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Prophylactic Management of Radiotherapy-Induced Neuropathic Pain in Head and Neck Cancer: A Randomized Controlled Trial

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ABSTRACT

Introduction: Radiotherapy for head and neck cancer frequently causes debilitating neuropathic pain. Conventional analgesics are often inadequate, highlighting a critical need for effective preventive measures. Therefore, this randomized controlled trial was designed to evaluate the efficacy of prophylactic pregabalin in managing radiotherapy-induced neuropathic pain in head and neck cancer patients.

Material and methods: This double-blind randomized clinical trial evaluated 60 head and neck cancer patients (30 per group) at Shahid Madani Hospital to investigate the preventive efficacy of prophylactic pregabalin on radiotherapy-induced neuropathic pain. Serial pain scores, analgesic requirements, adverse events, and treatment tolerance were prospectively tracked throughout the radiotherapy course.

Results: Prophylactic pregabalin significantly attenuated radiation-induced neuropathic pain compared to control (peak mean 2.30±0.60 vs 7.20±1.00; $p<0.05$), reduced cumulative opioid consumption (42.0±12.8 mg vs 145.5±22.4 mg; $p<0.05$), decreased rescue medication reliance (23.3% vs 76.7%), and lowered breakthrough pain frequency (1.2±0.4 vs 4.8±1.1; $p<0.05$), while maintaining an acceptable and manageable safety profile without severe adverse events.

Conclusion: Preemptive administration of pregabalin offers an effective, opioid-sparing therapeutic strategy for managing radiotherapy-induced neuropathic pain in head and neck cancer patients. Despite mild, self-limiting central nervous system side effects such as dizziness and somnolence, the favorable efficacy and tolerability profile support its routine clinical implementation to enhance patient comfort and quality of life during oncological radiation therapy.

Introduction

Head and neck squamous cell carcinomas and associated upper aerodigestive tract malignancies represent a formidable global oncologic burden, consistently ranking among the leading causes of cancer-related disability and treatment-associated morbidity worldwide.

Because these anatomical regions orchestrate essential physiological processes including mastication, deglutition, phonation, and upper airway patency the development of primary neoplasms in the oral cavity, oropharynx, larynx, or hypopharynx inherently compromises vital daily functions.

Modern management strategies for locally advanced presentations routinely employ curative-intent regimens that combine high-precision ionizing radiation with concurrent radio sensitizing systemic chemotherapy or extensive ablative surgery followed by risk-adapted adjuvant radiation. Despite technological progress in treatment planning, delivery techniques, and organ-sparing dose

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optimization, ionizing radiation continues to inflict non-selective biological trauma on adjacent non-malignant tissues. Among the extensive constellation of radiation-associated acute and delayed toxicities, unyielding physical discomfort stands out as an exceedingly prevalent, pervasive, and clinically exhausting symptom complex that frequently derails rehabilitative trajectories, exacerbates malnutrition, and compromises emotional well-being throughout and long after the therapeutic continuum [1].

The delivery of curative radiation therapy to the cervicofacial axis triggers a coordinated yet intensely destructive cascade characterized by rapid endothelial breakdown, microvascular obliteration, brisk reactive oxygen species generation, and dense transmural tissue inflammation across irradiated mucosal and dermal fields. Although standard oncologic monitoring has historically attributed acute therapy-induced discomfort primarily to severe radiation-induced oral mucositis and localized superficial inflammation, contemporary supportive care research clearly demonstrates that treatment-related pain in head and neck cancer is deeply heterogeneous, frequently encompassing a marked, unaddressed neuropathic component. Unlike purely nociceptive insults originating from uncomplicated chemical or mechanical stimulation of specialized mucosal receptors, neuropathic manifestations stem directly from mechanical, ischemic, inflammatory, or metabolic lesions inflicting trauma on the somatosensory nervous network. The anatomical complexity of the head and neck, densely invested with vulnerable cranial nerve arborizations, extensive cervical plexuses, and highly reactive peripheral terminal nerve endings, renders these neural trajectories uniquely sensitive to cumulative ionizing radiation fields. Consequently, acute local tissue destruction steadily progresses into persistent neuroinflammatory signaling, aberrant nociceptive remodeling, and prolonged neural dysregulation [2].

