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Effectiveness of Vitamin D Supplementation on Therapy Response of Nasopharyngeal Carcinoma Patients with Chemotherapy

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ABSTRACT

Background: The current standard therapy approach for NPC is radiotherapy alone or with concurrent chemotherapy. In patients receiving chemotherapy, vitamin D is inversely correlated with the percentage of pathological complete response. This study aims to determine the effectiveness of vitamin D supplementation on therapy response in nasopharyngeal carcinoma patients with chemotherapy.

Methods: A quasi-experimental study was undertaken at Dr. Mohammad Hoesin Hospital, Palembang from April to October 2024. A total of 26 samples of patients newly diagnosed with nasopharyngeal carcinoma and receiving chemotherapy who met the study criteria were obtained. The dose of vitamin D intervention was 2000 IU and the therapy response was evaluated after 3 series of chemotherapy.

Results: The highest therapy response was complete response (50%), followed by partial response (23.1%) and progressive response and stable response each 7.7%. The therapy response of both interventions did not show significant results (p = 0.207) but complete response was more common in the chemotherapy add on vitamin D group (75%) compared to the chemotherapy group (36.4%) and progressive disease was only found in the chemotherapy group (18.2%).

Conclusion: Add on supplementation of 2000 IU vitamin D in chemotherapy for 3 series has not shown significant results on therapy response in nasopharyngeal carcinoma patients with chemotherapy

Keywords: *Chemotherapy, NPC, therapy response, supplementation, vitamin D.*

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1. INTRODUCTION

Nasopharyngeal carcinoma (NPC) is a malignant tumor originating from the epithelium and mucosal lining of the nasopharynx with the most common predilection in the Rosenmuller fossa.[1,2,3] Nasopharyngeal carcinoma occurs due to the interaction between genetic factors, Epstein Barr virus (EBV) infection, and environmental factors such as exposure to carcinogens, smoke, and foods containing nitrosamines such as salted fish.[1,4,5]

Nasopharyngeal carcinoma ranks 23rd out of all malignancies in the world, with around 80,000 new cases of NPC diagnosed each year.[1,5,6] Nasopharyngeal carcinoma ranks 5th out of all malignancies in Indonesia with the incidence of NPC in Indonesia reaching 4.7 per 100,000 population per year, and the highest in the 4th-5th decade with a ratio between men and women of 2-3:1.[1,6]

Neck enlargement often occurs (60%-97.5%) in NPC. Tumor metastasis to cervical lymph nodes can occur unilaterally or bilaterally.[1] Distant bone metastasis is seen in 3-6% of cases at initial presentation and can occur in 18-50% of cases during the course of the disease. [4]

Nasopharyngeal carcinoma is chemosensitive and radiosensitive.[5,7,8] The current standard treatment approach for NPC, according to international guidelines, is radiotherapy alone or with concomitant chemotherapy. [5,6]

Vitamin D deficiency is very common in the general population (approximately 50%) and even more so in cancer patients.[9-11] Current guidelines recommend vitamin D daily supplementation. In patients receiving chemotherapy, vitamin D is inversely correlated with the percentage of pathological complete response, a strong prognostic factor, and may be explained by the potential anticancer effects of vitamin D.[9] Vitamin D is considered a promising agent to counteract several epigenetic changes associated with carcinogenesis, which increase tumor gene expression and reduce tumor suppressor genes. Vitamin D affects the proliferation of cancer cells at different stages, environments, including immune cells and fibroblasts, and addresses several tumor-relevant pathways.[11]

This study aimed to determine the effectiveness of vitamin D supplementation on treatment response in patients with nasopharyngeal carcinoma undergoing chemotherapy.

2. METHOD

An experimental analytical study with a quasi-experimental design was undertaken at Dr. Mohammad Hoesin Central General Hospital, Palembang from April to October 2024.

