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Celecoxib in Reducing Cognitive Impairment with Neoadjuvant Chemotherapy or Definitive Chemoradiation for Head and Neck Carcinoma (CELCI-HN): A Phase II Randomized Trial

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Research Article

Keywords:

Posted Date: November 11th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-10641489/v1

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Additional Declarations: No competing interests reported.

Abstract

Purpose

Chemotherapy-related cognitive impairment (CRCI) is an under-recognized consequence of cancer therapy, particularly in head and neck squamous cell carcinoma (HNSCC) patients receiving neoadjuvant chemotherapy (NACT) or definitive chemoradiation (CTRT). Celecoxib, a selective Cyclo-oxygenase-2 (COX-2) inhibitor, has demonstrated neuroprotective effects in preclinical models.

Methods

This single-centre, randomized, double-blind, placebo-controlled phase II trial evaluated the efficacy of celecoxib in reducing CRCI among patients with locally advanced HNSCC undergoing NACT followed by surgery or definitive CTRT. Patients were randomized (1:1) to receive celecoxib 100 mg twice daily or matched placebo for up to six months. Cognitive function (FACT-Cog), quality of life (FACT-H&N), psychological well-being (HADS), and neurocognition (PGI-BBD) were assessed at baseline, post-treatment, and at 3- and 6-month follow-up.

Results

Ninety-two patients were enrolled (45 placebo, 47 celecoxib). Baseline characteristics were balanced between arms. In the overall cohort, cognitive and QoL scores declined significantly from baseline to post-NACT/CTRT (FACT-Cog mean difference: 6.15; 95% CI: 1.54–10.76; p = 0.01; FACT-H&N mean difference: 9.57; 95% CI: 3.11–16.03; p = 0.004). However, no statistically significant inter-arm differences were observed at any assessment point for cognition, QoL, HADS scores, or objective neurocognitive assessment.

Conclusion

The addition of celecoxib (200 mg/day for six months) did not significantly impact cognitive function, quality of life, or psychological distress compared with placebo in patients with HNSCC receiving NACT or definitive CTRT. Further studies incorporating higher doses, and longer duration are warranted.

Trial registration

CTRI/2022/09/045579 (registered on 16/09/2022)

Introduction

Head and neck squamous cell carcinoma (HNSCC) is common in the Indian subcontinent, with the majority of patients (65%) presenting at an advanced stage (Stage III/IV).(1, 2) In cases of locally advanced HNSCC, first-line management typically involves curative-intent definitive chemoradiation (CTRT), or neoadjuvant chemotherapy (NACT) followed by surgery.(3) Though not standard, NACT is increasingly used in borderline resectable HNSCC to facilitate downstaging.(4–6)

Chemotherapy-related cognitive impairment (CRCI) is increasingly recognized as a sequel of cancer treatment and is currently an active area of research. The underlying mechanisms are still being elucidated and are thought to involve defective DNA repair pathways, microtubule disruption, reduced gliogenesis, and neuroinflammation.(7)

Most of the evidence on the incidence of chemotherapy-related cognitive impairment (CRCI) comes from studies in breast cancer cohorts(8), with limited data available for patients with HNSCC. These patients are particularly susceptible to neurocognitive decline due to exposure to chemoradiation and the involvement of central nervous system (CNS) structures within the radiation fields. Tobacco use and alcohol consumption – major etiological factors in the development of HNSCC, may also contribute to cognitive decline.(9) Existing literature suggests that approximately 40% of patients undergoing definitive or curative-intent therapy for HNSCC experience declines in both subjective and objective neurocognitive parameters, significantly impacting survivors' quality of life.(10)

The protective role of anti-inflammatory agents has been demonstrated in various neurocognitive disorders, including Alzheimer's disease.(11) Epidemiological studies have shown an association between the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and a reduced risk of developing Alzheimer's disease (AD).(12) Celecoxib, a selective cyclo-oxygenase-2 (COX-2) inhibitor, has been studied in preclinical models for its potential neuroprotective effects.(13) Proposed mechanisms include the reduction of neuroinflammation, inhibition of amyloid plaque aggregation, and suppression of prostaglandin synthesis via cyclooxygenase-2 (COX-2) inhibition.(14)

To our knowledge, there are no randomized, placebo-controlled trials in literature to systematically investigate celecoxib as a potential neuroprotective intervention in patients receiving NACT or definitive CTRT for HNSCC. The hypothesis of the current study was that the addition of an anti-inflammatory agent, celecoxib, during definitive treatment of HNSCC may reduce or prevent the development of cognitive impairment. The study was conducted with the objective of evaluating the efficacy of celecoxib in mitigating cognitive decline in patients undergoing NACT or definitive CTRT for HNSCC, compared to a placebo.

Methods

Study patients

The study included patients aged 18 to 70 years with histopathologically confirmed HNSCC who were undergoing NACT followed by surgery or definitive CTRT, and had an Eastern Cooperative Oncology

Group Performance Status (ECOG PS) of 0–2. Selection of patients for NACT followed by surgery was based on multidisciplinary discussion; patients with borderline resectable disease, high tumor burden, or anticipated surgical morbidity, where tumor downstaging was considered beneficial, were offered NACT. Patients were excluded if they had pre-existing neuropsychiatric conditions such as psychosis, schizophrenia, depression, or anxiety; were taking medications such as antipsychotics or antidepressants; were receiving psychological therapy; or had recurrent disease, metastatic disease, a secondary primary malignancy, a history of coronary artery disease, or prior use of NSAIDs for other medical conditions.