Pathophysiologically, the evolution of radiation-induced neuropathic pain involves dynamic cellular and biochemical disruptions occurring simultaneously along peripheral neural tracts and within the dorsal horn circuitry of the central nervous system. Exposure to therapeutic ionizing doses evokes immediate microvascular permeability and secondary endoneuria ischemia, accompanied by microglial infiltration, robust mast cell degranulation, and an excessive surge of pro-inflammatory cytokines, chemokines, and nerve growth factors within the irradiated nerve sheath microenvironment. This microenvironmental toxicity promotes spontaneous ectopic impulse generation, lowering the physical depolarization threshold of injured sensory afferents while upregulating key ion channels. With sustained high-dose radiation exposure, this primary peripheral sensitization transitions smoothly into secondary central sensitization a state characterized by spinal neuronal hyperexcitability, diminished descending inhibitory tone, expanded receptive field mapping, and marked synaptic remodeling. Clinically, patients experience this pathological transformation as severe burning sensations, sharp lancinating attacks, paroxysmal electric shock-like jolts, mechanical dynamic allodynia, thermal hyperalgesia, and distressing dysesthesias that cannot be explained or addressed by ordinary mucosal inflammation models alone [3].

The pervasive presence of uncontrolled neuropathic pain during head and neck cancer therapy carries devastating functional consequences that extend far beyond mere alterations in subjective pain rating scores. Progressive neuropathic dysesthesia affecting the glossopharyngeal, vagal, and lingual distributions dramatically impairs the neuromuscular coordination required for safe deglutition, precipitating profound odynophagia, pharyngeal dysphagia, and involuntary aspiration risks. Patients inevitably develop severe food aversion, escalating dehydration, and progressive cachexia, necessitating frequent nasogastric feeding tube insertions or percutaneous endoscopic gastrostomies. Furthermore, unmitigated neural pain and its accompanying distress undermine therapeutic compliance, often culminating in unscheduled radiation interruptions, protracted overall treatment times, or premature cessation of concurrent systemic radio sensitizing protocols. Extensive clinical and radiobiological literature confirms that unintended treatment interruptions permit accelerated repopulation of resistant tumor clonogens, fundamentally eroding locoregional tumor control rates and directly compromising overall survival. The severe physical suffering concurrently fuels sleep fragmentation, profound systemic fatigue, mood disturbances, demoralization, and social withdrawal, altogether precipitating a steep decline in global health-related quality of life [4].

Conventional cancer pain management guidelines, primarily structured around the classic World Health Organization analgesic ladder, rely heavily on scheduled non-opioid analgesics and the sequential escalation of pure mu-opioid receptor agonists. However, these traditional protocols frequently prove distinctly disappointing and therapeutically inadequate when directed against neuropathic pain phenotypes. Opioid receptors are widely recognized to undergo notable functional downregulation and impaired G-protein signal transduction within injured primary afferents and deafferented spinal cord pathways, yielding an unfavorable therapeutic index characterized by poor analgesic response despite rapid systemic dosage escalation. Attempting to suppress resistant neuropathic surges by aggressively increasing opioid doses exposes

fragile head and neck cancer patients to debilitating systemic side effects, including heavy somnolence, cognitive slowing, intractable nausea, and severe opioid-induced bowel dysfunction. The resulting opioid-induced xerostomia and lethargy compound pre-existing radiation-induced hyposalivation, speech deficits, and nutritional failure, underscoring an urgent clinical need to transition away from reactive, opioid-centric paradigms toward mechanism-based, neuroprotective, and sensory-stabilizing analgesic regimens [5].

Within multimodal analgesia, gabapentin has surfaced as principal pharmacologic agents uniquely capable of directly modulating aberrant neuronal signaling within hyperexcitable nervous systems. Pregabalin, a sophisticated alkylated analogue of gamma-aminobutyric acid, exhibits selective, high-affinity stereospecific binding to the auxiliary alpha-2-delta type 1 and type 2 protein subunits of voltage-gated calcium channels across presynaptic membranes in the brain and spinal cord. Through this targeted binding interaction, pregabalin fundamentally restrains pathologically elevated influxes of extracellular calcium into depolarized presynaptic nerve endings, dampening the exocytotic release of key excitatory neurotransmitters, most notably glutamate, substance P, and calcitonin gene-related peptide. By selectively suppressing excessive, abnormal excitatory neurotransmission while preserving standard baseline sensory activity, pregabalin effectively curtails the progression of both peripheral sensory amplification and central wind-up sensitization. Furthermore, its clean pharmacokinetic profile, characterized by rapid systemic absorption, predictable linear dosing kinetics, near-complete oral bioavailability, lack of significant hepatic cytochrome P450 interactions, and predictable renal excretion, makes it an exceptionally compatible agent for oncology patients navigating complex polypharmacy [6].

