RESEARCH ARTICLE

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Serotonin Levels and Chemotherapy-Induced Nausea and Vomiting in Cancer Patients: A Cross-Sectional Study

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Abstract

Introduction: Nausea and vomiting are distressing symptoms experienced by cancer patients undergoing treatment, impacting their physical well-being and quality of life. Serotonin, a neurotransmitter known for its role in regulating mood and gastrointestinal function, has been implicated in chemotherapy-induced nausea and vomiting (CINV). This study aimed to investigate serotonin level differences between CINV and non-CINV groups among cancer patients undergoing chemotherapy. **Methods:** An analytical observational investigation utilizing a cross-sectional design was conducted at Dr. Kariadi General Hospital from 2021-2022. Non-random consecutive sampling was employed to select participants meeting inclusion criteria, including age between 18 and 65 years, undergoing chemotherapy, non-smoking, and no recent antibiotic use. Platelet-poor plasma samples were analyzed for serotonin levels using a radioimmunoassay kit (Microplate reader ELx800). **Results:** This study included 61 subjects compared serotonin levels in two groups to investigate their potential association with chemotherapy-induced nausea and vomiting (CINV). The non-CINV group (n=31) had a median serotonin level of 70 (IQR: 20) ng/mL, while the CINV group (n=30) had a significantly higher median of 170 ng/mL (IQR: 50) ng/mL. Age was associated with a 1.2 ng/mL increase in serotonin per year (95% CI: 0.5-1.9, p = 0.002), adjusted for sex. Being male correlated with a 40 ng/mL increase (95% CI: 10-70, p = 0.010), adjusted for age. **Conclusion:** This study underscores the importance of understanding serotonin's role in CINV and highlights the need for tailored treatment approaches based on chemotherapy emetogenicity.

Keywords: Cancer- chemotherapy- serotonin

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Introduction

Nausea and vomiting are among the most distressing symptoms experienced by cancer patients undergoing treatment. These symptoms not only affect patients' physical well-being but also significantly impact their quality of life. While various factors contribute to nausea and vomiting in cancer patients, one neurotransmitter that has garnered considerable attention in recent research is serotonin [1].

Serotonin, often referred to as the "feel-good" neurotransmitter, plays a crucial role in regulating mood, appetite, and gastrointestinal function. In cancer patients, alterations in serotonin levels have been implicated in the development of nausea and vomiting, particularly in those undergoing chemotherapy. Research highlights chemotherapy-induced serotonin release triggers 5-HT3 receptors, causing nausea. Antiemetics like ondansetron block this. Variable drug responses suggest non-serotonin factors in CINV. Mechanisms of chemotherapy's serotonin effects in cancer patients are unclear, prompting investigation into broader pathways for improved treatment [1,2]. Serotonin is primarily produced in the gastrointestinal tract, where it acts as a signaling molecule involved in peristalsis and gut motility. Additionally, serotonin receptors are found in the chemoreceptor trigger zone (CTZ) and the vomiting center of the brainstem, areas responsible for coordinating the emetic response [3].

Chemotherapy-induced nausea and vomiting (CINV) is a common side effect of cancer treatment, affecting up to 80% of patients. Despite advancements in antiemetic medications, many patients still experience inadequate relief, highlighting the need for a deeper understanding of the underlying mechanisms [4]. Research suggests that chemotherapy drugs can disrupt serotonin signalling pathways, leading to increased serotonin release and

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activation of serotonin receptors in the CTZ and vomiting center [5]. This heightened serotonin activity triggers nausea and vomiting in susceptible individuals. The objective of this study was to investigate the differences in serotonin levels between CINV and non-CINV patients among cancer patients undergoing chemotherapy.

Materials and Methods

This study employs a cross-sectional approach to assess variances in serotonin levels between two groups: those experiencing CINV and those not experiencing CINV among cancer patients undergoing chemotherapy at Dr. Kariadi General Hospital between 2021 and 2022. The research sample was selected through non-random sampling, specifically utilizing the consecutive sampling method based on the admission of all type of cancer patients undergoing chemotherapy at the Dr. Kariadi General Hospital, Semarang. This research adheres to the STROBE guideline.

The inclusion criteria for this study are as follows: individuals aged between 18 and 65 years, cancer patients undergoing chemotherapy at the research hospital location, non-smokers, and those who have not taken antibiotics within 1 week before the intervention. The exclusion criteria include lack of willingness to participate in the study, use of psychiatric medication, consumption of antibiotics, presence of comorbidities, and consumption of antiemetic drugs prior to the research.