Ethical approval and consent to participate

The trial was approved by the institutional ethics committee, and written informed consent was obtained from all participants. The study was conducted in compliance with the Declaration of Helsinki and good clinical practice guidelines.

Trial design

This was a single-centre, randomized, double-blind, placebo-controlled phase II clinical trial conducted at a leading tertiary care cancer centre in North India.

Randomization

Double-blind, stratified randomization was carried out, with allocation concealment ensured through a computer-generated randomization table. Block randomization was employed with a 1:1 allocation ratio between the two study arms. Stratification was performed based on the following factors: (1) primary site of HNSCC and (2) treatment modality (NACT or definitive CTRT).

Study interventions

Patients were randomized to either Arm A (placebo – control arm) or Arm B (celecoxib – experimental arm). Participants in the experimental arm received celecoxib 100 mg oral tablets, while those in the control arm received matched placebo tablets. Both were administered twice daily, starting from day 1 of NACT/CTRT and continued for a maximum duration of six months or until the occurrence of unacceptable toxicity. Tablets were dispensed monthly, and compliance was monitored through the return of empty medication strips during follow-up visits. Study medication was withheld during NACT/CTRT-related adverse events graded as Common Terminology for Criteria for Adverse Events version 5 (CTCAE v5) grade 3–4 and was restarted once the adverse event resolved to grade 0–1, at the investigator's discretion. If the adverse event did not resolve to grade 0–1 within 14 days, the study treatment was discontinued.

Trial end points and assessments

Cognitive function was assessed using validated patient-reported outcome measures, including the Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog),(15) the Functional Assessment of Cancer Therapy – Head and Neck (FACT-HN),(16) and the Hospital Anxiety and Depression Scale (HADS).(17) Neurocognitive function was assessed objectively using the Post-Graduate Institute Battery of Brain Dysfunction (PGI-BBD).(18) Assessments were conducted at baseline (prior to the initiation of therapy), upon completion of NACT/CTRT, and at 3- and 6-months post-therapy.

The primary endpoint was the mean difference in cognitive scores between the experimental and control arms at the end of NACT/CTRT, as measured by the FACT-Cog questionnaire. Secondary endpoints included the mean difference in FACT-HN, HADS, and PGI-BBD scores between the two arms at the end of NACT/CTRT, the mean difference in cognitive scores and neurocognitive assessment at 3- and 6-months post-treatment, and the incidence of any-grade adverse events (as per CTCAE v5.0). The exploratory endpoint involved measuring plasma COX-2 levels, serum interleukins, and serum tumor necrosis factor (TNF) concentrations.

Statistical analysis

The sample size was estimated using a repeated measures design. Assuming a moderate standardized effect size of 0.5, with one pre- and one post-intervention measurement and an intra-subject correlation of 0.5, a total of 42 participants per group (84 in total) was required. After adjusting for an anticipated 10% attrition rate, the final target sample size was set at 92 participants.

Missing outcome data from patients lost to follow-up were not imputed, and the analysis was conducted using an intention-to-treat approach. Only those patients who received the assigned intervention and had cognitive scores assessed at both baseline and completion of NACT/CTRT were included in the primary analysis.

For baseline comparisons between the two arms, chi-square or Fisher’s exact tests were used for categorical variables, while independent t-tests or Wilcoxon rank-sum tests were applied for continuous variables, depending on data distribution. The mean difference in cognitive scores between the experimental and control arms was compared using an independent t-test. Univariable and multivariable logistic regression analyses were performed to identify factors associated with cognitive decline, with results reported as odds ratios and corresponding 95% confidence intervals.

All statistical analyses were performed using STATA version 13 (StataCorp, TX, USA). Safety analyses included all participants who received at least one dose of the study intervention.

Results

A total of 92 patients with HNSCC were enrolled, with 45 allocated to the placebo control arm (Arm A) and 47 to the celecoxib experimental arm (Arm B). One patient in Arm B withdrew consent, leaving 46 patients for the final analysis (Fig. 1).

Baseline demographic characteristics, summarized in Table 1, were comparable between the two arms. The median age was 51 years (range: 30–69) in Arm A and 48 years (range: 18–70) in Arm B. The majority of patients were male (93.3% in Arm A and 93.5% in Arm B). The most common primary tumor site was the oral cavity (44.4% in Arm A and 52.2% in Arm B), followed by the oropharynx (33.3% and 30.4%, respectively). Disease stage distribution was also similar, with advanced stages predominating; Stage IVA was the most frequent (37.8% in Arm A and 50.0% in Arm B). Non-keratinizing squamous cell carcinoma was the predominant histopathological subtype (82.2% in Arm A and 84.8% in Arm B).

Table 1
Baseline demographics and disease characteristics of all recruited patients

Median (range) age, years	**Arm A (Placebo – control arm)**	**Arm B (Celecoxib – experimental arm)**
	N = 45	**N = 46**
	51 (30–69)	**48 (18–70)**
Sex		
· Male	42 (93.3)	43 (93.5)
· Female	3 (6.7)	3 (6.5)
Primary tumor site		
· Oral cavity	20 (44.4)	24 (52.2)
· Nasopharynx	1 (2.2)	1 (2.2)
· Oropharynx	15 (33.3)	14 (30.4)
· Hypopharynx	4 (8.9)	4 (8.7)
· Larynx	5 (11.1)	3 (6.5)
Clinical T stage		
· T1	1 (2.2)	2 (4.3)
· T2	5 (11.1)	5 (10.9)
· T3	19 (42.2)	14 (30.4)
· T4a	15 (33.3)	17 (37.0)
· T4b	5 (11.1)	8 (17.4)
Clinical N stage		
· N0	19 (42.2)	10 (21.7)
· N1	7 (15.6)	13 (28.3)
· N2a	2 (4.4)	1 (2.2)
· N2b	2 (4.4)	8 (17.4)
· N2c	8 (17.8)	9 (19.6)
· N3a	0 (0.0)	1 (2.2)
· N3b	7 (15.6)	4 (8.7)
Stage group		

