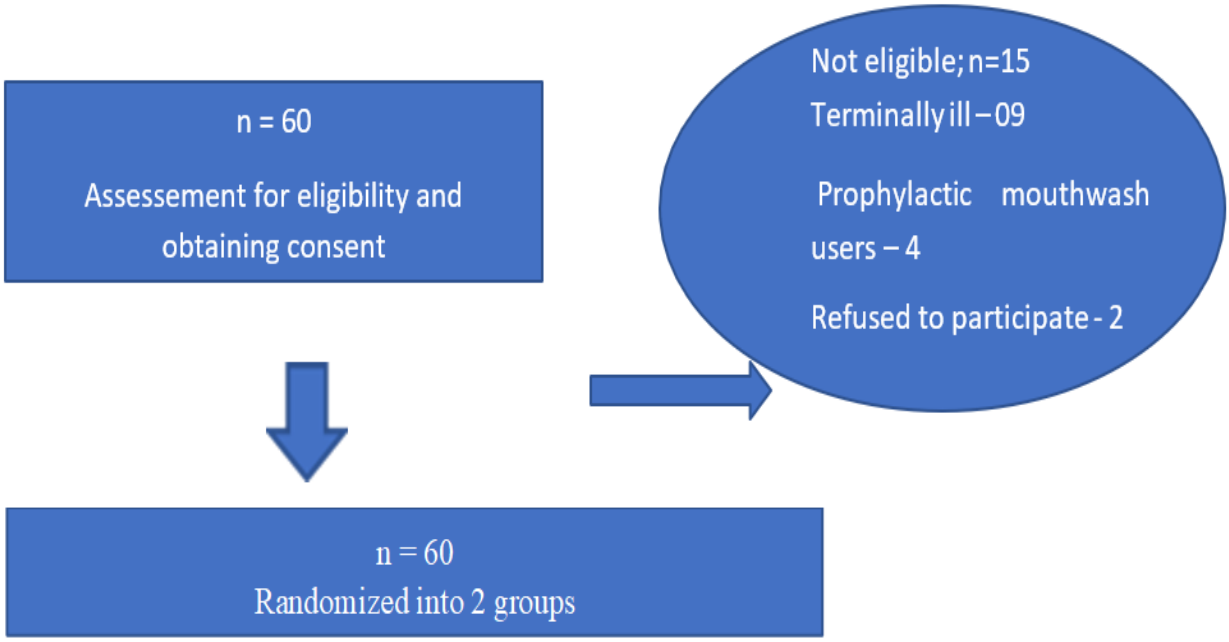
Total of sixty patients with radiotherapy induced mucositis were equably randomized into two groups. Randomization was carried out through the computer-generated random number method. One group was given the curcumin and the other was given Povidine Iodine solution.

Group I : 10 ml Curcumin mouthwash TID
Group II : 1:100 diluted 1ml Povidone Iodine solution mouthwash TID

Patients baseline characteristics, details of the presenting complaints, medications using for the current illness, details of local examination for the oral mucosal changes were recorded at the first visit.( Table III )Patients were followed-up at 4th week, 8th week and 12th week after the administration of the test and control drugs. During each visit, the details of the oral examination, pain scores, severity of the mucositis, concomitant drugs and the details of any untoward medical occurrences due to the interventions were recorded. Adherence to the treatment was evaluated by using the compliance card.

**Statistical analysis:**
Data were managed and analysed using the microsoft excel and the SPSS software 26.0. Quantitative variables were expressed using the mean ± SD and the categorical variables as percentages. Comparison of the pain scores was done using the ANOVA test with repeated measure analysis and with Bonferroni corrections. P value of less than 0.05 was considered as significant

**Results:**
Seventy five patients were screened for the study, 60 patients with mild, moderate radiotherapy induced oral mucositis, who met inclusion and exclusion criteria were enrolled in the study. The flow chart of recruitment, randomization and follow up is depicted in figure I. Age, gender and NRS and RTOG grading scores were matched at baseline (Table III).



