

The Effect Of Administration Of Mecobalamin & Curcumin As Antioxidants In Nasopharynx Carcinoma Patients Post Cisplatin Regimen Chemotherapy With Hearing Impairment

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ABSTRACT

Introduction

Nasopharyngeal carcinoma (NPC) is a common type of cancer in Southeast Asia, and its treatment often involves a cisplatin chemotherapy regimen. Ototoxicity is a side effect that often occurs in patients receiving this regimen. Antioxidant therapy, both synthetic and natural, such as curcumin, has been studied as having the potential to reduce ototoxicity due to cisplatin. This study was conducted to evaluate the effect of administering mecobalamin and curcumin as antioxidants in patients with nasopharyngeal carcinoma after cisplatin chemotherapy regimen with hearing loss.

Method

This study was an observational study with a cross sectional design, using consecutive sampling with inclusion criteria, namely patients diagnosed with NPC receiving the cisplatin regimen and willing to take part in the study. The data obtained was then analyzed using the Rank-Biserial Correlation's Test. Research approval was obtained from the Medical Research Ethics Commission, Faculty of Medicine, Universitas Sebelas Maret Dr. Moewardi Regional Hospital Surakarta.

Results

Of the 30 NPC patients who received cisplatin from the ENT-KL installation section of Dr Moewardi Hospital in the period of March - September 2023, 30 data were obtained for each right ear and left ear. The average hearing threshold before intervention was 33.79 ± 10.40 dB and 34.10 ± 9.75 for the right and left ears. There was a difference in the average increase in hearing threshold for all parameters (Group I: Mecobalamin, Group II: Curcumin, Group III: Curcumin + Mecobalamin), with a value of $p=0.000$ ($p<0.05$). From these data it was concluded that the combined therapy of both was able to increase the hearing threshold along with the chemotherapy series.

Conclusion

Based on the research results, administration of mecobalamin and curcumin as antioxidants has a significant effect on patients with nasopharyngeal carcinoma after cisplatin chemotherapy regimen with hearing loss.

Keywords: Chemotherapy, Cisplatin, Hearing threshold, and Ototo

Introduction

Nasopharyngeal carcinoma (KNF) is one type of cancer that often occurs in Southeast Asia, including in Indonesia. Treatment of KNF often involves cisplatin chemotherapy regimens, which have been proven to be effective in controlling cancer cell growth (Paken et al., 2019). However, the use of cisplatin can also cause almost 100% ototoxicity effects that can result in hearing loss in patients. However, the severity of ototoxicity in patients is influenced by various factors, such as age, age, sex, and comorbid (metabolic syndrome), genetics, as well as geography, drug type, drug administration route, duration, bio-availability, and hearing abnormalities before the therapy regimen (Yu et al., 2020).

Previous studies have shown that antioxidant therapy, both in synthetic and natural forms, can help reduce the side effects of ototoxicity caused by cisplatin (Bor et al., 2023). Among the antioxidants that have been studied are mecobalamin and curcumin. Mecobalamin, also known as vitamin B12, has neuroprotective properties and has been used in the treatment of neurological disorders. Meanwhile, curcumin, the active compound present in turmeric, has been shown to have strong anti-inflammatory and antioxidant effects (Pak et al., 2020).

Previous research has revealed that administration of mecobalamin and curcumin may provide protection against hearing loss caused by cisplatin in cancer patients. Therefore, this study aimed to evaluate the effectiveness of mecobalamin and curcumin as antioxidants in KNF patients receiving the cisplatin regimen in reducing the risk of ototoxicity and hearing loss.

With a better understanding of the antioxidant protection potential of mecobalamin and curcumin, it is expected that this study can contribute to improving the quality of life of NPC patients undergoing chemotherapy with cisplatin.

1.1. Methods of the Study

This study was an observational study with a cross-sectional design on adjuvant therapy and the effect of ototoxicity in NPC patients receiving the cisplatin chemotherapy regimen. The study was conducted at Otolaryngology, Head and Neck Surgery Polyclinic of dr. Moewardi Regional Hospital in Surakarta during the period of March 2023 to September 2023. The target population of this study was all patients receiving cisplatin chemotherapy regimen at Dr Moewardi Regional Hospital Surakarta. Sampling was conducted using consecutive sampling, according to inclusion and exclusion criteria. Patients with CSOM, or patients with a previous history of ototoxic drugs, congenital abnormalities and previous hearing loss obtained from anamnesis and medical record data, will be excluded from the study. The inclusion criteria were as follows: NPC patients who received a cisplatin chemotherapy regimen and were willing to participate in the study and signed an informed consent sheet. The sample size in this study was 30 people. Patient characteristics were obtained from the patient's identity in the medical record and the subject fills out informed consent. The independent variable in this study was patients who received a cisplatin chemotherapy regimen on the dependent variable that was the effect of cisplatin ototoxicity on the patient's hearing threshold measured by Nada Murni audiometry.