Median (range) age, years	Arm A (Placebo – control arm) N = 45	Arm B (Celecoxib – experimental arm) N = 46
	51 (30–69)	**48 (18–70)**
· Stage II	2 (4.4)	1 (2.2)
· Stage III	14 (31.1)	10 (21.7)
· Stage IVA	17 (37.8)	23 (50.0)
· Stage IVB	12 (26.7)	12 (26.1)
Histopathology		
· Keratinizing squamous cell carcinoma	8 (17.8)	7 (15.2)
· Non-keratinizing squamous cell carcinoma	37 (82.2)	39 (84.8)

Treatment modalities are detailed in Table 2. NACT was administered to 31.1% of patients in Arm A and 43.5% in Arm B; the remaining patients received definitive CTRT (68.9% and 56.5%, respectively). The most common NACT regimen was docetaxel/cisplatin/5-fluorouracil, used in 64.3% of Arm A and 50.0% of Arm B recipients, with a median of 4 cycles (range: 3–6) in Arm A and 3 cycles (range: 2–6) in Arm B. Approximately half of the patients receiving NACT underwent surgery thereafter (50.0% in Arm A and 45.0% in Arm B). All patients received cisplatin in the concurrent setting, with a median of 4 cycles in both arms (range: 2–6 in Arm A and 1–6 in Arm B).

Table 2
Treatment details of all recruited patients

Treatment modality	**Arm A (Placebo – control arm)** **N = 45**	**Arm B (Celecoxib – experimental arm)** **N = 46**
· NACT	14 (31.1)	20 (43.5)
· Definitive CTRT	31 (68.9)	26 (56.5)
NACT regimen	N = 14	N = 20
· Docetaxel/Cisplatin/5-FU	9 (64.3)	10 (50.0)
· Docetaxel/Cisplatin	4 (28.6)	7 (35.0)
· Docetaxel/Carboplatin	0 (0.0)	2 (10.0)
· Gemcitabine/Cisplatin	1 (7.1)	1 (5.0)
Median (range) number of cycles of NACT	4 (3–6)	3 (2–6)
Post-NACT those who underwent surgery	7 (50.0)	9 (45.0)
Adjuvant chemoradiation received among those who underwent surgery	5 (71.4)	6 (66.7)
Concurrent chemotherapy regimen	N = 31	N = 26
· Cisplatin	31 (100.0)	26 (100.0)
Median (range) number of cycles of concurrent chemotherapy	4 (2–6)	4 (1–6)

In the overall cohort, there was a significant reduction in cognitive function (assessed using FACT-cog scale, Fig. 2) from baseline to post-NACT or definitive CTRT (mean difference: 6.15; 95% CI: 1.54–10.76; p = 0.01). However, there was no statistically significant differences between arms at any time point (baseline, post-NACT/CTRT, 3 months, or 6 months) as highlighted in Table 3. At baseline, mean total scores (± SD) were 117.49 ± 15.82 in Arm A and 119.26 ± 13.17 in Arm B (mean difference: −1.77; 95% CI: −7.82 to 4.28; p = 0.562). Post-treatment, scores declined to 111.73 ± 13.65 and 112.71 ± 16.82 (mean difference: −0.98; p = 0.790). At 3 months, scores were 111.40 ± 20.38 and 113.56 ± 14.86 (mean difference: −2.16; p = 0.797), and at 6 months, 113.50 ± 13.92 and 111.75 ± 19.43 (mean difference: 1.75; p = 0.888). Subdomains such as Perceived Cognitive Abilities (CogPCA), Perceived Cognitive Impairments (CogPCI), Comments from Others (CogOth), and Impact of Perceived Cognitive Impairments on Quality of Life (CogQoL) demonstrated similar trends, with minor score fluctuations without statistically significant difference between the two arms.

Table 3
FACT-cog scale

Domains of FACT-cog scale	Arm A Mean ± SD	Arm B Mean ± SD	Mean difference	95% CI of the difference	P value
At baseline					
FACT-cog Total score	117.49 ± 15.82	119.26 ± 13.17	-1.77	-7.82–4.28	0.562
CogPCA	24.29 ± 5.60	24.96 ± 4.37	-0.67	-2.76–1.42	0.527
CogPCI	68.51 ± 7.46	69.04 ± 5.60	-0.53	-3.28–2.21	0.701
CogOth	14.44 ± 2.13	14.63 ± 1.50	-0.19	-0.95–0.58	0.630
CogQoL	10.24 ± 4.96	10.63 ± 4.75	-0.39	-2.41–1.64	0.705
After NACT or Definitive CTRT					
FACT-cog Total score	111.73 ± 13.65	112.71 ± 16.82	-0.98	-8.31–6.34	0.790
CogPCA	22.21 ± 5.09	23.76 ± 5.25	-1.55	-4.01–0.91	0.212
CogPCI	67.97 ± 7.10	67.26 ± 8.65	0.71	-3.08–4.49	0.711
CogOth	13.85 ± 2.17	14.00 ± 2.33	-0.15	-1.22–0.92	0.778
CogQoL	7.70 ± 3.85	7.68 ± 4.12	0.02	-1.89–1.91	0.989
At 3 months post treatment completion					
FACT-cog Total score	111.40 ± 20.38	113.56 ± 14.86	-2.16	-19.60–15.29	0.797
CogPCA	21.40 ± 5.19	23.89 ± 3.92	-2.49	-6.98–2.01	0.259
CogPCI	66.70 ± 10.31	67.11 ± 7.08	-0.41	-9.07–8.25	0.921
CogOth	13.50 ± 3.27	13.78 ± 1.20	-0.28	-2.72–2.17	0.813
CogQoL	9.80 ± 4.76	8.78 ± 5.65	1.02	-4.02–6.06	0.674
At 6 months post treatment completion					