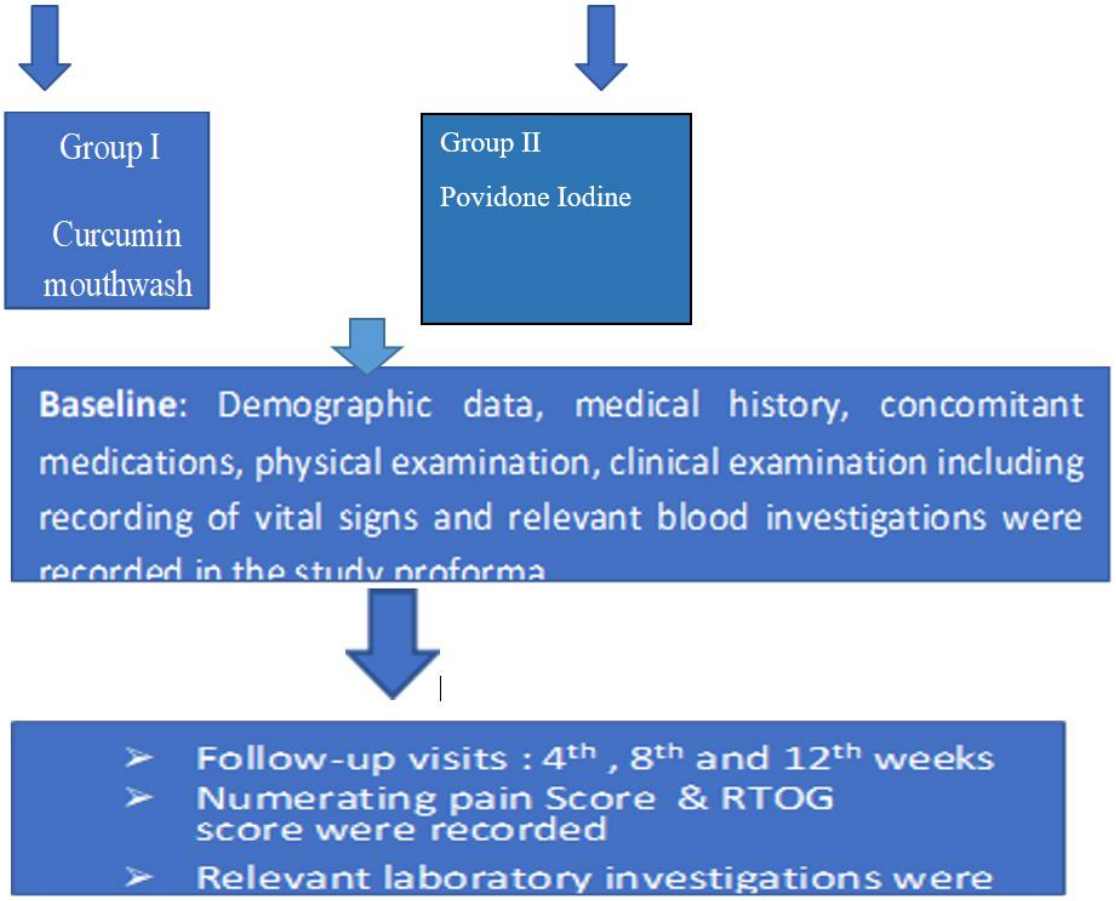



**Figure I: Methodology**

**Demographic Characteristics**

Table III represents the demographic profile of the patients included in the study. Both the treatment groups were matched with respect to baseline demographic characteristics.

**Table III: Baseline demographic characteristics**

| | Group A Curcumin (n= 30) | Group B Povidone Iodine (n= 30) | p Value |
|---|---|---|---|
| **Age (years) (Mean ± SD)** | 61.26 ± 8.84 | 62.63 ± 8.40 | 1.000 |
| **Gender – n (%)** | | | 0.605 |
| **Male** | 14 (46.6%) | 16 (53.4%) | |
| **Female** | 16 (53.4%) | 14 (46.6%) | |
| **Weight (Kg) Pre-op** | 57.66 ± 7.43 | 56.86 ± 7.24 | 0.804 |
| **Post-op** | 20 (66.6%) | 19 (63.3%) | 0.910 |
| | 10 (33.3%) | 11 (36.6%) | 1.000 |

Baseline Numerical Rating Scale (NRS) were 5.2 (2.75) in the Curcumin group, 5.5 (2.47)) in the Povidone Iodine group (Table IV).