All patients newly diagnosed with stage II-IVA nasopharyngeal carcinoma undergoing chemotherapy, aged 18-70 years and willing to participate in the study were included in the study sample. Patients who had undergone chemotherapy, residual cancer, had undergone radiotherapy, had a history of consuming vitamin D supplements, diagnosed with other malignancies and patients with kidney failure were excluded from the study sample. The study sample was divided into two groups, the control group received chemotherapy alone while the test group was given chemotherapy plus vitamin D supplementation.

The dependent variable in this study was the administration of 2000 IU vitamin D with independent variables such as stadium, primary tumor (T), regional lymph nodes (N), metastasis (M), treatment response based on RECIST criteria and serum vitamin D levels.

Vitamin D is consumed once a day during chemotherapy 3 times (6 weeks) starting from chemotherapy 1 to 3. A total of 42 capsules are given. After completing chemotherapy 3, the patient's serum vitamin D levels will be rechecked and then an evaluation of the treatment response will be carried out by examining the head and neck, CTScan of the nasopharynx, chest X-ray, USG abdomen and bone survey.

Monitoring of medication compliance is done by packing capsules per piece and on each pack is written a serial number from 1 to 42. Each patient control must return the empty capsule pack. In addition, a WhatsApp group will be created containing all research subjects, researchers will remind subjects to take capsules every day and ask subjects to photograph empty capsule packs.

3. RESULTS

Sociodemographic Characteristics of Research Samples

In this study, it was found that the majority of nasopharyngeal carcinoma (NPC) patients were male (69.2%) with an age range of 30-49 (50%) and 50-70 years (50%) equally**.**

NPC patients in this study who had a history of smoking were only 34.6%. Statistical analysis showed that there was no difference in gender (p = 0.673); age (p = 1.000); and smoking status (p = 0.411) between patients with chemotherapy + vitamin D intervention and chemotherapy alone **(Table 1)**

Table 1 Sociodemographic Characteristics of Research Samples

Characteristic	Intervention		Total	P value
	Chemotherapy + Vitamin D	Chemotherapy		
Gender				
- **Male**	8 (61.5)	10 (76.9)	18 (69.2)	0.673[a]
- **Female**	5 (38.5)	3 (23.1)	8 (30.8)	

Age				
- **30 – 49 years old**	7 (53.8)	6 (46.2)	13 (50.0)	1.000[b]
- **50 – 70 years old**	6 (46.2)	7 (53.8)	13 (50.0)	
Smoking History				
- **Smoking**	6 (46.2)	3 (23.1)	9 (34.6)	0.411[a]
- **No-Smoking**	7 (53.8)	10 (76.9)	17 (65.4)	
Total	13	13	26	

[a]*Fisher Exact Test,* *p <0.05

[b]*Chi Square Test,* *p <0.05

Clinical Characteristics of the Study Sample

The majority of nasopharyngeal carcinoma (NPC) patients in this study were stage IVA (57.7%) with the majority of primary tumors T3 (42.3%) and regional lymph nodes N2 (53.8%). There were no patients with distant metastasis (M) in this study and 3 patients (11.5%) without regional lymph node metastasis. Statistical analysis showed that there was no difference in stage (p = 0.915), primary tumor (p = 0.624) and regional lymph nodes (p = 0.214) between patients with chemotherapy + vitamin D intervention and chemotherapy alone **(Table 3)**

Table 2. Clinical Characteristics of the Study Sample

Characteristic	Intervention		Total	P value
	Chemotherapy + Vitamin D	Chemotherapy		
Stadium				
- **Stadium II**	1 (7.7)	1 (7.7)	2 (7.7)	0.915
- **Stadium III**	5 (38.5)	4 (30.8)	9 (34.6) 15 (57.7)	
- **Stadium IVA**	7 (53.8)	8 (61.5)		
Primary Tumor (T)				
- **T1**	1 (7.7)	0 (0)	1 (3.8)	0.624
- **T2**	4 (30.8)	4 (30.8)	8 (30.8) 11 (42.3) 6 (23.1)	
- **T3**	6 (46.2)	5 (38.5)		
- **T4**	2 (15.4)	4 (30.8)		
Regional Lymph Nodes				
- **N0**	1 (7.7)	2 (15.4)	3 (11.5)	
- **N1**	2 (15.4)	6 (46.2)	8 (30.8)	0.214
- **N2**	9 (69.2)	5 (38.5)	14 (53.8)	
- **N3**	1 (7.7)	0 (0)	1 (3.8)	
Total	13	13	26	