Domains of FACT-cog scale	Arm A Mean ± SD	Arm B Mean ± SD	Mean difference	95% CI of the difference	P value
FACT-cog Total score	113.50 ± 13.92	111.75 ± 19.43	1.75	-27.49–30.99	0.888
CogPCA	22.75 ± 3.50	25.00 ± 4.08	-2.25	-8.83–4.33	0.435
CogPCI	69.75 ± 2.22	67.75 ± 7.23	2.00	-7.25–11.25	0.616
CogOth	12.75 ± 2.22	12.25 ± 2.36	0.50	-3.46–4.46	0.768
CogQoL	8.25 ± 7.37	6.75 ± 7.27	1.50	-11.17–14.17	0.782

Quality of life, assessed by the FACT-H&N scale (Table 4), also revealed significant reduction in scores in the overall cohort post-NACT or definitive CTRT (mean difference: 9.57; 95% CI: 3.11–16.03, p = 0.004). However, there were no significant inter-arm differences at any assessment point. At baseline, mean total scores (± SD) were 115.47 ± 24.45 in Arm A and 115.19 ± 20.14 in Arm B (mean difference: 0.28; p = 0.953). Post-treatment, scores declined to 104.33 ± 18.39 and 107.08 ± 19.14 (mean difference: −2.75; p = 0.541). At 3 months, Arm A scored higher (119.30 ± 16.31) than Arm B (109.00 ± 27.56) (mean difference: 10.30; p = 0.329), while at 6 months, scores were 107.25 ± 29.76 and 92.75 ± 34.19 (mean difference: 14.50; p = 0.546). Subdomains, including Physical Well-Being (PWB), Social/Family Well-Being (SWB), Emotional Well-Being (EWB), Functional Well-Being (FWB), and Head and Neck Cancer Subscale (HNCS) showed comparable patterns, with declines following treatment and partial recovery thereafter, without statistical significance.

Table 4
FACT-H&N scale

Domains of FACT-H&N scale	Arm A Mean ± SD	Arm B Mean ± SD	Mean difference	95% CI of the difference	P value
At baseline					
FACT-H&N Total score	115.47 ± 24.45	115.19 ± 20.14	0.28	-9.04–9.60	0.953
PWB	21.96 ± 6.32	21.65 ± 6.09	0.31	-2.28–2.89	0.816
SWB	26.47 ± 3.53	27.17 ± 2.37	-0.70	-1.95–0.55	0.269
EWB	19.84 ± 5.63	19.61 ± 5.13	0.23	-2.01–2.48	0.835
FWB	20.07 ± 6.16	20.15 ± 5.70	-0.08	-2.56–2.39	0.945
HNCS	27.13 ± 7.61	26.61 ± 5.89	0.52	-2.31–3.36	0.525
After NACT or Definitive CTRT					
FACT- H&N Total score	104.33 ± 18.39	107.08 ± 19.14	-2.75	-11.67–6.18	0.541
PWB	19.18 ± 4.90	18.71 ± 6.17	0.47	-2.20–3.14	0.725
SWB	26.36 ± 3.38	27.37 ± 2.10	-1.01	-2.32–0.31	0.132
EWB	18.97 ± 4.87	18.82 ± 4.78	0.15	-2.13–2.44	0.894
FWB	16.61 ± 4.26	17.29 ± 4.94	-0.68	-2.86–1.50	0.534
HNCS	23.82 ± 5.31	25.39 ± 5.90	-1.57	-4.25–1.10	0.244
At 3 months post treatment completion					
FACT- H&N Total score	119.30 ± 16.31	109.00 ± 27.56	10.30	-11.34–31.94	0.329
PWB	23.40 ± 3.06	19.78 ± 8.07	3.62	-2.17–9.41	0.204
SWB	26.30 ± 3.83	27.00 ± 2.29	-0.70	-3.80–2.40	0.640

Domains of FACT-H&N scale	Arm A Mean ± SD	Arm B Mean ± SD	Mean difference	95% CI of the difference	P value
EWB	22.20 ± 3.71	17.56 ± 7.04	4.64	-0.72–10.01	0.085
FWB	19.90 ± 3.90	18.22 ± 5.70	1.68	-3.00–6.36	0.460
HNCS	27.50 ± 5.13	26.44 ± 7.60	1.06	-5.16–7.27	0.724
At 6 months post treatment completion					
FACT- H&N Total score	107.25 ± 29.76	92.75 ± 34.19	14.50	-40.96–69.96	0.546
PWB	20.50 ± 7.05	16.75 ± 9.91	3.75	-11.13–18.63	0.560
SWB	27.50 ± 0.58	27.50 ± 0.58	0.00	-1.00–1.00	1.000
EWB	18.00 ± 6.93	12.50 ± 9.04	5.50	-8.43–19.43	0.371
FWB	17.50 ± 6.56	15.50 ± 7.23	2.00	-9.95–13.95	0.696
HNCS	23.75 ± 9.74	20.50 ± 8.96	3.25	-12.95–19.45	0.641

Anxiety and depression, assessed using HADS, likewise showed no significant differences between the groups (Table 5). Baseline depression scores (± SD) were 2.80 ± 3.22 in Arm A and 2.85 ± 3.70 in Arm B (mean difference: −0.05; p = 0.948), and baseline anxiety scores were 3.07 ± 4.31 and 3.04 ± 4.04, respectively (mean difference: 0.03; p = 0.979). Post-treatment, depression scores increased to 4.52 ± 2.80 in Arm A and 4.16 ± 3.14 in Arm B (mean difference: 0.36; p = 0.617), and anxiety scores increased to 3.76 ± 3.10 and 4.32 ± 3.97 (mean difference: −0.56; p = 0.516).