**Table IV – Numerical Rating Score at different visits**

| Variable | Group A **Curcumin (n= 30)** Mean (SD) | Group B **Povidone Iodine (n= 30)** Mean (S) | p Value* |
|---|---|---|---|
| Baseline | 5.2 (2.75) | 5.5 (2.47) | 0.90 |
| 4th week | 3.7 (1.79) | 4.8 (2.11) | 0.13 |
| 8th week | 2.0 (1.40) | 3.6 (1.67) | 0.33 |
| 12th week | 0.6 (0.75) | 1.9 (0.80) | 0.0008 |

** One way Anova for significance*

Numerical Rating Score at 8th and 12th week visit with Post Hoc Tukey HSD test showed Mean of Curcumin Group vs Mean of Povidone Iodine Group – $p < 0.05$, which were statistically significant.

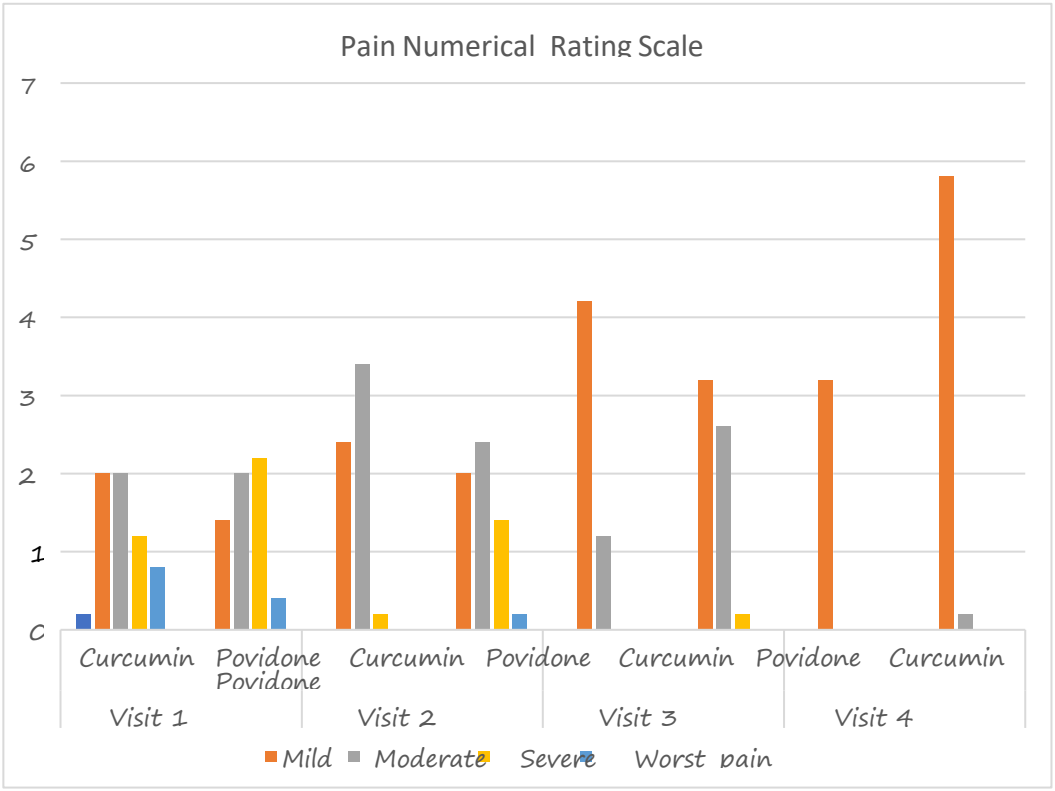



**Fig II. Graphical plot of Pain Numerical Rating Scale (PNRS) at different follow up**

**Table V : Radiation Therapy Oncology Group score at different visits**

| Variable | Group A **Curcumin (n= 30)** Mean (SD) | Group B **Povidone Iodine (n= 30)** Mean (SD) | p Value* |
|---|---|---|---|
| Baseline | 2.9 (0.78) | 2.4 (0.85) | 0.7 |
| 4th week | 1.8 (0.73) | 2.2 (0.78) | 0.9 |
| 8th week | 1.3 (0.54) | 1.8 (0.71) | 0.8 |
| 12th week | 1.1 (0.30) | 1.5 (0.57) | 0.0037 |