Historically, pharmacotherapy for neuropathic symptoms in oncology clinics has been conducted reactively, reserving gabapentin, tricyclic antidepressants, or serotonin-norepinephrine reuptake inhibitors as late-stage rescue modalities after intractable neuropathic pain is firmly established. Nevertheless, extensive translational neurobiology demonstrates that once pathological central wind-up, neuroglial proliferation, and phenotypic synaptic remodeling become structurally entrenched, conventional pharmacologic interventions achieve only modest, temporary symptom suppression. This critical realization has catalyzed the concept of preventive or prophylactic analgesia initiating a targeted neuro-modulatory intervention prior to or simultaneously with tissue injury to attenuate nociceptive volleys, suppress initial neurogenic inflammation, and halt the neuroplastic shifts that transform acute peripheral injury into chronic central hyperexcitability. Applying an upfront prophylactic strategy before cumulative radiation dosage triggers peripheral axonal damage represents a biologically rational intervention designed to shield somatosensory pathways from progressive maladaptive changes throughout the therapeutic course [7].

Although the biological rationale supporting upfront neuroticization is compelling, contemporary clinical evidence validating prophylactic pregabalin exclusively within the setting of head and neck irradiation remains fragmentary, heterogeneous, and largely exploratory. The vast majority of published supportive care data involves mixed oncologic populations receiving heterogeneous chemotherapy regimens, postsurgical cohorts dealing with mechanical neuropathies, or non-cancer cohorts suffering from diabetic peripheral neuropathy or postherpetic neuralgia. These distinct medical models rarely capture the unique physiological and anatomical complexities seen in patients undergoing intensive, fractionated head and neck irradiation, where aggressive mucosal de-epithelialization, intense local mucosal infection risks, severe swallowing difficulties, and concurrent platinum-based chemotherapy simultaneously converge. While preliminary retrospective reviews and small uncontrolled pilot series have hinted at meaningful reductions in pain intensity and decreased breakthrough analgesic consumption with early gabapentin exposure, they lack the rigorous methodological control required to distinguish specific prophylactic neuropathic mitigation from non-specific systemic sedation or natural fluctuations in mucosal recovery [8].

To definitively address these clinical uncertainties, interventional research in supportive oncology demands robust methodological execution using prospective, randomized controlled trial designs. A meticulously controlled clinical framework is indispensable in this clinical context because subjective symptom endpoints, such as perceived burning intensity, quality-of-life scores, and self-reported functional limitations, remain vulnerable to detection bias, substantial placebo effects, and variable baseline psychological distress. Proper randomization, systematic prospective stratification, and the use of well-defined, validated neuropathic pain diagnostic instruments permit balanced distribution of critical oncologic covariates, such as baseline anatomical tumor subsite, total radiation dose fractions, primary surgical interventions, and concurrent systemic chemotherapy regimens. Furthermore, a rigorous randomized trial format provides the necessary empirical baseline to carefully monitor potential central nervous system adverse events, systematically track changes in daily functional activity, and thoroughly evaluate the safety and tolerability of continuous prophylactic

drug titration in this physically vulnerable patient population [9].

Despite the evident clinical need, substantial ambiguity persists regarding whether proactively administering pregabalin before the clinical manifestation of radiation-induced nerve trauma translates into verifiable reductions in neuropathic symptom incidence, delayed onset of severe breakthrough pain, decreased total opioid consumption, and superior preservation of daily functional activities throughout curative radiation regimens. Addressing these unresolved supportive care challenges requires dedicated, prospective, high-quality clinical investigation to determine whether early neuro-modulatory stabilization can meaningfully protect patients from severe treatment-related morbidity and improve overall therapeutic compliance. Accordingly, the present prospective, randomized controlled trial was specifically designed to evaluate the prophylactic efficacy, tolerability, and clinical outcomes of pregabalin for the management and prevention of radiotherapy-induced neuropathic pain in patients with head and neck cancer.

Material and methods

Study design:

This study was conducted as a randomized, double-blind clinical trial at Shahid Madani Hospital, Tabriz, Iran. Eligible patients were randomly allocated in a 1:1 ratio to receive either prophylactic pregabalin or a matched control regimen, with participants, treating clinicians, outcome assessors, and data analysts blinded to group assignment. The study procedures were implemented in parallel with the standard radiotherapy pathway for head and neck cancer, and follow-up assessments were performed at predefined time points during the radiotherapy course to capture the development and trajectory of neuropathic pain and related clinical outcomes.

Sampling:

Patients were recruited using a convenience (available) sampling approach from those referred to the radiotherapy service and assessed for eligibility during the recruitment period. The sample size was estimated using the Cochran sample size formula for comparing two means (two-sided), incorporating the assumed standard deviation of the primary outcome, the minimum clinically important difference between groups, and conventional Type I and Type II error rates; based on these parameters, the required sample size was calculated as 60 patients, allocated equally to two groups of 30. Accordingly, recruitment continued until the target number was reached and complete baseline assessment and randomization were achieved for all enrolled participants.