Table S1
Longitudinal neurocognitive assessment using PGI-BDD scale

Normally distributed variables represented as mean ± SD, independent t-test				
Domain	Time point	Arm A Mean ± SD	Arm B Mean ± SD	p value
Remote Memory	Baseline	5.88 ± 0.35	5.67 ± 0.59	0.369
	Post-NACT/CTRT	5.13 ± 0.83	5.65 ± 0.49	NS
	6 months	5.63 ± 0.52	5.56 ± 0.62	NS
Recent Memory	Baseline	4.75 ± 0.46	4.56 ± 0.62	0.434
	Post-NACT/CTRT	4.13 ± 0.83	4.29 ± 0.69	NS
	6 months	4.38 ± 0.52	4.72 ± 0.57	NS
Mental Balance	Baseline	5.00 ± 1.41	5.28 ± 2.35	0.760
	Post-NACT/CTRT	4.50 ± 2.39	5.35 ± 2.76	NS
	6 months	6.00 ± 2.07	5.94 ± 2.29	NS
Attention & Concentration	Baseline	7.38 ± 2.07	7.22 ± 1.83	0.852
	Post-NACT/CTRT	6.88 ± 1.64	7.24 ± 1.60	NS
	6 months	5.75 ± 1.75	6.56 ± 1.95	NS
Delayed Recall	Baseline	7.38 ± 1.77	7.72 ± 1.45	0.602
	Post-NACT/CTRT	6.88 ± 1.55	7.24 ± 1.79	NS
	6 months	6.25 ± 1.98	7.00 ± 1.78	NS
Immediate Recall	Baseline	8.75 ± 1.83	8.94 ± 1.66	0.792
	Post-NACT/CTRT	9.63 ± 0.74	10.00 ± 1.37	NS
	6 months	8.25 ± 0.71	9.33 ± 1.24	NS
Retention – Similar Pairs	Baseline	3.75 ± 0.71	3.67 ± 1.14	0.851
	Post-NACT/CTRT	3.50 ± 1.20	3.82 ± 1.19	NS
	6 months	3.38 ± 0.52	3.72 ± 0.83	NS
Recognition	Baseline	8.63 ± 1.06	8.06 ± 1.35	0.303
	Post-NACT/CTRT	8.50 ± 1.20	7.88 ± 1.58	NS
	6 months	7.00 ± 1.31	7.39 ± 1.24	NS
Performance IQ	Baseline	94.0 ± 27.2	95.2 ± 34.5	0.934

Normally distributed variables represented as mean ± SD, independent t-test				
	Post-NACT/CTRT	90.8 ± 18.8	96.4 ± 17.9	NS
	6 months	81.9 ± 16.1	84.9 ± 20.1	NS
TQ – Information	Baseline	13.3 ± 4.7	14.5 ± 5.1	0.558
	Post-NACT/CTRT	12.5 ± 4.3	13.6 ± 5.5	NS
	6 months	12.75 ± 4.10	12.28 ± 2.61	NS
TQ – Digit Span	Baseline	7.88 ± 1.25	7.56 ± 2.23	0.709
	Post-NACT/CTRT	7.00 ± 1.77	7.53 ± 1.91	NS
	6 months	6.25 ± 1.49	6.67 ± 1.68	NS
TQ – Arithmetic	Baseline	7.88 ± 1.64	7.61 ± 1.61	0.705
	Post-NACT/CTRT	8.63 ± 1.19	8.53 ± 2.72	NS
	6 months	6.50 ± 1.20	7.56 ± 2.59	NS
TQ – Comprehension	Baseline	20.3 ± 4.3	20.9 ± 5.2	0.764
	Post-NACT/CTRT	17.8 ± 5.6	20.3 ± 5.0	NS
	6 months	16.0 ± 3.2	14.8 ± 2.6	NS
Nahor & Benson test	Baseline	4.13 ± 2.42	4.11 ± 1.91	0.988
	Post-NACT/CTRT	4.00 ± 2.20	3.88 ± 1.87	NS
	6 months	3.75 ± 0.71	3.11 ± 1.28	NS
Skewed variables represented as Median (IQR), Mann Whitney test				
Retention – Dissimilar	Baseline	6 (4.5–7.5)	7 (4–8)	0.673
	Post-NACT/CTRT	6.5 (4.5–8)	7 (6–11)	NS
	6 months	7.5 (6.5–8.5)	7 (6–8)	NS
Visual Retention	Baseline	8 (6–8.5)	8.5 (5–10)	0.738
	Post-NACT/CTRT	7 (7–10)	7 (4–9)	NS
	6 months	7.5 (6.5–8.5)	7 (6–8)	NS
P/K ×100	Baseline	167 (121–275)	127 (107–236)	0.304
	Post-NACT/CTRT	150 (138–195)	150 (135–236)	NS
	6 months	184 (142–227)	150 (133–178)	NS
PQ–VQ Difference	Baseline	17.5 (13–19.5)	8.5 (7–17)	0.066