Pearson Chi Square Test, *p <0.05

Vitamin D Baseline Data

Vitamin D levels of NPC patients in this study were measured before the intervention, the average vitamin D was 29.34 ± 6.81 with a range of 15.3 - 74. The majority of patients had insufficiency (46.2%) and sufficiency of vitamin D (38.5%) and vitamin D deficiency was only found in 15.4% of NPC patients. Statistical analysis showed that there was no difference in the average vitamin D levels (p = 0.837) and vitamin D classification (p = 0.693) between patients with chemotherapy + vitamin D intervention and chemotherapy alone (**Table 3**).

Table 3. Base Vitamin D Baseline Data

Characteristic	Intervention		Total	P value
	Chemotherapy + Vitamin D	Chemotherapy		
Vitamin D Level				
- **Mean ± SD**	30.3±14.83	28.42±6.81	29.34±11.35	0.837[a]
- **Median**	27.8	29.6	28.1	
- **Min - Max**	15.3 - 74	16.7 – 36.8	15.3 - 74	
Vitamin D Category				
- **Deficiency**	2 (15.4)	2 (15.4)	4 (15.4)	0.693[b]
- **Insuficiency**	7 (53.8)	5 (38.5)	12 (46.2)	
- **Suficiency**	4 (30.8)	6 (46.2)	10 (38.5)	
Total	13	13	26	

[a]*Mann Whitney Test,* *p <0.05

[b]*Pearson Chi Square Test,* *p <0.05

Vitamin D Levels and Clinical Characteristics After Intervention

Vitamin D levels after intervention in the chemotherapy + vitamin D group were slightly higher (35.02 ± 6.26) compared to vitamin D levels in the chemotherapy alone group (29.54 ± 8.49) but were not statistically significant (p = 0.073) (**Table 4**). In addition, there were no differences in primary tumors (p = 0.416); regional lymph nodes (p = 0.415); stadium (p = 0.420) and vitamin D classification (p = 0.204) between patients with chemotherapy + vitamin D and chemotherapy alone interventions (**Table 4 and 5**).

Table 4 Vitamin D Levels Post Intervention

Characteristic	Intervention		Total	P value
	Chemotherapy + Vitamin D	Chemotherapy		
Vitamin D Level				
- **Mean ± SD**	35.02±6.26	29.54±8.49	32.28±7.82	0.073[a]
- **Median**	32.6	30.4	31.9	
- **Min - Max**	24.9 – 48.4	11.8 – 48	11.8 – 48.4	
Vitamin D Category				
- **Deficiency**	0 (0)	1 (7.7)	1 (3.8)	0.204[b]
- **Insuficiency**	2 (15.4)	5 (38.5)	7 (26.29)	
- **Suficiency**	11 (84.6)	7 (53.8)	18 (69.2)	
Total	13	13	26	

[a]*Independent T Test,* *p <0.05

[b]*Pearson Chi Square Test,* *p <0.05

Table 5 Clinical Characteristics Post Intervention

Characteristic	Intervention		Total	P value
	Chemotherapy + Vitamin D	Chemotherapy		
Stadium				