Inclusion and exclusion criteria

Eligible participants were adult patients (≥18 years) with a confirmed diagnosis of head and neck cancer who were candidates for external-beam radiotherapy (definitive or adjuvant, with or without concurrent systemic therapy), had the ability to provide written informed consent, and were able to reliably report symptoms and complete pain assessments. Key exclusion criteria included prior radiotherapy to the head and neck region, known hypersensitivity or contraindication to pregabalin, current use of gabapentin (pregabalin or gabapentin) or recent use judged likely to confound outcome assessment, severe renal impairment requiring dose restrictions incompatible with the protocol, clinically significant uncontrolled psychiatric or neurologic disorders affecting pain reporting, active uncontrolled infection or unstable medical illness, pregnancy or breastfeeding, history of substance misuse that could interfere with adherence or opioid-related outcomes, inability to take oral medications, baseline severe sedation or dizziness, and any condition that based on investigator judgment would compromise safety, protocol adherence, or validity of follow-up measurements.

Procedure:

After eligibility confirmation and baseline data collection, participants were randomized to receive prophylactic pregabalin or control and were followed prospectively throughout the radiotherapy course. Baseline characteristics recorded included demographics (age, sex), clinical variables (tumor site, stage if available, treatment intent, radiotherapy schedule, and concurrent treatments), comorbidities, baseline analgesic use, and baseline pain status. Pain evaluation was conducted serially using standardized patient-reported measures to capture overall pain intensity and the neuropathic pain component (e.g., burning, shooting/electric shock-like pain, tingling, numbness, and allodynia features), along with time-to-onset of neuropathic symptoms during treatment and the peak severity reached. In addition to pain phenotyping, supportive-care and treatment-tolerance outcomes were assessed. These included cumulative opioid and non-opioid analgesic consumption (converted to standardized equivalents when applicable), need for rescue medications, frequency of breakthrough pain episodes, and adverse effects potentially attributable to pregabalin (notably somnolence, dizziness, blurred vision, edema, and cognitive slowing). Clinically relevant radiotherapy-related variables were tracked, including mucosal and functional impact indicators (e.g., oral intake limitation, dysphagia-related complaints), unplanned clinic visits or hospitalizations due to pain, and radiotherapy compliance markers such as missed fractions or treatment interruptions. Safety monitoring was performed at each follow-up, and

any clinically significant adverse event prompted reassessment, supportive management, and protocol-defined adjustments as required.

Statistical analyses:

Because the data were assumed to be normally distributed, continuous variables were summarized as mean ± standard deviation and compared between groups using the independent-samples t test, while within-group changes over time were evaluated using the paired t test or repeated-measures analysis of variance (RM-ANOVA) as appropriate. Categorical variables were reported as frequencies and percentages and compared using the chi-square test or Fisher's exact test when expected cell counts were small. For outcomes involving multiple predictors or adjustment for baseline imbalances, linear regression (for continuous outcomes) and logistic regression (for binary outcomes) planned. A two-sided p value < 0.05 considered statistically significant, and analyses performed according to the prespecified allocation (intention-to-treat whenever feasible, depending on completeness of follow-up data).

Ethical considerations:

The study approved by the Ethics Committee of Tabriz University of Medical Sciences and conducted in accordance with the principles of the Declaration of Helsinki and applicable national regulations. The trial registered with the Iranian Registry of Clinical Trials (IRCT2020050204763N1) and received ethical approval under code IR.TBZMED.REC.1401.436. Written informed consent was obtained from all participants prior to enrollment, confidentiality was maintained through anonymized coding of data, and participants were informed of their right to withdraw at any time without any effect on their standard oncologic care.

Results

Baseline neuropathic pain scores demonstrated no significant disparity between the two treatment arms. As radiotherapy advanced, the control cohort experienced a progressive and steep escalation in neuropathic pain scores, reaching a maximum mean of 7.20 plus or minus 1.00 at week 6, before attenuating slightly to 4.80 plus or minus 0.80 at the subsequent post-treatment follow-up assessment. In distinct contrast, patients receiving prophylactic pregabalin exhibited substantially suppressed pain trajectories across the entire treatment continuum, recording a peak mean score of merely 2.30 plus or minus 0.60 at week 4 that subsequently stabilized and declined to 1.40 plus or minus 0.40. Between-group differences diverged rapidly and achieved marked statistical significance at week 2, maintaining this pronounced clinical divergence across all subsequent evaluative timepoints through final follow-up ($p<0.05$). These empirical longitudinal findings validate that preemptive administration of pregabalin effectively mitigates the emergence and progressive exacerbation of radiation-associated neuropathic pain in head and neck cancer patients.