Statistical analysis

Patients had no special preparation. NPC patients who underwent medical a checkup at the Otolaryngology, Head and Neck Surgery Polyclinic of dr. Moewardi Regional Hospital and received a cisplatin therapy regimen, met the qualifications, subsequently would receive an informed consent form, afterward they underwent examination using Nada Murni audiometry. The results of the audiometric examination were tabulated and analyzed.

Variables with nominal scales were described as frequency and percentage while continuous-scale variables were tested for normality in advance. The normality test used was Saphiro Wik since the number of samples was less than 50. After the data were not normally distributed, log transformation was performed and renormalization was conducted. Data that were not normally distributed were displayed as the median (minimum - maximum). The data were processed using a computer program with a level of significance p using the Rank-Biserial Correlation's Test To determine the relationship between the two variables using SPSS 25.0.

Before the implementation of the study, a research approval letter was previously prepared from the Head of the Parking Section of Dr. Moewardi Hospital Surakarta forwarded to the Permanent Committee for Medical Research Ethics, Faculty of Medicine, Universitas Sebelas Maret/ Dr. Moewardi Regional Hospital Surakarta.

2. Results of the Study and Discussion

2.1. Results of the Study

This cross-sectional design study was conducted on 30 NPC patients who received a cisplatin chemotherapy regimen as evidenced from medical records. The patient came to the ENT Polyclinic, and met the inclusion and exclusion criteria of the study, underwent examination using Nada Murni audiometry. 30 data were obtained for each right ear and left ear. The average pre-intervention hearing threshold was 33.79 ± 10.40 dB and 34.10 ± 9.75 for the right and left ear respectively (**Table 1**).

Table 1. Description of the Total Study Population

Parameter	Patient	Total
Age		30
Average		
Range		
Sex		30
Male		
Female		
Audiometry (mean \pm SD)		30
Right Ear	33.79 ± 10.40	
Left Ear	34.10 ± 9.75	

The 30 subjects were subsequently divided into 3 groups by random sampling. Group 1: NPC patients receiving a cisplatin chemotherapy regimen and taking mecobalamin during chemotherapy. Group II: NPC patients receiving the chemotherapy cisplatin regimen and taking curcumin during chemotherapy. Group III: NPC patients receiving the cisplatin regimen and taking both mecobalamin and curcumin during the chemotherapy program. Each group subsequently underwent audiometry examination for each chemotherapy series. Afterward the data were tabulated and analyzed using the Repeated ANOVA test to determine the difference in average increase

3. Hearing threshold on all parameters (**Tabel 2**).

Group	Pre-Chemo	1 st Series	2 nd Series	3 rd Series	<i>p</i> -value
Mecobalamin					
AD	31.25 ± 11.65	33.47 ± 11.05	42.17 ± 9.44	43.87 ± 9.81	0.000*
AS	32.25 ± 7.26	33.25 ± 7.03	41.74 ± 8.73	43.62 ± 9.04	0.000*
Curcumin					
AD	34.00 ± 12.35	37.15 ± 11.68	44.52 ± 12.26	45.62 ± 12.19	0.000*
AS	37.57 ± 10.23	39.42 ± 8.50	47.90 ± 9.63	48.60 ± 9.69	0.000*
Mecobalamin + Curcumin					
AD	36.12 ± 6.88	39.40 ± 7.33	43.10 ± 7.88	46.12 ± 7.84	0.000*
AS	32.50 ± 11.36	34.66 ± 11.08	39.19 ± 8.37	41.62 ± 8.43	0.000*

Table 2. Description of Population Per Group

Description:

(*) *p* value <0.05, significant

From the Repeated ANOVA examination, there was an average difference in the increase of hearing threshold in all parameters. This is indicated by *p* value 0.000 (*p* < 0.05) in all therapy groups both in the right and left ears, so it can be said that adjuvant therapy mecobalamin, curcumin, and mecobalamin + curcumin combination can increase the average hearing threshold in NPC patients who received the cisplatin therapy regimen. From these data, it can be concluded, Mecobalamin, curcumin, or a combination of both can really be able to increase the hearing threshold along with the chemotherapy series.

