Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 3
Open Access

Exploring Oxidative Stress Markers Catalase and Malondialdehyde in Chemotherapy-Induced Neuropathy in Head and Neck Cancer Patients: A Prospective Study

Yadav Nabin[1] Kalra Juhi[2] Nautiyal Vipul[3] Dhasmana DC[4] Goel Deepak[5]

1. Research scholar, Department of Pharmacology, Himalayan Institute of Medical Science, Dehradun-248016

2 &4. Professor, Department of Pharmacology, Himalayan Institute of Medical Science, Dehradun-248016

3. Professor, Department of Radiation Oncology, Cancer Research Institute, Himalayan Institute of Medical Dehradun-248016

5. Professor, Department of Neurology, Himalayan Institute of Medical Science, Dehradun-248016

Corresponding author: 2. Kalra Juhi, Professor, Department of Pharmacology, Himalayan Institute of Medical Science, Dehradun-Uttarakhand- 248016

juhikalra@srhu.edu.in

Cite this paper as: Yadav Nabin, Kalra Juhi, Nautiyal Vipul, Dhasmana DC, Goel Deepak (2024) Exploring Oxidative Stress Markers Catalase and Malondialdehyde in Chemotherapy-Induced Neuropathy in Head and Neck Cancer Patients: A Prospective Study. *Frontiers in Health Informatics, 13* (3), 11329-11337

Background: Chemotherapy-induced neuropathy (CIPN) is a common and debilitating side effect of cancer treatment, significantly impacting patients' quality of life. Oxidative stress has been implicated in the pathogenesis of CIPN, with markers such as catalase and malondialdehyde (MDA) serving as indicators of oxidative damage and antioxidant defense. This study aims to explore the roles of catalase and MDA as oxidative stress markers in CIPN.

Methods: A prospective cohort study was conducted with 42 patients undergoing chemotherapy for Head and neck solid tumors. Blood samples were collected to measure serum levels of catalase and MDA. Neuropathy severity was assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE). Statistical analyses, including Pearson correlation and multiple regression, were performed to evaluate the relationships between catalase, MDA levels, and neuropathy severity.

Results: Patients with severe neuropathy exhibited significantly higher levels of MDA (mean: 7.8 ± 1.5 µmol/L) compared to those with mild or no neuropathy (mean: 4.2 ± 1.1 µmol/L, $p<0.001$). Conversely, catalase activity was significantly lower in patients with severe neuropathy (mean: 45.3 ± 10.2 U/mg protein) than in those with mild or no neuropathy (mean: 68.7 ± 12.5 U/mg protein, $p<0.001$). A significant positive correlation was found between MDA levels and neuropathy severity ($r=0.52$, $p<0.001$), while catalase activity showed a significant negative correlation with neuropathy severity ($r=-0.46$, $p<0.001$). Multiple regression analysis identified MDA levels ($\beta=0.38$, $p<0.001$) and catalase activity ($\beta=-0.32$, $p<0.001$) as independent predictors of neuropathy severity.

Conclusion: Elevated MDA levels and reduced catalase activity are significantly associated with increased severity of chemotherapy-induced neuropathy, highlighting the role of oxidative stress in CIPN pathogenesis. These findings suggest that oxidative stress markers such as MDA and catalase could serve as potential biomarkers for CIPN risk and severity. Further research is warranted to explore antioxidant-based interventions as potential therapeutic strategies for mitigating CIPN.

Keywords: Chemotherapy-induced neuropathy, oxidative stress, catalase, malondialdehyde, biomarkers, cancer treatment.

Introduction:

Chemotherapy-induced neuropathy (CIPN) is a prevalent and often debilitating side effect of cancer treatment that affects a significant proportion of patients undergoing chemotherapy(1). CIPN can manifest as sensory and motor dysfunctions, including pain, tingling, numbness, and weakness, significantly impairing patients' quality of life and sometimes necessitating dose reductions or discontinuation of chemotherapy (2). Despite its clinical importance, the exact mechanisms underlying CIPN are not fully understood, and effective preventive and therapeutic strategies remain limited.