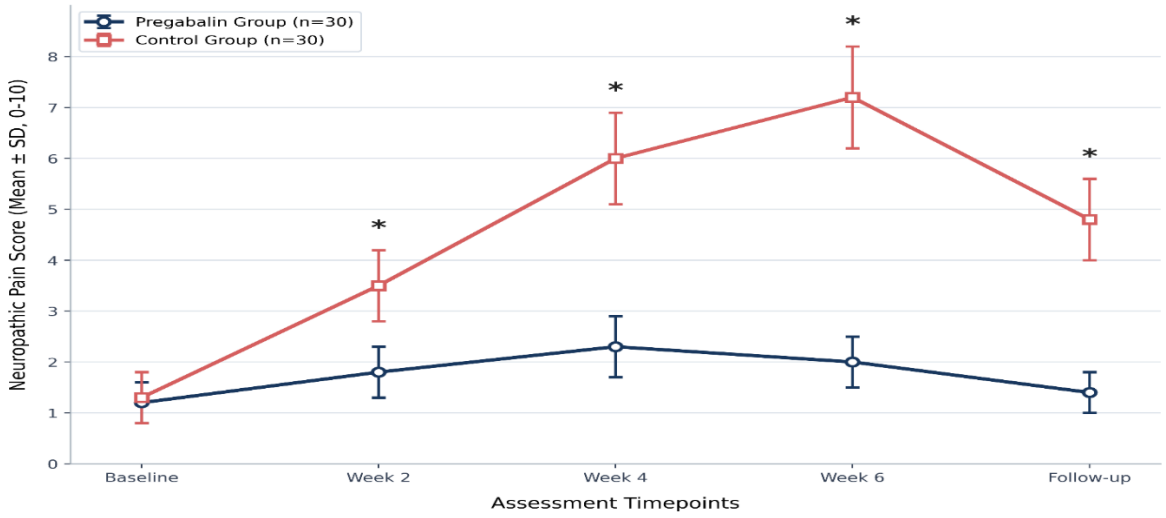


Figure 1. Longitudinal assessment of neuropathic pain severity throughout radiotherapy and follow-up between the pregabalin and control groups.

Quantitative evaluation of secondary clinical endpoints revealed a profound opioid-sparing effect and superior pain control in subjects treated with prophylactic pregabalin compared with the control cohort. The cumulative mean morphine milligram equivalent requirement was reduced more than three-fold in the intervention arm (42.0 plus or minus 12.8 mg) relative to the control arm (145.5 plus or minus 22.4 mg; $p<0.05$). Consistent with this reduction, rescue analgesic administration was

necessitated by only 23.3 percent (7/30) of patients in the pregabalin arm, whereas 76.7 percent (23/30) of control individuals required breakthrough medical intervention ($p<0.05$). Furthermore, the weekly frequency of breakthrough pain exacerbations was markedly curtailed among pregabalin-treated patients (1.2 plus or minus 0.4 episodes per week) compared to control subjects (4.8 plus or minus 1.1 episodes per week; $p<0.05$). Collectively, these findings provide compelling empirical evidence that preemptive pregabalin administration significantly limits the demand for escalating systemic opioid doses while concurrently suppressing transient spikes in radiation-induced pain.