- **Stadium I**	1 (7.7)	2 (15.4)	3 (11.5) 10 (38.5) 11 (42.3) 2 (7.7)	0.420
- **Stadium II**	6 (46.2)	4 (30.8)		
- **Stadium III**	6 (46.2)	5 (38.5)		
- **Stadium IVA**	0 (0)	2 (15.4)		
Primary Tumor (T)				
- **T1**	4 (30.8)	5 (38.5)	9 (34.6)	0.416
- **T2**	3 (23.1)	2 (15.4)	5 (19.2)	
- **T3**	1 (7.7)	2 (15.4)	3 (11.5)	
- **T4**	5 (38.5)	2 (15.4)	7 (26.9)	
	0 (0)	2 (15.4)	2 (7.7)	
Regional Lymph Nodes				
- **N0**	5 (38.5)	6 (46.2)	11 (42.3) 9 (34.6) 6 (23.1)	0.415
- **N1**	6 (46.2)	3 (23.1)		
- **N2**	2 (15.4)	4 (14.8)		
- **N3**				
Total	13	13	26	

Pearson Chi Square Test, *p <0.05

Table 6. Effectiveness of Vitamin D 2000 IU Supplementation in Clinical Characteristics

Characteristic	Intervention		Total	P value
	Chemotherapy + Vitamin D	Chemotherapy		
Stadium Alteration				
- **Stable**	4 (30.8)	5 (38.5)	9 (34.6) 17 (65.4)	1.000[a]
- **Menurun**	9 (69.2)	8 (61.5)		
Primary Tumor Alteration				
- **Stable**				
- **Decrease**	4 (30.8)	4 (30.8)	8 (30.8)	0.589[b]
- **Increase**	9 (69.2)	8 (61.5)	17(65.4) 1 (3.8)	
	0 (0)	1 (7.7)		
Regional Lymph Nodes Alteration				
- **Stable**	3 (23.1)	7 (53.8)	10 (38.5)	0.046[b]*
- **Decrease**	10 (76.9)	4 (30.8)	14 (53.8)	
- **Increase**	0 (0)	2 (15.4)	2 (7.7)	
Total	13	13	26	

[a]*Fisher Exact Test,* *p <0.05

[b]*Chi Square Test,* *p <0.05

Effectiveness of Vitamin D 2000 IU Supplementation on Alteration in Clinical Characteristics

This study also found that there was no difference alteration in primary tumors (p = 0.589); and stadium (p = 1.000) between patients with chemotherapy + vitamin D intervention and chemotherapy alone. However, there was a difference in regional lymph nodes (p = 0.046) between patients with chemotherapy + vitamin D intervention and chemotherapy alone where the

percentage of regional lymph node decrease was significantly more found in NPC patients with chemotherapy + vitamin D intervention (76.9%) compared to NPC patients with chemotherapy intervention alone (30.8%) and an increase in regional lymph nodes was only found in patients with chemotherapy intervention alone (15.4%) (**Table 6**).

Tabel 7. Effectiveness of Vitamin D 2000 IU Supplementation on Alteration in Clinical Characteristics

Characteristic	Intervention		Total	P value
	Chemotherapy + Vitamin D	Chemotherapy		
Therapy Response				
- ***Complete Response***	9 (69,2)	4 (30,8)	13 (50,0)	
- ***Partial Response***	2 (15,4)	1 (7,7)	3 (11,5)	2 0,100
- ***Progressive Disease***	0 (0)	2 (15,4)	(7,7)	
- ***Stable Disease***	2 (15,4)	6 (46,2)	8 (30,8)	
Total	13	13	26	

Pearson Chi Square Test, *p <0.05

Effectiveness of Vitamin D 2000 IU Supplementation on Treatment Response of Nasopharyngeal Carcinoma Patients with Chemotherapy.

In this study, the therapeutic response of both interventions did not show significant results (p = 0.207) but complete response was found more in the chemotherapy + vitamin D group (75%) compared to the chemotherapy alone group (36.4%) and progressive disease was only found in the chemotherapy alone group (18.2%). (**Table 7**).