Normally distributed variables represented as mean ± SD, independent t-test				
	Post-NACT/CTRT	14 (9.5–24)	14 (7–18)	NS
	6 months	7 (4–16.5)	11 (4–28)	NS
Bender–Gestalt test	Baseline	11 (4.5–13)	7.5 (4–12)	0.522
	Post-NACT/CTRT	14 (11.5–17)	9 (5.4–13)	NS
	6 months	11 (5–17)	9 (7–13)	NS

Table 5
HADS scale

Domains of HADS scale	Arm A Mean ± SD	Arm B Mean ± SD	Mean difference	95% CI of the difference	P value
At baseline					
Depression score	2.80 ± 3.22	2.85 ± 3.70	-0.05	-1.49–1.40	0.948
Anxiety score	3.07 ± 4.31	3.04 ± 4.04	0.03	-1.72–1.76	0.979
After NACT or Definitive CTRT					
Depression score	4.52 ± 2.80	4.16 ± 3.14	0.36	-1.06–1.78	0.617
Anxiety score	3.76 ± 3.10	4.32 ± 3.97	-0.56	-2.27–1.15	0.516
At 3 months post treatment completion					
Depression score	2.10 ± 1.79	3.78 ± 4.79	-1.68	-5.11–1.75	0.316
Anxiety score	1.60 ± 2.32	4.00 ± 5.87	-2.40	-6.64–1.84	0.248
At 6 months post treatment completion					
Depression score	5.25 ± 5.50	6.25 ± 7.09	-1.00	-11.98–9.98	0.831
Anxiety score	5.00 ± 6.27	7.75 ± 8.42	-2.75	-15.60–10.10	0.619

The objective neurocognitive assessment was done using PGI-BBD scale (Supplementary table 1). At baseline, there were no statistically significant differences between the two arms across neurocognitive domains including memory, attention, intelligence quotient measures, and visuospatial function.

Following treatment, both arms demonstrated preservation of neurocognitive performance across most domains, with no significant between-group differences observed at the post-NACT/CTRT or 6-month follow-up assessments. Longitudinal comparison at each time point revealed comparable scores for remote and recent memory, attention and concentration, recall, performance IQ, and executive function between the two arms. Overall, treatment-related neurocognitive outcomes remained stable over time, with no evidence of differential cognitive decline between celecoxib and placebo groups.

Discussion

This is the first clinical trial to evaluate the potential of celecoxib to mitigate CRCI in patients with locally advanced HNSCC undergoing either NACT followed by surgery or definitive CTRT. The current study aligns with prior evidence that chemoradiation causes cognitive impairment and poor QoL in patients with HNSCC.

A systematic review on nasopharyngeal carcinoma (73% received radiation, 61% received chemotherapy) reported inferior neurocognitive outcomes, particularly in domains such as memory and language.(19) A small prospective study (n = 55) involving patients with head and neck cancer receiving primary or adjuvant CTRT showed a 22% decline in neurocognitive performance after treatment completion, with the greatest decline seen in language function.(20) Another prospective longitudinal study (n = 80) revealed that head and neck cancer survivors experience neurocognitive sequelae persisting up to two years post-CTRT.(10) In the present study, there was a significant decline in mean FACT-Cog and FACT-H&N scores from baseline to post-NACT or definitive CTRT, highlighting the need for preventive measures.

However, celecoxib at a dose of 100 mg twice daily for up to six months did not confer a statistically significant benefit over placebo in preserving cognitive function, QoL, or psychological well-being at any assessed time point. Preclinical data support celecoxib's neuroprotective potential via prostaglandin E2 suppression and microglial modulation,(13) but clinical translation appears to vary across contexts. In non-oncologic settings, celecoxib has shown mixed results. It reduced the incidence of Post-Operative Cognitive Decline (POCD) from 34.1% to 12.3% ($p < 0.05$) seven days after total knee arthroplasty in geriatric patients.(21) Celecoxib at 200–400 mg/day improved delayed recall scores versus placebo in adults with age-associated memory loss.(14) Conversely, in amyotrophic lateral sclerosis (ALS), celecoxib (800 mg/day) did not slow the reduction in muscle strength, vital capacity, motor unit number estimates, or ALS Functional Rating Scale-Revised.(22) A systematic review and meta-analysis found that observational studies supported the use of both aspirin and non-aspirin NSAIDs in preventing Alzheimer's disease,(23) although RCTs such as ADAPT showed no cognitive benefit from rofecoxib (25 mg/day) or naproxen (220 mg twice daily).(24)

In the oncologic setting, a retrospective study (n = 61) on nasopharyngeal carcinoma reported that combining celecoxib with hippocampal-sparing Intensity Modulated Radiation Therapy (IMRT) preserved

cognitive function, improved QoL, and reduced adverse effects compared with hippocampal-sparing IMRT or IMRT alone.(25) No other comparable studies are available in the literature.

Several factors may explain the negative findings of the current study. First, the dose used (200 mg/day) may have been subtherapeutic, as neuroprotective effects have typically been observed with doses ranging from 400 to 800 mg/day in studies on POCD, ALS, and AD. Second, a longer treatment duration with follow-up assessments at one and two years might have revealed delayed benefits, as previous studies indicate that cognitive impairments in HNSCC can persist beyond two years post-treatment. Third, treatment heterogeneity may have influenced the observed outcomes, including the use of different NACT regimens, variation in the number of NACT cycles administered (4 vs 3 in arms A and B, respectively), and differences in the proportion of patients who received radiotherapy (68.9% vs 56.5% in arms A and B). Although such variability reflects real-world practice, it may have introduced confounding effects on cognitive outcomes and limits the ability to attribute changes solely to the intervention under study. In patients receiving head and neck radiotherapy, incidental irradiation of the temporal lobes may contribute to neurocognitive decline and act as a potential confounder in interpreting cognitive outcomes. Additionally, age heterogeneity and the lack of age-stratified analysis due to the small sample size may have further influenced cognitive outcomes. The sample size calculation was based on an assumed effect size of 0.5, which may have been overestimated, potentially resulting in an underpowered study. Standardized normative data for several neurocognitive assessment tools in the Indian population are limited, restricting comparison of observed scores with population-based reference values.