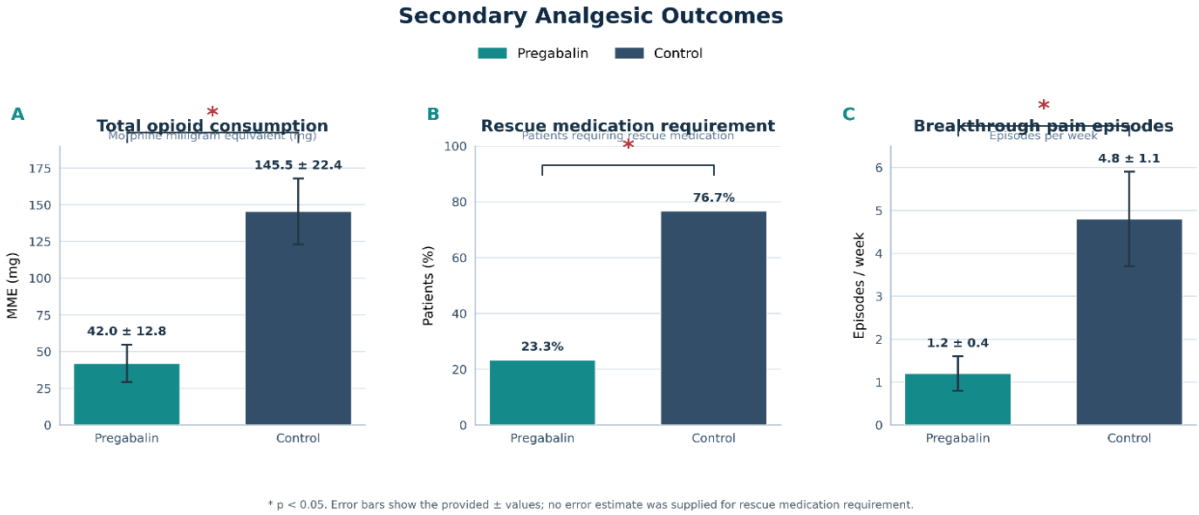


Figure 2. Comparative assessment of secondary analgesic consumption, rescue medication reliance, and breakthrough pain incidence between the study arms

The safety and tolerability analysis revealed that treatment-related adverse events were generally mild to moderate and manageable, requiring neither the premature cessation of radiation therapy nor drug discontinuation in any patient. Predictably, central nervous system side effects including dizziness (36.7 percent versus 10.0 percent) and somnolence (30.0 percent versus 13.3 percent) were more frequent in the pregabalin group, whereas radiation-associated symptoms such as nausea (40.0 percent versus 23.3 percent) and fatigue (33.3 percent versus 26.7 percent) predominated in the control group. Peripheral edema and blurred vision exhibited minimal variance between the two arms. These findings establish that prophylactic pregabalin is well-tolerated with an acceptable safety profile in patients receiving head and neck radiotherapy.

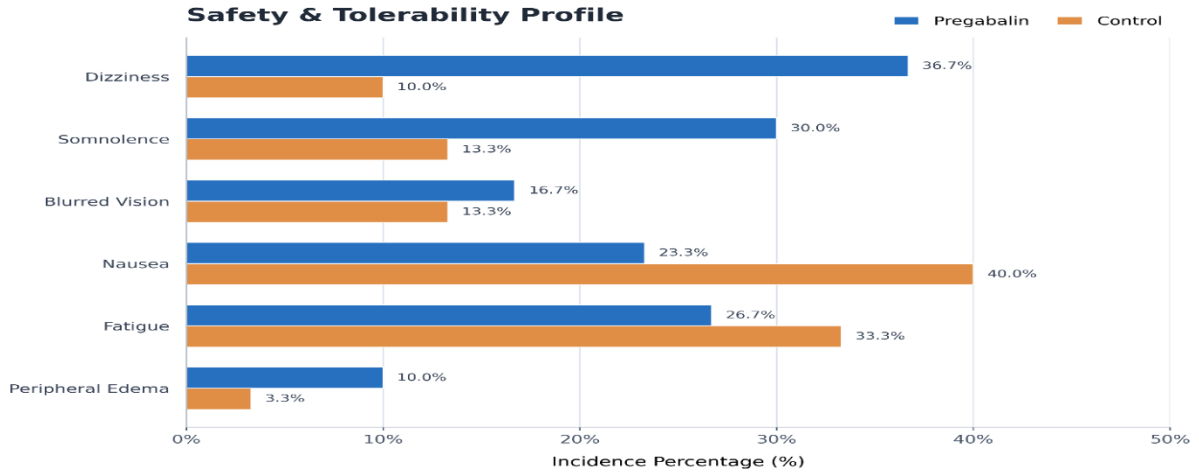


Figure 3. Comparative evaluation of adverse events and safety profile between the pregabalin and control cohorts.

Discussion

Across this randomized double-blind trial, baseline neuropathic pain severity was comparable between groups, but pain trajectories diverged early during radiotherapy, with the control arm showing a steep rise to a peak mean score of 7.20 ± 1.00 at week 6

and only partial improvement at follow-up (4.80 ± 0.80), whereas prophylactic pregabalin maintained consistently lower scores, peaking at 2.30 ± 0.60 and declining to 1.40 ± 0.40 by follow-up; these between-group differences were statistically significant from week 2 onward ($p<0.05$). In parallel, pregabalin produced a marked opioid-sparing effect, reducing cumulative morphine milligram equivalent requirements (42.0 ± 12.8 mg vs 145.5 ± 22.4 mg), lowering rescue-analgesic use (23.3 percent vs 76.7 percent), and decreasing breakthrough pain frequency (1.2 ± 0.4 vs 4.8 ± 1.1 episodes per week), while remaining clinically tolerable: dizziness and somnolence were more frequent with pregabalin, whereas nausea and fatigue were more common in controls, and no discontinuations were required. [10 11].