4. DISCUSSION

In this study, the results showed that the majority of nasopharyngeal carcinoma (NPC) patients were male (69.2%) with a male:female ratio of 2.5:1. These results are in line with studies conducted by Jayalie et al., 2016; Li et al., 2021; Hong et al., 2021, which reported that the majority of NPC patients were male with a ratio from 2.5:1 to 4:1.[12-14]

The age range of NPC patients 30-49 and 50-70 years in this study was found to be the same. The incidence of NPC increased in the 30-49 age group in this study, possibly due to the influence of hereditary factors, environmental variables, or early exposure to carcinogenic substances. The results of this study are in line with the research of Rahman et al., 2015 at Dr. Soetomo General Hospital. M. Djamil Padang found that the incidence of nasopharyngeal cancer increased at ages above 30 years and peaked at ages 45-55 years.[15] However, another study conducted by Utomo et al., in 2023 reported that the largest age range of NPC patients was 51-60 years (32.44%).[16]

Smoking has been consistently associated with an increased risk of NPC. Smokers who have ever smoked have a 32% higher risk of NPC than those who have never smoked.[96] In the study, the majority of NPC patients did not smoke and only 34.6% of patients with a history of smoking. In line with this study, studies by Li et al., in 2021 and Chang et al., in 2017 also found that the majority of NPC patients did not smoke and only.[13,17]

Vitamin D potentiates the antitumor activity used in adjuvant and neoadjuvant chemotherapy. High-dose vitamin D regimens increase the percentage of normalization in cancer patients undergoing adjuvant chemotherapy.[9] Vitamin D has immunosuppressive properties, which are beneficial for cancer treatment, and can affect the efficacy of cancer therapy.[18]

NPC patients in this study were given 3 series of chemotherapy and one group was additional vitamin D. After three series of chemotherapy, the therapy response, alteration in primary tumors, regional lymph nodes and stadium were assessed. In this study, post-intervention, there was no difference in therapy response between patients with and without additional vitamin D. However, patients with complete response were found more in patients with additional vitamin D (69.2% versus 30.8%) and progressive disease was only found in patients without additional vitamin D. However, this difference was not statistically significant.

In this study, there was also no difference in stadium, primary tumor and regional lymph nodes between patients with and without additional vitamin D. However, when viewed based on the percentage of alteration, a decrease in stadium and primary tumor was slightly more found in the vitamin D group but not significant (69.2% versus 61.5%; p> 0.05) and a significant decrease in regional lymph nodes was found more in the group with additional vitamin D (79.9% vs 30.8%; p = 0.049). In addition, in the group without vitamin D supplementation, patients were found to have increased primary tumors (7.7%) and increased regional lymph nodes (15.4%), whereas in patients with vitamin D supplementation, this did not occur.

In this study, vitamin D levels post- intervention were also evaluated and the results showed that there was no significant difference in vitamin D levels after the intervention between the two groups. Vitamin D levels in the group with additional vitamin D had a higher average than the group without additional vitamin D with a difference of 6 ng/mL, but the difference was not statistically significant. This could possibly be caused by two things, namely the first, the lack of vitamin D dose given (in this study the dose of vitamin D given was 2000 IU) so that an increase in the dose was needed for better results. Second, the administration time was only for 3 series so that additional time was needed until 1 cycle of chemotherapy (6 series) was completed so that the changes that occurred were meaningful.

Research undertaken by Dewi et al., in 2024 reported that there was a significant effect of giving 1000 IU of vitamin D3 on chemotherapy response in advanced NPC patients receiving Cisplatin-based chemotherapy ($p = 0.037$). The difference in the results of these two studies is likely due to the outcome of the therapy response in the Dewi et al. study, only 2, namely positive and negative responses, while the therapy response in this study was divided into 4 categories. [19]

5. CONCLUSION

The therapy response of both interventions did not show significant results, but complete responses were more common in the chemotherapy + vitamin D group compared to the chemotherapy alone group, and progressive disease was only found in the chemotherapy alone group.

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