Platelet-poor plasma samples for serotonin level determination were prepared in strict accordance with the protocols outlined by Brand et al. for serotonin analysis. Venous blood was collected from control participants upon entry into the study. The blood samples underwent centrifugation at 200×g for 10 minutes at room temperature to yield platelet-rich plasma, followed by centrifugation at 4500×g for 10 minutes at 4°C to obtain platelet-free plasma. Subsequently, the plasma was extracted and stored at -80°C until analysis. Serotonin levels in the plasma were quantified in duplicate using a commercial radioimmunoassay kit (Microplate reader ELx800) as per the manufacturer's guidelines.6 The final value was determined by averaging the results of the two measurements. The individual conducting the assays remained blinded to the sample identities and clinical information.

In this study, we investigated the difference in serotonin levels (ng/mL) between cancer patients undergoing chemotherapy with and without CINV. Comprehensive statistical analysis was conducted using Statistical Package for the Social Sciences (SPSS) version 25. Categorical variables were presented as counts (percentage), while continuous variables were expressed as median with interquartile range (IQR). The Mann-Whitney U test was employed to compare serotonin levels between the CINV and non-CINV groups. Linear regression statistical tests were also performed, adjusting for age and sex in the context of CINV. A confidence interval of 95% and a p-value <0.05 were considered statistically significant. Variables under investigation included age, gender, marital status, alcohol and narcotic consumption, occupation, medical history, and duration of cancer diagnosis.

This research has been approved by the Ethics Committee of Dr. Kariadi General Hospital, with the research ethics study number being 1496/EC/KEPK-RSDK 2023.

Results

In total, we found 61 research samples included in this study. Table 1 provides an overview of the demographic data collected for the study participants. The median age of the participants was 50 years (IQR: 45 years old). Regarding gender distribution, 31 participants were male (50.8%), while 30 were female (49.2%). Marriage status varied among the participants, with 48 individuals reported as married (80.0%), 7 as unmarried (11.7%), and 6 as widowed (8.3%).

A small portion of participants reported a history of diseases (8.2%), while the majority did not (91.8%). The duration of cancer diagnoses varied, with 6 individuals diagnosed within less than 3 months (9.8%), 16 between 3 and 6 months (26.2%), 18 between 6 months and 1 year (29.5%), 19 between 1 and less than 5 years (31.1%), and 2 between 5 and 10 years (3.3%).

A comparison of serotonin levels between two groups was conducted, to understand its potential association with CINV. The non-CINV group, comprised of 31 individuals, exhibited a median serotonin level of 70 ng/mL (IQR: 20). In contrast, the CINV group, consisting of 30 participants, demonstrated markedly higher serotonin levels, with a median of 170 ng/mL (IQR: 50). This significant discrepancy in serotonin levels between the two groups was confirmed by statistical analysis, yielding a p-value of 0.005. (Table 2). In linear regression test, we found that each additional year of age was associated with a 1.2 ng/mL increase in serotonin levels (95% CI: 0.5-1.9, p = 0.002), adjusting for sex. Additionally, being male (compared to female) was associated with a 40 ng/mL increase in serotonin levels (95% CI: 10-70, p = 0.010), adjusting for age. These findings suggest that both age and sex contribute significantly to serotonin levels in patients experiencing CINV, highlighting their importance as covariates in future research and clinical assessments.

Discussion

This study represents the first of its kind in Indonesia, to our knowledge, to assess serotonin levels in patients with CINV undergoing chemotherapy for cancer. We found there was a difference in serotonin levels between the CINV and non-CINV groups in patients undergoing chemotherapy. Enterochromaffin cells in the gastrointestinal tract are responsible for producing over 90% of the body's serotonin (5-HT) and significant amounts of substance P (SP), both crucial for gastrointestinal functions, nausea, and vomiting. Various triggers such as chemical, mechanical, or neurological factors prompt the release of 5-HT and/or SP from these cells in a calcium-dependent manner [5]. Upon release, 5-HT and possibly SP activate their respective emetic receptors (5-HT3 for serotonin and NK1 for substance P) on vagal afferents, initiating

Table 1. Demographic Data

Variable		Median (min-max)
Age		50 (21-76)
Variable	n	%
Gender		
Male	31	50.8%
Female	30	49.2%
Marriage status		
Married	48	80.0%
Not married	7	11.7%
Widowed	6	8.3%
Education		
None	3	4.9%
Primary School	9	14.8%
Middle School	15	24.6%
High School	19	31.1%
Diploma	3	4.9%
Bachelor Degree	10	16.4%
Master Degree	2	3.3%
Alcohol and narcotics consumption		
Yes	4	6.6%
No	57	93.4%
Occupation		
Housewife	9	14.8%
Farmer	4	6.6%
Labore	3	4.9%
Private sector worker	11	18.0%
Self-employement	13	21.3%
Employee	3	4.9%
Government empoyee	5	8.2%
Retired	6	9.8%
Other work	7	11.5%
History of diseases		
Yes	5	8.2%
No	56	91.8%
Duration diagnoses of cancer		
< 3 months	6	9.8%
3 – 6 months	16	26.2%
6 month – 1 year	18	29.5%
1 – < 5 year	19	31.1%
5 – 10 year	2	3.3%

Table 2. Comparison of Serotonin Levels between Group

Variable	Median (IQR)	p value
Serotonin level in non-CINV group (n= 31)	70 (IQR: 20) ng/mL	0.005*
Serotonin level in CINV group (n=30)	170 (IQR: 50) ng/mL	

* Mann Whitney U Test

the sensation of nausea and subsequent vomiting. While 5-HT in the bloodstream is unlikely to reach the brainstem emetic nuclei due to ionization at physiological pH. However, substance P has an active transport mechanism to reach these nuclei in the brainstem [7].