Although, adjunctive celecoxib at 200 mg/day for six months did not mitigate CRCI, QoL deterioration, or psychological distress in patients with HNSCC receiving NACT or definitive CTRT, the findings from the current study underscore the need for targeted strategies to address cognitive decline. Future phase III trials should incorporate higher dosing, longer treatment duration, or alternative agents such as ibuprofen or naproxen, along with biomarker-based stratification to identify responders. In addition to COX-2 inhibition, other pharmacological strategies aimed at mitigating treatment-related cognitive impairment warrant exploration. Memantine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has demonstrated potential in preserving cognitive function in patients receiving brain irradiation, suggesting a possibility of further evaluation.(26, 27) Non-pharmacological cognitive rehabilitation strategies, such as computer-assisted training, aerobic exercise, music therapy, yoga, and meditation, may offer supportive benefits for cognitive function. Multimodal approaches hold promise for improving survivorship and cognitive outcomes in this vulnerable group.

Conclusion

The trial results indicate that the addition of celecoxib (200 mg/day for six months) does not significantly affect cognitive function, QoL, or psychological distress compared with placebo in patients with HNSCC receiving NACT or definitive CTRT.

Declarations

Previous presentations

The study protocol was presented in ASCO 2024 Annual meeting (abstract no. TPS12150)

Ethics approval:
The study is approved by the Institute Ethics Committee for Post Graduate Research, All India Institute of Medical Sciences, New Delhi – 110029 (Ref. No.: IECPG-426/26.05.2022)

Competing interests:

All authors declare no conflicts of interest.

Funding:

Funded by ASCO-IIG (Grant no. 2023IIG-2027394517)

Author Contribution

Swasthik Upadhya, Atul Sharma, Aparna Sharma were major contributors in study conception, analysis and interpretation of results and writing the manuscript. Alok Thakar, Kapil Sikka, Rajeev Kumar, Amit Chirom Singh, Smriti Panda, Suman Bhasker, Ahitagni Biswas, Aman Sharma, Vaibhav Patil, Abhinav Sharma, Sanjay Kumar Meena, Raja Pramanik, Babita Kataria, Akash Kumar and Sameer Bakhshi helped with data collection, interpretation of results and editing the manuscript. Rahul Bisht and Varsha Tiwari helped with data collection and neuropsychiatric assessment. All authors read, reviewed and approved the final manuscript.

Acknowledgement

This trial was conceptualized during the Asia-Pacific Clinical Oncology Research Development (ACORD) 2021 online workshop and was supported by the American Society of Clinical Oncology International Innovation Grant (ASCO-IIG; Grant No. 2023IIG-2027394517). We acknowledge the support of ACORD and ASCO, and we thank all the patients who consented to participate in this study.