** One way Anova for significance*

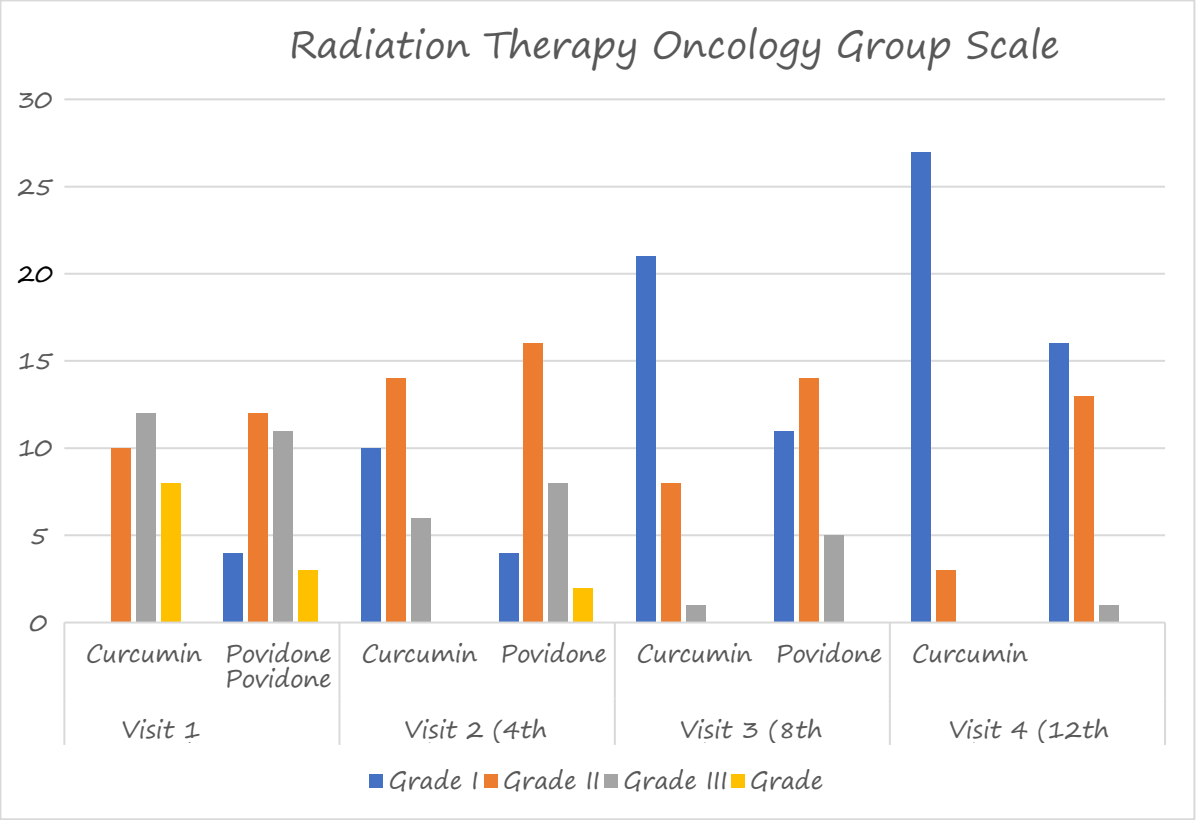



**Fig III. Graphical plot of Radiation Therapy Oncology Group Score (RTOG) at different follow up**

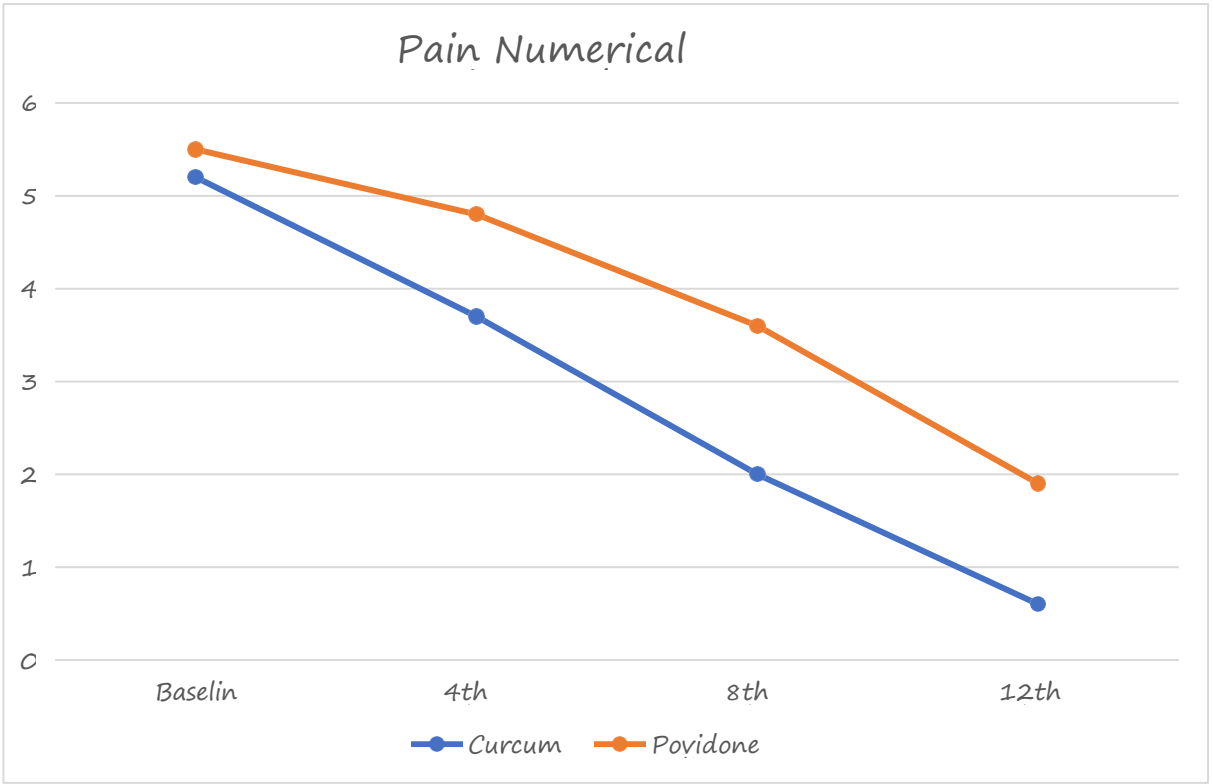



**Fig IV. Graphical plot of Pain Numerical Rating Scale (PNRS) at different follow up**

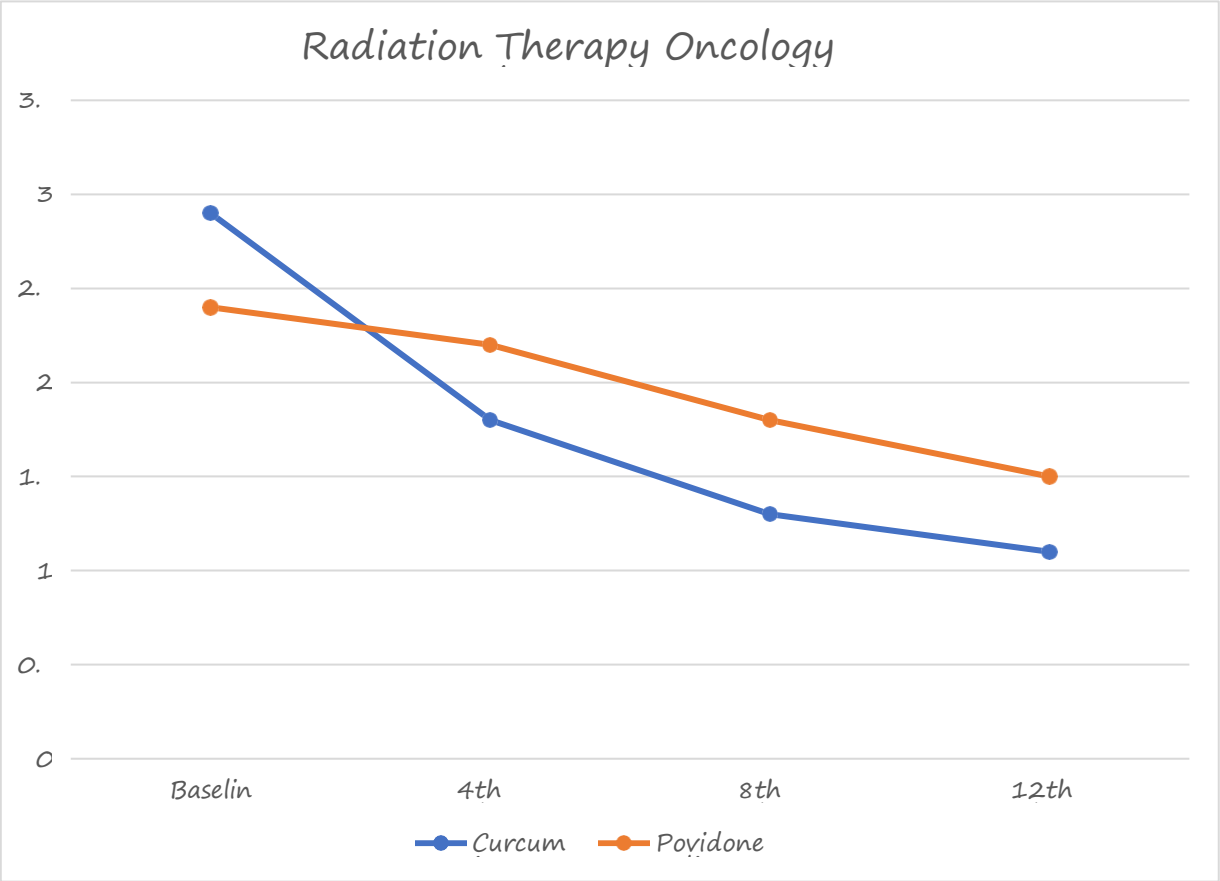



**Fig V. Graphical plot of Radiation Therapy Oncology Group Score (RTOG) at different follow up**

**DISCUSSION:**

The multifactorial aetiology of radiotherapy induced mucositis and lack of effective treatment modality makes it a challenge to relieve the patient from the morbidity associated with radiotherapy induced mucositis6. As the treatment aims at providing symptomatic relief for the patient, the goals of treatment include reduction in healing time of ulcer, decrease pain, size, and number of ulcers7. Current treatment modalities include use of systemic and topical steroids, cauterization, and antibiotics, mouth rinses containing active enzymes, laser treatments, and combination therapy8. Current treatment modalities include use of topical steroids like Triamcinolone acetonide gel, which is a fluoride synthetic corticosteroid. As corticosteroids are known to get absorbed systemically even on topical application, they can lead to certain adverse reactions9. So nowadays, herbal medicines are gaining more attention due to their decreased side effects.

