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EFFECT OF AREA POSTERMA AND DORSAL VAGAL COMPLEX (AP/DVC) SPARING ON THE INCIDENCE AND SEVERITY OF ACUTE NAUSEA AND VOMITING IN PATIENTS UNDERGOING WHOLE BRAIN RADIOTHERAPY (WBRT)

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ABSTRACT:
Objectives: To compare the incidence of grade ≥2 nausea and vomiting among patients undergo whole-brain radiotherapy (WBRT) with and without area postrema (AP) and dorsal vagal complex (DVC) sparing.
Materials and Methods: After approval from the Hospital Ethical Review Committee and CPSP, 106 eligible patients were enrolled after obtaining written informed consent. Demographic data and baseline nausea and vomiting were recorded using CTCAE grading. Patients underwent CT simulation and were randomized to AP/DVC-sparing or conventional WBRT, receiving 30 Gy in 10 fractions. Nausea and vomiting were reassessed after 14 days using CTCAE criteria and recorded on a pre-designed proforma. Data quality was ensured through completeness checks and quality-control measures, and SPSS version 25 was used for data entry and analysis.
Results: Both groups comprised 53 patients. AP/DVC-sparing WBRT was associated with significantly less Grade ≥2 nausea than conventional WBRT (20.8% vs. 56.6%, p=0.00), while Grade ≥2 vomiting was also lower but not statistically significant (11.3% vs. 24.5%, p=0.07). Nausea severity varied significantly by some age and gender categories, whereas vomiting showed no significant association with age, gender, or number of brain metastases.
Conclusion: It was concluded that AP/DVC-sparing WBRT significantly reduced the incidence and severity of acute nausea compared with conventional WBRT, while a non-significant reduction in vomiting was observed. These findings suggest that AP/DVC sparing may be a useful planning strategy for reducing acute radiation-induced nausea during WBRT without compromising the treatment approach.

KEYWORDS: Nausea, vomiting, whole-brain radiotherapy

INTRODUCTION:

Whole-brain radiotherapy (WBRT) remains a cornerstone in the management of multiple brain metastases and central nervous system prophylaxis (1-3). However, conventional WBRT is frequently accompanied by acute adverse effects, most notably radiation-induced nausea and vomiting (RINV), which can significantly impair a patient's quality of life and compliance with treatment (4). Physiologically, acute emesis is primarily mediated by the chemoreceptor trigger zone located within the area postrema and the surrounding dorsal vagal complex (AP/DVC) in the brainstem (5). During standard WBRT, these critical emetic structures invariably receive high radiation doses, triggering severe gastrointestinal symptoms that often necessitate aggressive pharmacological intervention (4). With recent advancements in modern conformal radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT) and volumetric-modulated arc therapy (VMAT), it has become dosimetrically feasible to selectively spare specific functional brain regions, analogous to hippocampal-sparing strategies (6). Although emerging data suggest that minimizing the radiation dose to the AP/DVC can substantially mitigate the incidence and severity of acute nausea and vomiting, clinical evidence directly comparing AP/DVC-sparing WBRT with conventional WBRT remains limited. Therefore, this study aims to evaluate the clinical impact of AP/DVC-sparing whole-brain radiotherapy on the incidence and severity of acute nausea and vomiting, potentially offering a safer, more tolerable therapeutic alternative for patients requiring cranial irradiation.
Objective: To compare the incidence of grade ≥2 nausea and vomiting among patients undergo whole-brain radiotherapy (WBRT) with and without area postrema (AP) and dorsal vagal complex (DVC) sparing.

MATERIALS AND METHODS:

Study Design: Prospective, randomized, controlled trial.

Study setting: Department of Radiation oncology at INMOL Hospital.
Duration of the study: The study duration was 3 month from 7 April 2026 to 7 July 2026.
Sampling Technique:
Non-probability Consecutive sampling.
Sample size: A total of 106 patients were enrolled, with 53 patients allocated to each group**.** The sample size was calculated using a 95% confidence level and 90% statistical power**,** assuming an expected incidence of nausea of 45.7% (7) in the conventional WBRT group and 17% (8) in the AP/DVC-sparing group**.**
Selection criteria:
Inclusion criteria:
- Patients aged 18–70 years.
- Patients with histologically confirmed solid malignancy with brain metastases, as defined by the operational criteria, requiring WBRT (30 Gy in 10 fractions).