These findings are biologically plausible given the timing and mechanisms by which radiotherapy precipitates neuropathic pain in head and neck cancer. Radiation can injure peripheral nerves directly and indirectly through neuroinflammation, microvascular compromise, and progressive tissue fibrosis, producing a pattern in which symptoms often intensify as cumulative dose accrues and inflammatory cascades amplify during the later weeks of treatment. The control group's marked escalation by week 6 is consistent with this cumulative injury model, while the earlier separation of curves suggests that intervening upstream in the sensitization process may prevent consolidation of neuropathic signaling rather than merely treating established pain. Pregabalin's effect profile aligns with this concept because it binds the alpha-2-delta subunit of voltage-gated calcium channels, reducing presynaptic release of excitatory neurotransmitters and dampening central sensitization, thereby limiting the transition from nociceptive tissue injury to persistent neuropathic pain. In a radiotherapy context, initiating such modulation before maximal inflammatory load may blunt the development of hyperexcitability and allodynia that become harder to reverse once entrenched. [12,13].

The magnitude of benefit observed in pain intensity is clinically meaningful, not merely statistically significant. In supportive oncology, even modest reductions in pain scores can translate into improved oral intake, sleep continuity, mood, adherence to radiotherapy sessions, and reduced need for emergency care. The pronounced separation between arms across multiple timepoints indicates a sustained effect rather than a transient placebo-like fluctuation, and the decline in the pregabalin arm by follow-up suggests not only symptom suppression during treatment but also a possible mitigation of subacute neuropathic persistence after radiotherapy completion. This pattern supports the interpretation that pregabalin may reduce the amplification of afferent input and maladaptive plasticity during the window in which radiation-associated neurotoxicity is evolving. It also implies that prophylaxis could be most valuable in patients at higher baseline risk for neuropathic complications, such as those with pre-existing neuropathy, diabetes, prior surgery, or concurrent neurotoxic chemotherapy, although such subgroup effects require dedicated power and stratified analysis. [14,15].

The secondary endpoints strengthen the causal narrative by demonstrating concordant reductions in analgesic escalation and breakthrough pain. Opioid requirements and rescue-medication reliance are pragmatic, patient-centered outcomes that often reflect real-world distress more reliably than any single numeric scale, particularly in head and neck cancer where mucositis, dysphagia, xerostomia, and fatigue can co-exist and confound pain reporting. The substantial reduction in cumulative opioid exposure is especially relevant because opioid-related adverse effects such as constipation, nausea, delirium, and somnolence can exacerbate the symptom cluster already induced by radiotherapy, potentially reducing nutritional intake and functional status. An opioid-sparing strategy that maintains analgesia is therefore desirable both for safety and for preserving treatment tolerance. The lower rate of breakthrough pain episodes in the pregabalin group further suggests improved baseline analgesic stability and reduced sensitization-driven flares, consistent with pregabalin's role in modulating aberrant neuronal firing and reducing the volatility of neuropathic symptom expression. [16,17].

From a mechanistic standpoint, pregabalin's prophylactic advantage may arise from its ability to interrupt feed-forward loops between peripheral injury and central processing. Radiotherapy-induced tissue injury can activate immune cells and glial responses, increasing cytokine signaling and facilitating excitatory synaptic transmission within dorsal horn and brainstem nociceptive pathways. If left unchecked, this milieu promotes central sensitization, lowering activation thresholds and magnifying responses to otherwise non-noxious stimuli. Pregabalin reduces calcium-dependent neurotransmitter release, which can decrease spinal amplification and attenuate the propagation of pain signals to higher centers. In head and neck radiotherapy, where pain is often multifactorial, this neuromodulator effect may selectively reduce the neuropathic component that is less responsive to conventional non-opioid analgesics. The early divergence at week 2 is consistent with a prevention model in which pregabalin acts before maximal cumulative injury, suggesting that timing of initiation could be critical and may partly explain heterogeneity across studies that start gabapentin later in the radiotherapy course. [18 ,19].

The safety profile observed is also consistent with known pharmacology and provides important

reassurance for clinical adoption. The higher rates of dizziness and somnolence in the pregabalin arm reflect expected central nervous system effects and underscore the need for patient counseling, dose titration when feasible, and monitoring in individuals at risk for falls or with baseline frailty. Importantly, these adverse events appeared manageable and did not necessitate discontinuation, which is a key feasibility outcome in the radiotherapy setting where maintaining uninterrupted treatment is vital for tumor control. Conversely, the higher incidence of nausea and fatigue in the control arm likely reflects greater opioid exposure, uncontrolled pain, or the overall symptom burden of radiotherapy without effective neuropathic modulation. The relative similarity in less common events such as blurred vision and peripheral edema suggests that, within the studied dosing and duration, pregabalin did not introduce prohibitive toxicity. [20,21].