Curcumin is a main pigment of principle spice in India, turmeric. It is bright yellow in colour and is known from centuries10 for its strong antioxidant, antiseptic, antibacterial, anti- inflammatory, immunomodulatory, and analgesic properties11. The anti-inflammatory properties of curcumin may be attributed to its ability to inhibit both biosynthesis of inflammatory prostaglandins which further blocks cyclooxygenase and lipoxygenase activity, thereby inhibiting prostaglandin leukotriene release and neutrophil function during inflammatory states12

Comparative study done by Charantimath S et.al concluded Curcumin and Povidone Iodine mouthwash have been proved to be safe and well-tolerated topical medication for radiotherapy induced oral mucositis[13]. The current study resounded the same, and the medications were found to be safe, with minimal transient side effects of burning sensation and taste impairment noticed by a

few patients. Most patients responded to treatment and were willing to continue the mouthwash, if indicated.
Efficacy of these mouthwashes over placebo has been proved in previous study done by Mansourian et.al. Both these medications showed significant relief in symptoms of pain, erythema and ulcer, which was proved statistically [14]. The current study showed that both study medications provide significant relief in symptoms from baseline to 12th week.

Study done by Adhvaryu M et.al compared incidence of any grade of mucositis in the control group was 92% as against 51% in trial group (Curcumin Longa) (p=0.0074). A highly significant reduction in incidence of mucositis was chiefly due to a drastic reduction in grade 3 mucositis cases; from 47% incidence in control group to mere 11% in trial group (p< 0.0001)15. The current study results also showed reduction in the incidence of mucositis grade in the Curcumin group (1.1+0.30) compared to Povidone Iodine (1.5+0.57) which was statistically significant (p=0.0037).
Rao S et.al an investigational study showed that exposure to ionizing radiation caused mucositis in both povidone-iodine and turmeric cohorts. However, in the participants using turmeric, the clinical appearance of mucositis was delayed and the intolerable mucositis was reduced, indicating turmeric to be effective in preventing mucositis16.
The current study showed reduction in pain in Curcumin group (0.6+0.75) and Povidone Iodine group (1.9+0.80) with p value 0.0008 which was statistically significant at the end of the 12th week whereas the current study results are in line with study done by Charantimath Set.al determined that reduction in pain in both the groups according to NRS scale i.e Curcumin group 41.3% (p=0.0098) and povidone Iodine group 18.2% (p=0.0002) which was statistically significant13.
Study done by P Arun et.al showed that there was no statistical difference between the groups in terms of oral mucositis severity until the end of the second week of treatment. However, from the third week, mucositis severity in group A (turmeric extract group) was significantly lower compared to that in group B (placebo control group). After three weeks of treatment,
86.7 per cent of patients in group A had only grade 1 mucositis, in comparison to 71 per cent with grade 2 mucositis in group B; this difference was statistically significant ( $p < 0.001$). At the end of four weeks of treatment, the majority of patients (73.3 per cent) in group A had only grade 1 mucositis17. The current study represented the same results showing no significant in terms of pain and severity of mucositis until the end of the 2nd week. However, from 3rd week severity in Curcumin group was significantly reduced compared to Povidone Iodine group. Clinical trials, thus, proved efficacy of Curcumin extract for relief of symptoms of radiotherapy induced oral mucositis and found differences between medications in one or the other parameters18. In the current study, Curcumin mouthwash is effective in reducing the pain and severity of radiotherapy induced oral mucositis with statistically significant results.

**Strengths:** Study medications with standard doses were compared with adequate sample size in a single randomised study. Randomisation, blinding of the patients and evaluation of the effect of the study medications on clinical assessment of signs and symptoms provided an evidence – based option which was safe and effective.

**Limitations**: The current study was conducted in a single centre, hence considering multi – centre with larger subset of population would further aids in generalizability of results.

**Conclusion:** Oral administration of bioavailable turmeric extract reduced mucositis severity when compared to patients in a control group who underwent the same modality of treatment but without the turmeric extract. The lack of systemic toxicity and the diverse inhibitory effect of turmeric extract on various inflammation pathways makes it an ideal agent in the treatment of radiation-induced mucositis. As highlighted in our study, turmeric extract can significantly reduce mucositis severity, which can benefit patients undergoing radiation or chemoradiation

**Conflict of interest:** None declared

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