Exclusion criteria:
- Patients planned for hippocampal-avoidance WBRT or stereotactic radiosurgery (SRS) alone.
- Intracranial lesions located within 1 cm of the contoured AP/DVC volume.
- Pre-existing nausea or vomiting (CTCAE grade ≥1) within 24 hours before WBRT.
- Concurrent emetogenic chemotherapy during WBRT.
- Medical conditions causing chronic nausea or vomiting.

Methods: After obtaining approval from the hospital's Ethical Review Committee and CPSP, 106 patients meeting the selection criteria were identified and approached for participation. Written informed consent was obtained from eligible patients. Demographic information, including age and sex, was recorded. Baseline nausea and vomiting were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) grading system. Patients underwent CT simulation for WBRT planning, and the AP/DVC was contoured according to the study protocol. Patients were randomized into either the experimental group (AP/DVC sparing) or control group. WBRT was administered according to the standardized protocol of 30 Gy in 10 fractions. During treatment, patients completed symptom questionnaires to assess nausea and vomiting after 14 days. The severity of nausea and vomiting was graded using the CTCAE system. Data were collected on a pre-designed proforma and checked for completeness and accuracy. Quality-control procedures were performed to ensure data reliability, while potential bias was minimized through appropriate exclusion criteria. The SPSS version 25 was used to enter and analyze the gathered data.

RESULTS:
The study compared two groups of 53 patients each undergoing AP/DVC sparing versus conventional whole-brain radiotherapy (WBRT). The AP/DVC sparing group had a mean age of 44.47±11.86 years with 33 males (62.3%) and 20 females (37.7%), while the conventional WBRT group had a mean age of 48.22±13.79 years with 28 males (52.8%) and 25 females (47.2%). Across both cohorts, the age distribution included 8 patients aged 20-30 years (15.1% in each group); 15 (28.3%) versus 11 (20.8%) aged 31-40 years; 8 (15.1%) in each group aged 41-50 years; 18 (34.0%) versus 12 (22.6%) aged 51-60 years; and 4 (7.5%) versus 14 (26.4%) older than 60 years. Regarding brain metastases, 35 patients (66.0%) in the AP/DVC sparing group and 32 (60.4%) in the conventional WBRT group had 1–3 metastases, while 18 (34.0%) and 21 (39.6%) had more than 3 metastases, respectively. Finally, regarding toxicity outcomes, nausea of grade less than 2 was observed in 42 patients (79.2%) of the AP/DVC sparing group versus 23 (43.4%) in the conventional WBRT group, whereas grade 2 or higher nausea occurred in 11 (20.8%) versus 30 patients (56.6%). Vomiting of grade less than 2 was reported in 47 patients (88.7%) in the AP/DVC sparing group compared to 40 (75.5%) in the conventional WBRT group, with grade 2 or higher vomiting seen in 6 (11.3%) versus 13 patients (24.5%) (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics (n=106)

	Groups	
	AP/DVC Sparing (n=53)	Conventional WBRT (n=53)
Age (Years)	44.47±11.86	48.22±13.79
Gender		
Male	33(62.3%)	28(52.8%)
Female	20(37.7%)	25(47.2%)
Age Groups		
20-30 years	8(15.1%)	8(15.1%)
31-40 years	15(28.3%)	11(20.8%)
41-50 years	8(15.1%)	8(15.1%)

51-60 years	18(34.0%)	12(22.6%)
>60 years	4(7.5%)	14(26.4%)
Number of brain metastases		26.80±3.42
1–3	35(66.0%)	32(60.4%)
>3	18(34.0%)	21(39.6%)
Incidence of nausea		
Grade <2	42(79.2%)	23(43.4%)
Grade ≥2	11(20.8%)	30(56.6%)
Vomiting		
Grade <2	47(88.7%)	40(75.5%)
Grade ≥2	6(11.3%)	13(24.5%)

Regarding nausea, Grade <2 nausea was observed in 42 (79.2%) patients in the AP/DVC-sparing group compared with 23 (43.4%) in the conventional WBRT group, while Grade ≥2 nausea occurred in 11 (20.8%) and 30 (56.6%) patients, respectively, showing a statistically significant difference (p=0.00). For vomiting, Grade <2 was observed in 47 (88.7%) patients in the AP/DVC-sparing group and 40 (75.5%) in the conventional WBRT group, whereas Grade ≥2 vomiting occurred in 6 (11.3%) and 13 (24.5%) patients, respectively; however, this difference was not statistically significant (p=0.07) (Table 2).