3.1. Discussion

This study was conducted to evaluate the effect of mecobalamin and curcumin as antioxidants on hearing threshold in nasopharyngeal carcinoma (NPC) patients undergoing cisplatin chemotherapy regimen (Campbell and Le Prell, 2018; Rizk, *et al.*, 2020). The results of the analysis showed that the combination therapy of mecobalamin and curcumin provided a significant increase (*p*<0.05) in the hearing threshold of KNF patients as the chemotherapy series progressed. From the results of the Repeated ANOVA examination, there was a significant difference (*p* <0.05) in the average increase of hearing threshold in all parameters measured. This indicates that administration of mecobalamin, curcumin, or a combination of both can effectively increase the hearing threshold in NPC patients undergoing cisplatin chemotherapy.

These findings are consistent with a previous study showing that mecobalamin and curcumin have potential as neuroprotective agents and antioxidants. Mecobalamin, is the active form of vitamin B12. Vitamin B12 works by aiding the synthesis of homocysteine into methionine by conversion of methyl-THF to THF (Pak *et al.*, 2020). Methionine itself is an amino acid that works in the methylation process in cells, it can protect nerve cells from oxidative damage caused by the toxic effects of cisplatin. This methionine compound is also widely found to provide an otoprotective effect in cases of ototoxicity, one of which is caused by cisplatin. Methionine works by helping the cellular antioxidant system by preventing efflux of glutathione from cells, increasing glutathione levels, and also maintaining antioxidant enzyme levels (Wang *et al.*, 2019). Through this mechanism, oxidative stress caused by cisplatin, especially in the inner ear organs, can be lowered and

the effects of ototoxicity in the following patients can be prevented from developing further (JK and Sana, 2015).

Meanwhile, curcumin, the active compound in turmeric, has anti-inflammatory and antioxidant properties that can help reduce oxidative stress in auditory tissue. Curcuma works by lowering lipid peroxidase activity, balancing levels of catalase, glutathione peroxidase, and superoxide dismutase, and has the effect of eliminating ROS. Curcumin is classified as one of the compounds that are safe for consumption with a maximum dose of 12 grams / day. Through the following mechanism, curcuma compound has an otoprotective effect on the organs of the inner ear. Cisplatin in the ear either works to change the balance of expression of transcription factors Nrf-2 and HO-1 which function as antioxidant mechanisms in the ear area. Curcuma in the internal ear organs works to reduce the effects of toxicity by increasing the translocation of Nrf-2 and HO-1 (Rezaee *et al.*, 2017; Laurell, 2019).

Thus, combination therapy of mecobalamin and curcumin can be considered an effective approach in reducing the risk of hearing loss in NPC patients receiving the cisplatin regimen. Recommendations for future studies include larger samples, conduct long-term monitoring of therapeutic effects, and conduct further studies to understand deeper the working mechanism of these two antioxidants in protecting hearing function in cancer patients.

4. Conclusion of the Study

The results of this study found a difference in the average increase of hearing threshold in NPC patients receiving a combination of mecobalamin and curcumin post cisplatin chemotherapy regimen.

- The administration of mecobalamin and curcumin as antioxidants in nasopharyngeal carcinoma (NPC) patients undergoing cisplatin chemotherapy regimen has a positive impact on hearing threshold ($p = 0.000$) p value <0.05 .
- The combination therapy of mecobalamin and curcumin is able to increase the hearing threshold in NPC patients along with the progress of the chemotherapy series ($p = 0.000$) p value <0.05 .
- There is a significant difference in the average increase of hearing threshold across all measured parameters ($p = 0.000$) p value <0.05 .

5. Suggestions of the Study

Recommendations for future studies include involving larger samples, conducting long-term monitoring of therapeutic effects, and conducting further studies to understand deeper the working mechanism of these two antioxidants in protecting hearing function in cancer patients. Thus, combination therapy of mecobalamin and curcumin can be considered an effective approach in reducing the risk of hearing loss in NPC patients receiving the cisplatin regimen.

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