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Figures

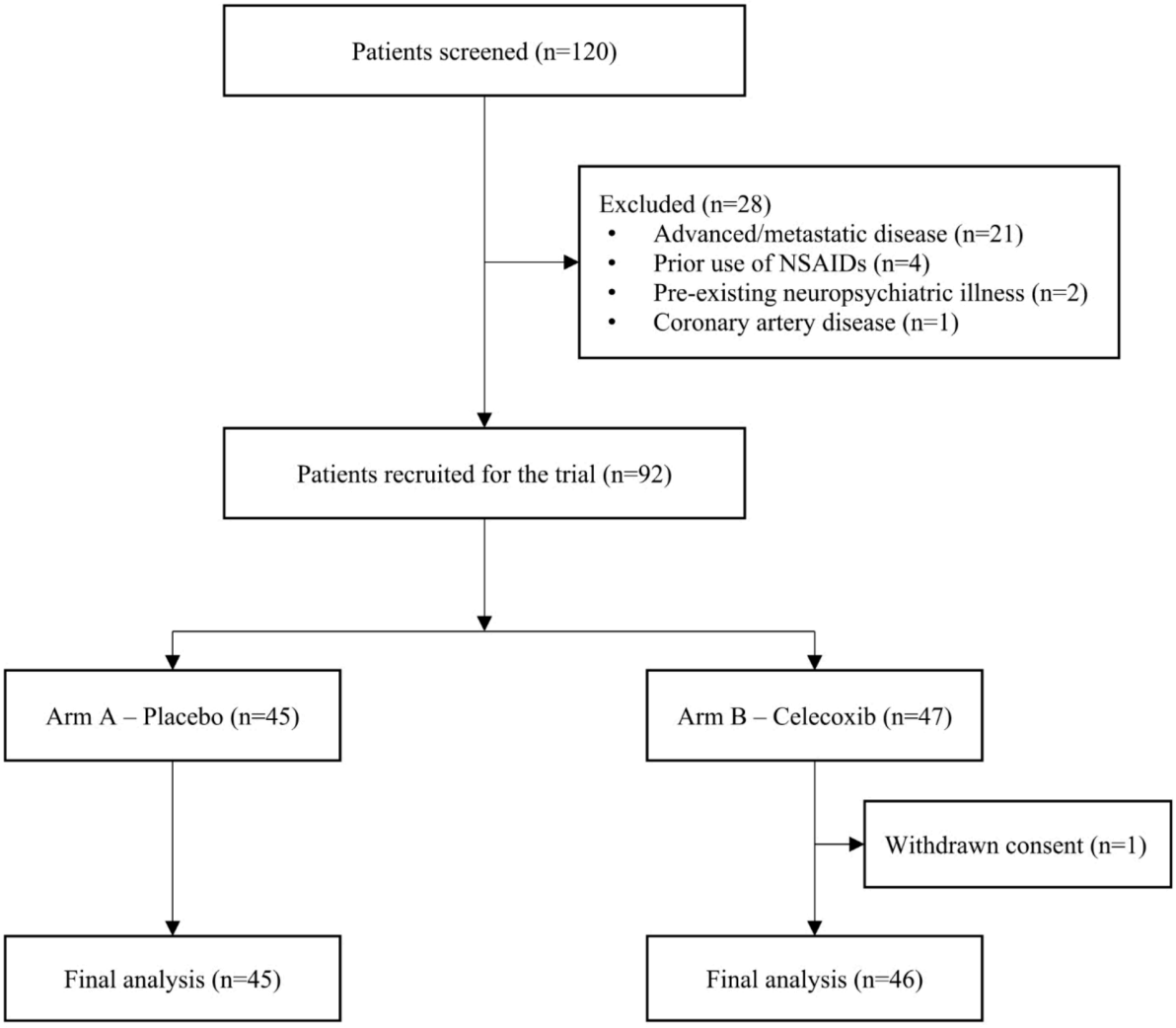


Figure 1

CONSORT diagram

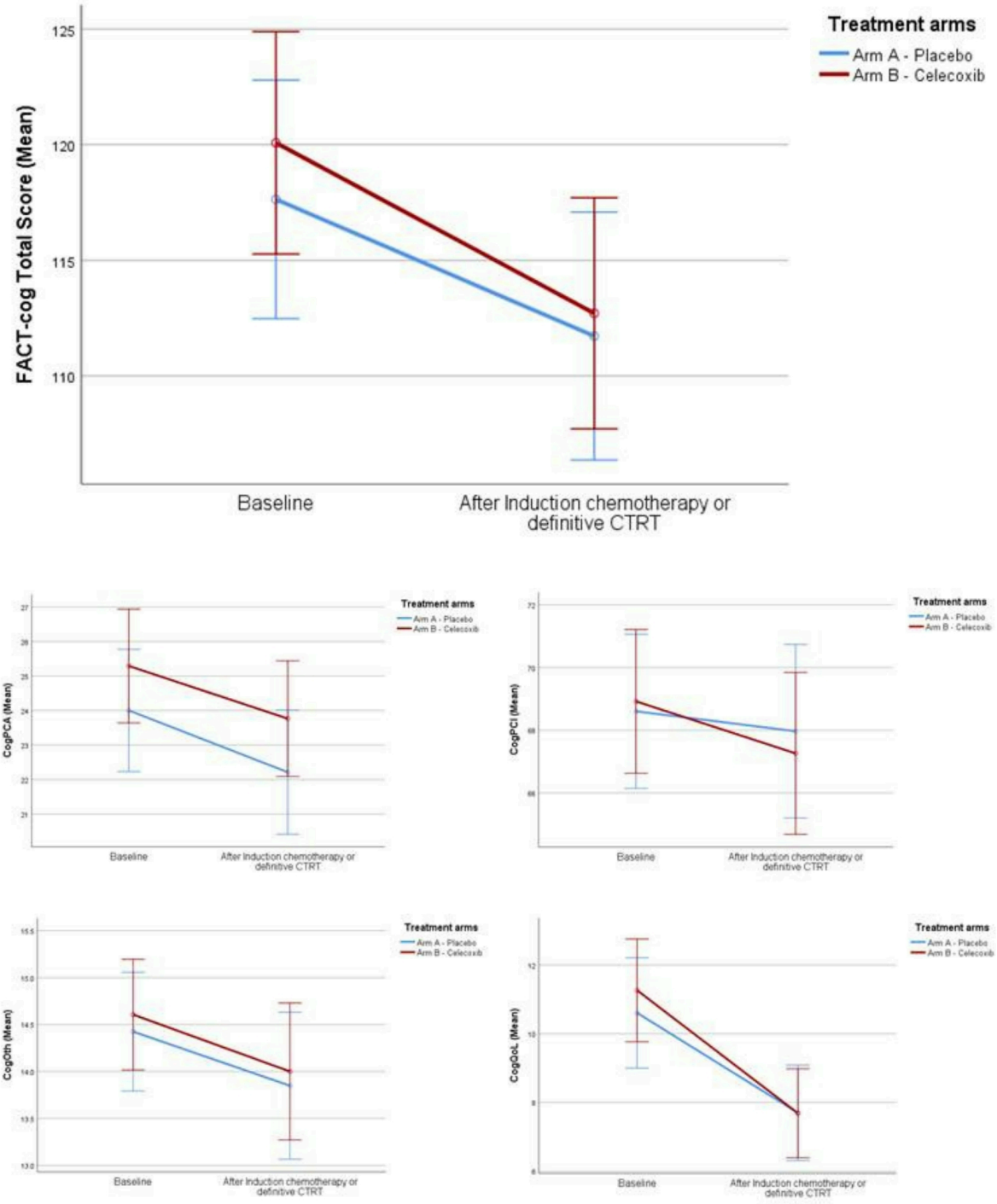


Figure 2

FACT-cog scale before and after treatment

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