Table 2: Stratification of Hypertriglyceridemia on the basis of Demographic and Clinical Characteristics (n=106)

Variables	**Groups**		
	AP/DVC Sparing (n=53)	Conventional WBRT (n=53)	P-Value
Nausea			
Grade <2	42(79.2%)	23(43.4%)	
Grade ≥2	11(20.8%)	30(56.6%)	0.00
Vomiting			
Grade <2	47(88.7%)	40(75.5%)	0.07
Grade ≥2	6(11.3%)	13(24.5%)	

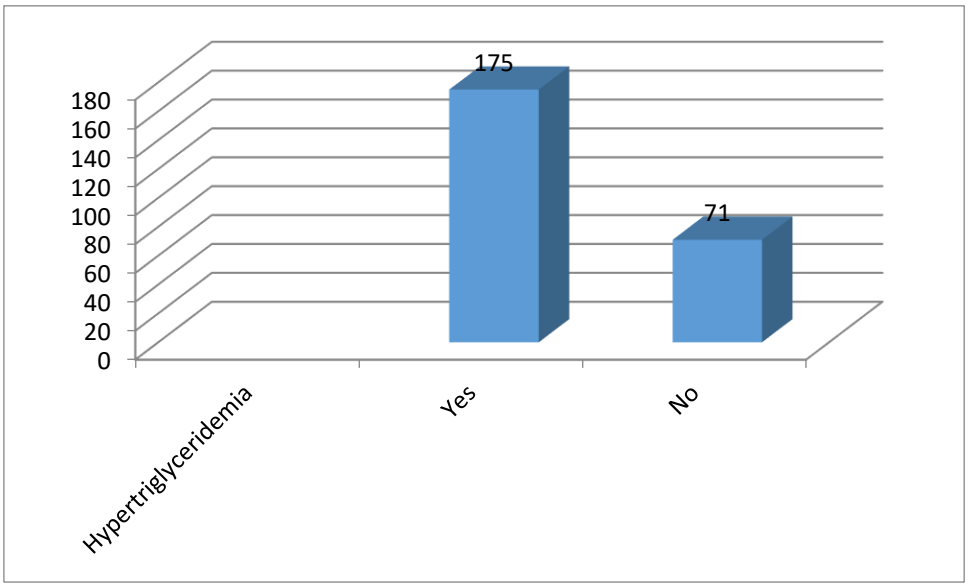


Fig 1: Frequency of patients on the basis of Hypertriglyceridemia

Regarding age, Grade <2 nausea was more frequent in the AP/DVC-sparing group than in the conventional WBRT group among patients aged 20–30 years (87.5% vs. 12.5%, p=0.03), 31–40 years (66.7% vs. 33.3%, p=0.27), 41–50 years (100.0% vs. 0.0%, p=0.00), 51–60 years (77.8% vs. 22.2%, p=0.04), and >60 years (75.0% vs. 25.0%, p=0.68). Conversely, Grade ≥2 nausea was more common in the conventional WBRT group across all age categories. Regarding gender, Grade <2 nausea was observed in 24 (66.7%) male patients in the AP/DVC-sparing group compared with 12 (33.3%) in the conventional WBRT group (p=0.01), while Grade ≥2 nausea occurred in 9 (36.0%) and 16 (64.0%) patients, respectively. Among females, Grade <2 nausea was reported in 18 (62.1%) patients in the AP/DVC-sparing group compared with 11 (37.9%) in the conventional WBRT group (p=0.00), whereas Grade ≥2 nausea occurred in 2 (12.5%) and 14 (87.5%) patients, respectively (Table 3).

Table 3: Association of Demographic Characteristics with Nausea Severity in AP/DVC-Sparing and Conventional WBRT Groups (n=106)