Serotonin is extensively studied as a key neurotransmitter in CINV, making 5-HT3 receptor antagonists the primary choice for preventing CINV. Clinical trials have shown that drugs like ondansetron, granisetron, and palonosetron, which are 5-HT3 receptor antagonists, effectively suppress both the immediate and delayed phases of CINV, reducing nausea (88-93% and 73-75%, respectively) and vomiting (93% and 75-93%, respectively) [8]. Combining granisetron with the NK1 receptor antagonist aprepitant yields similar anti-nausea (100% and 62%, respectively) and antiemetic (100% and 85%) effects during both phases. Chemotherapy drugs often cause various side effects, including CINV, which are mediated by serotonin acting on 5-HT3 receptors and substance P targeting NK1 receptors. Combining a 5-HT3 receptor antagonist (5HT3-RA) with an NK1 receptor antagonist (NK1-RA) along with dexamethasone has proven highly effective for CINV prophylaxis, particularly for highly emetogenic chemotherapy regimens. NEPA (netupitant/palonosetron) is the sole fixed combination antiemetic available, consisting of the long-acting second-generation 5HT3-RA palonosetron and the highly selective NK1-RA netupitant [7-9].

Various antineoplastic medications elicit diverse patterns of emesis concerning intensity, duration, and peak severity. Chemotherapeutic agents that induce vomiting in over 90% of patients without prophylaxis are categorized as "highly emetogenic chemotherapy" (HEC), while those with a nausea and vomiting occurrence between 30% and 90% are termed "moderately emetogenic chemotherapy" (MEC) [10]. CINV can manifest either on the same day as the chemotherapy treatment (referred to as "acute") or in the days following treatment administration (termed "delayed"). Distinct physiological mechanisms underlie acute and delayed CINV. The acute phase primarily involves the peripheral pathway, occurring mainly in the gastrointestinal tract, and is mediated by serotonin's action on 5HT3 receptors located on vagal afferents. In contrast, delayed CINV is predominantly mediated by substance P acting on NK1 receptors, constituting the "central pathway" primarily within the central nervous system [11-14].

Previous research has suggested that serotonin may play a role in inducing CINV, but several other influencing factors have not been extensively studied. Variations in patient demographics, types of cancer, treatment regimens, and underlying health conditions may account for these differences, emphasizing the importance of context-specific interpretations. Patient characteristics, such as age and sex, emerged as significant factors influencing serotonin levels in our analysis. Each additional year of age was associated with a measurable increase in serotonin levels, while male patients exhibited higher serotonin levels compared to females, even after adjusting for age. Tailoring antiemetic therapy involves recognizing that different chemotherapy regimens vary in emetogenicity. Longer durations of cancer treatment may correlate with

increased risk of chemotherapy-induced nausea and vomiting (CINV). Clinicians can use this information to customize antiemetic prophylaxis, opting for more aggressive strategies when necessary. Personalized treatment plans consider individual patient risk factors, including treatment duration, to optimize antiemetic selection and dosing. This approach aims to enhance symptom management, improve patient adherence, and ultimately enhance the quality of life during cancer therapy.

The study's limitations encompass the utilization of a sole center setting, potentially constraining the applicability of the results to more extensive populations. Additionally, the study's reliance on cross-sectional data restricts the ability to establish causality between serotonin levels and CINV. Furthermore, potential confounding variables not accounted for in the analysis, such as specific chemotherapy regimens or cancer types, could impact study outcomes. Future research incorporating larger, more diverse samples and longitudinal designs could provide further insights into the relationship between serotonin levels and CINV in cancer patients undergoing chemotherapy.

In conclusion, our pioneering study in Indonesia has provided valuable insights into serotonin levels among patients experiencing CINV during cancer treatment. We have identified age and sex as critical factors influencing serotonin dynamics in this context, with older age and male sex correlating with higher serotonin levels. These findings highlight the need for tailored approaches to manage CINV, considering individual patient characteristics.

Author Contribution Statement

The research project involved a multidisciplinary team of experts: DS provided conceptual guidance, AF led the implementation, and KT handled statistical analysis. WS managed data tabulation, TH and TAS ensured data completeness, and IJ prepared blood samples. NDW educated participants, NK collected data, and FI coordinated sample delivery.

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Conflict of interest

There is no conflict of interest in this study.

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