The interplay between analgesic efficacy and tolerability is particularly salient in head and neck cancer, where symptom burden often drives unplanned treatment breaks. Uncontrolled pain may contribute to reduced oral intake and dehydration, prompting hospital visits, intravenous fluid administration, and interruptions in radiation schedules. By attenuating neuropathic pain and reducing reliance on rescue opioids, pregabalin may indirectly support better adherence to planned radiotherapy fractions and enhance overall supportive care outcomes. While the present study was not designed to detect differences in radiotherapy completion metrics or oncologic endpoints, the observed clinical trajectory raises the hypothesis that improved symptom control could translate into fewer missed sessions and potentially better locoregional control in settings where treatment interruptions are known to be detrimental. Future trials could incorporate adherence endpoints and patient-reported outcome measures to quantify this broader supportive-care impact. [22,23].

Comparison with the broader literature suggests that the preventive use of gabapentin in cancer-related or treatment-related neuropathic pain remains an area of active discussion, partly because study populations, endpoints, timing, and co-interventions differ across trials. Some studies have highlighted benefits in mucositis-related pain or reduction in opioid use during head and neck radiotherapy, while others have reported modest effects or tolerability concerns. The present findings add weight to the prophylaxis approach specifically targeting neuropathic pain trajectories, supported by consistent improvements across primary pain scores and multiple secondary analgesic outcomes. The coherence across endpoints strengthens internal validity: when reduced pain intensity aligns with reduced breakthrough episodes and decreased opioid exposure, the likelihood of a true clinical effect increase. Differences between studies may be attributable to variations in pregabalin dose, titration speed, baseline symptom severity, concurrent chemotherapy regimens, and the degree to which neuropathic pain was distinguished from inflammatory mucositis pain. [24,25].

Several methodological considerations should inform interpretation. The randomized, double-blind design reduces performance and detection bias, and the consistent divergence over time supports robustness. Nevertheless, pain is inherently subjective and can be influenced by mood, sleep, and expectations, even with blinding. Using a neuropathic-specific instrument helps isolate the component most likely to respond to pregabalin, but overlap with nociceptive pain may persist. Analgesic prescribing practices, although typically protocolized, can vary based on clinician judgment and patient preference, potentially affecting opioid consumption outcomes. Additionally, the follow-up window after radiotherapy may not capture late-onset neuropathic sequelae associated with radiation fibrosis or delayed nerve injury. Extending follow-up could clarify whether prophylactic pregabalin modifies longer-term neuropathic persistence, not only acute and subacute trajectories. [26, 27].

The balance between efficacy and adverse events also warrants nuanced clinical application. While the overall tolerability was acceptable, dizziness and somnolence can be clinically relevant, particularly in older adults or those taking concomitant sedating medications. A practical implication is to consider individualized dosing strategies, slow titration, evening dosing, or enhanced supportive counseling to minimize functional impairment. In settings with limited monitoring resources, clinicians may prefer to identify higher-risk patients for neuropathic pain and target prophylaxis to those most likely to benefit, thereby optimizing the risk-benefit ratio. Additionally, careful documentation of adherence, reasons for missed doses, and patient-perceived benefit could enhance implementation quality and guide real-world protocols. [28,29].

In sum, the pattern of results supports a model in which pregabalin, administered prophylactically, attenuates the development and escalation of radiotherapy-induced neuropathic pain, reduces breakthrough pain volatility, and meaningfully decreases opioid exposure without introducing unacceptable toxicity. The early and sustained separation of pain trajectories suggests an effect on sensitization processes rather than symptomatic masking alone, and the concordant opioid-sparing findings provide pragmatic evidence of clinical benefit. Taken together, these outcomes argue for considering pregabalin as part of an integrated supportive-care pathway for head and neck cancer patients undergoing radiotherapy, while encouraging future studies to refine patient

selection, dosing strategies, and longer-term outcomes. [30, 31].

Conclusion

Preemptive administration of pregabalin offers an effective, opioid-sparing therapeutic strategy for managing radiotherapy-induced neuropathic pain in head and neck cancer patients. Despite mild, self-limiting central nervous system side effects such as dizziness and somnolence, the favorable efficacy and tolerability profile support its routine clinical implementation to enhance patient comfort and quality of life during oncological radiation therapy.

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All authors of this article confirm the authenticity of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Disclosure Statement

No potential conflict of interest reported by the authors.

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Authors' Contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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