Variables		**Nausea**		
	Groups	Grade <2	Grade ≥2	P-Value
Age Groups				
20-30 years	AP/DVC Sparing	7(87.5%)	3(37.5%)	0.03
	Conventional WBRT	1(12.5%)	5(62.5%)	
31-40 years	AP/DVC Sparing	10(66.7%)	5(45.5%)	0.27
	Conventional WBRT	5(33.3%)	6(54.5%)	
41-50 years	AP/DVC Sparing	8(100.0%)	1(12.5%)	0.00
	Conventional WBRT	08(00.0%)	7(87.5%)	
51-60 years	AP/DVC Sparing	14(77.8%)	5(41.7%)	0.04
	Conventional WBRT	4(22.2%)	7(58.3%)	
>60 years	AP/DVC Sparing	3(75.0%)	9(64.3%)	0.68
	Conventional WBRT	1(25.0%)	5(35.7%)	
Gender				
Male	AP/DVC Sparing	24(66.7%)	9(36.0%)	0.01
	Conventional WBRT	12(33.3%)	16(64.0%)	
Female	AP/DVC Sparing	18(62.1%)	2(12.5%)	0.00
	Conventional WBRT	11(37.9%)	14(87.5%)	
Number of brain metastases				
1–3	AP/DVC Sparing	30(71.4%)	5(20.0%)	
	Conventional WBRT	12(28.6%)	20(80.0%)	0.00
>3	AP/DVC Sparing	12(52.2%)	6(37.5%)	0.36
	Conventional WBRT	11(47.8%)	10(62.5%)	

Regarding age, Grade <2 vomiting was more frequent than Grade ≥2 vomiting across most age groups in both treatment groups, with no statistically significant differences observed between the AP/DVC-sparing and conventional WBRT groups among patients aged 20–30 years (p=0.13), 31–40 years (p=0.37), 41–50 years (p=0.30), 51–60 years (p=0.80), and >60 years (p=0.31). Similarly, no significant association was observed between gender and vomiting severity among males (p=0.32) or females (p=0.13). Regarding the number of brain metastases, Grade <2 vomiting was observed in 30 (55.6%) patients with 1–3 metastases in the AP/DVC-sparing group compared with 24 (44.4%) in the conventional WBRT group (p=0.26), while among patients with >3 metastases, Grade <2 vomiting occurred in 17 (51.5%) and 16 (48.5%) patients, respectively (p=0.11). Overall, age, gender, and number of brain metastases were not significantly associated with vomiting severity between the two treatment groups (Table 4).

Table 4: Association of Age, Gender, and Number of Brain Metastases with Vomiting Severity among Patients Receiving AP/DVC-Sparing and Conventional Whole-Brain Radiotherapy (WBRT) (n=106)

Variables		**Vomiting**		
	Groups	Grade <2	Grade ≥2	P-Value
Age Groups				
20-30 years	AP/DVC Sparing	8(57.1%)	0(0.0%)	0.13
	Conventional WBRT	6(42.9%)	2(100.0%)	
31-40 years	AP/DVC Sparing	13(61.9%)	2(40.0%)	0.37

	Conventional WBRT	8(38.1%)	3(60.0%)	
41-50 years	AP/DVC Sparing	6(60.0%)	2(33.3%)	0.30
	Conventional WBRT	4(40.0%)	4(66.7%)	
51-60 years	AP/DVC Sparing	16(59.3%)	2(66.7%)	0.80
	Conventional WBRT	11(40.7%)	1(33.3%)	
>60 years	AP/DVC Sparing	4(26.7%)	0(00.0%)	0.31
	Conventional WBRT	11(73.3%)	3(100.0%)	
Gender				
Male	AP/DVC Sparing	29(56.9%)	4(40.0%)	0.32
	Conventional WBRT	22(43.1%)	6(60.0%)	
Female	AP/DVC Sparing	18(50.0%)	2(22.2%)	0.13
	Conventional WBRT	18(50.0%)	7(77.8%)	
Number of brain metastases				
1–3	AP/DVC Sparing	30(55.6%)	5(38.5%)	
	Conventional WBRT	24(44.4%)	8(61.5%)	0.26
>3	AP/DVC Sparing	17(51.5%)	1(16.7%)	0.11
	Conventional WBRT	16(48.5%)	5(83.3%)	

DISCUSSION:

The present study evaluated the effect of AP/DVC sparing on acute nausea and vomiting among 106 patients receiving WBRT, with 53 patients allocated to each group. The principal finding was that AP/DVC sparing was associated with a markedly lower frequency of clinically significant nausea. Grade ≥2 nausea occurred in 20.8% of patients in the AP/DVC-sparing group compared with 56.6% in the conventional WBRT group ($p<0.001$). In contrast, Grade ≥2 vomiting occurred in 11.3% and 24.5%, respectively, although this difference did not reach statistical significance ($p=0.07$). These findings suggest that reducing radiation exposure to the AP/DVC may particularly influence the severity of nausea, while the effect on vomiting may be less pronounced. The observed reduction in nausea is biologically plausible because the AP and DVC are important components of the brainstem emetic pathway. The DVC includes the area postrema, nucleus of the solitary tract, and dorsal motor nucleus of the vagus, and the area postrema functions as a chemoreceptor trigger zone involved in emesis (9). Previous clinical evidence supports a relationship between radiation dose to these structures and nausea. In a study of 70 patients receiving head-and-neck radiotherapy, nausea occurred in 37%, and patients receiving a DVC dose above 30 Gy had a higher incidence of nausea than those receiving lower doses (67% vs. <30%, $p=0.0255$)(10). Similarly, a study of 23 patients demonstrated higher median AP and DVC doses among patients who developed nausea, supporting the concept that these structures represent radiation-sensitive components of the emetic pathway (8). The magnitude of reduction in Grade ≥2 nausea in the present study is therefore consistent with previous dose-response observations. In the earlier IMRT study, patients without nausea had median DVC and AP doses of approximately 34.2 Gy and 32.6 Gy, respectively, whereas symptomatic patients received approximately 40.4 Gy and 38.7 Gy. Importantly, replanning reduced the AP and DVC doses by approximately 18% and 17%, respectively, without substantially compromising target coverage (11). These findings provide a dosimetric rationale for incorporating AP/DVC avoidance into WBRT planning when clinically feasible. The effect on vomiting in the present study was less definitive. Although Grade ≥2 vomiting was numerically lower with AP/DVC sparing (11.3% vs. 24.5%), the difference was not statistically significant. This finding is comparable with previous research in which AP/DVC dose was more clearly associated with nausea than vomiting. In the 23-patient study, AP and DVC doses differed significantly according to nausea status, whereas no significant difference was demonstrated for vomiting (11). This may indicate that vomiting is influenced by additional factors beyond radiation exposure to the AP/DVC, including tumor location, intracranial pressure, number and distribution of metastases, vestibular stimulation, medications, and individual susceptibility.

In the present study, stratified analysis showed that nausea severity differed significantly between treatment groups in some age categories, particularly among patients aged 20–30, 41–50, and 51–60 years, whereas the differences were not statistically significant in the 31–40 and >60-year groups. Gender-stratified analysis also demonstrated significant differences in nausea severity among both males and females. However, these subgroup findings should be interpreted cautiously because the numbers within individual age and sex categories were relatively small, increasing the possibility of unstable estimates. Previous literature has also identified age and other patient-related characteristics as potential determinants of radiation-induced nausea. A recent study of 102 patients receiving brain radiotherapy found that patients who developed nausea were significantly younger than those without nausea, although the authors emphasized the relationship between DVC dose and nausea.(12)

In contrast, vomiting severity was not significantly associated with age, gender, or number of brain metastases in the present study. This supports the possibility that the reduction in vomiting observed with AP/DVC sparing was primarily a treatment-related numerical difference rather than a statistically established effect. The lack of association with the number of brain metastases is also relevant because intracranial disease burden may contribute to nausea and vomiting through mechanisms other than direct irradiation of the emetic center.

Accurate identification of the AP/DVC is important when implementing this approach. Previous work has established MRI-based contouring guidelines for the DVC and related brainstem structures, with good interobserver reproducibility, supporting their use in radiation treatment planning (13). More recent evidence has further strengthened the dose-response hypothesis: in a 102-patient study of brain radiotherapy, mean DVC dose was 21.6 Gy in patients with nausea compared with 8.9 Gy in those without nausea, and a mean DVC dose threshold of 8.82 Gy was associated with substantially different nausea rates. The authors, however, emphasized that this proposed constraint requires prospective validation.

The present findings therefore add clinical evidence supporting AP/DVC sparing during WBRT, particularly for reducing moderate-to-severe acute nausea. Nevertheless, the absence of a statistically significant reduction in Grade ≥2 vomiting indicates that AP/DVC sparing should not be considered the sole determinant of radiation-induced gastrointestinal toxicity. Future prospective, preferably multicenter, studies should incorporate detailed AP and DVC dose-volume parameters, standardized antiemetic protocols, baseline nausea assessment, and longer follow-up to determine optimal dose constraints and to establish whether AP/DVC sparing consistently reduces both nausea and vomiting without compromising adequate WBRT target coverage.

Conclusion: It was concluded that AP/DVC-sparing WBRT significantly reduced the incidence and severity of acute nausea compared with conventional WBRT, while a non-significant reduction in vomiting was observed. These findings suggest that AP/DVC sparing may be a useful planning strategy for reducing acute radiation-induced nausea during WBRT without compromising the treatment approach.

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