Emerging evidence suggests that oxidative stress plays a critical role in the pathogenesis of CIPN. Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify these reactive intermediates or repair the resulting damage (3,4). Chemotherapeutic agents, particularly platinum-based drugs, taxanes, and vinca alkaloids, are known to induce oxidative stress, which can lead to neuronal damage and contribute to the development of neuropathy (5).

Catalase and malondialdehyde (MDA) are key markers of oxidative stress that have been studied in various neurodegenerative and neuropathic conditions (7). Catalase is an antioxidant enzyme that catalyzes the decomposition of hydrogen peroxide into water and oxygen, thereby protecting cells from oxidative damage. Reduced catalase activity has been associated with increased oxidative stress and neuronal damage in several neuropathic conditions (8,9). Conversely, MDA is a byproduct of lipid peroxidation and serves as a marker of oxidative damage to cell membranes. Elevated levels of MDA indicate increased lipid peroxidation and oxidative stress, which are detrimental to neuronal health(10).

Oxidative stress results when the production of reactive oxygen species (ROS) exceeds the capacity of the body's antioxidant defenses. ROS are highly reactive molecules that can damage cellular components, including lipids, proteins, and DNA. Neurons are particularly susceptible to oxidative damage due to their high metabolic rate and relatively low levels of antioxidant defenses. The excessive ROS generated during chemotherapy can disrupt neuronal function and integrity, contributing to the symptoms of neuropathy (11-12).

Catalase is one of the primary antioxidant enzymes involved in the detoxification of hydrogen peroxide (H_2O_2), a ROS. By converting H_2O_2 into water and oxygen, catalase plays a crucial role in protecting cells from oxidative damage (13). Reduced catalase activity has been observed in various neurodegenerative diseases and is thought to exacerbate oxidative stress, leading to increased neuronal vulnerability. Investigating catalase activity in the context of CIPN may reveal important insights into how antioxidant defenses are compromised during chemotherapy and how this contributes to neuropathy (14).

Malondialdehyde (MDA) is a byproduct of lipid peroxidation, the oxidative degradation of lipids. Elevated MDA levels indicate increased lipid peroxidation and oxidative stress. Lipid peroxidation damages cell membranes, leading to cell dysfunction and death (15). In the nervous system, this can result in neuronal damage and contribute to the development of neuropathy. Measuring MDA levels in patients undergoing chemotherapy could provide a direct indication of the oxidative damage occurring within the nervous system and its relationship to neuropathy severity (16).

The primary objectives of this study are to measure the levels of catalase and MDA in the serum of patients undergoing chemotherapy for solid tumors and to assess the severity of their neuropathy. We hypothesize that patients with severe CIPN will exhibit significantly lower catalase activity and higher MDA levels compared to patients with mild or no CIPN. Furthermore, we aim to establish whether these oxidative stress markers can serve as reliable indicators of neuropathy severity.

Methodology

Study Design

This study employs a prospective cohort design to investigate the correlation between oxidative stress markers (catalase and malondialdehyde) and the severity of chemotherapy-induced neuropathy (CIPN) in patients undergoing chemotherapy for solid tumors at CRI, HIMS, Dehradun between November 2022 to October 2024. It was registered in the Clinical Trials.gov database (ClinicalTrials.gov Identifier: NCT06491082). The study included adults aged 18 years or older diagnosed with solid tumors who were currently receiving chemotherapy known to induce neuropathy, such as platinum-based drugs, taxanes, or vinca alkaloids. Participants were required to have no pre-existing neuropathy from other causes, such as diabetic or hereditary neuropathy, and needed to demonstrate the ability to provide informed consent. Exclusion criteria comprised patients with severe liver or kidney disease, those using medications known to independently influence oxidative stress markers or neuropathy, and pregnant or breastfeeding women.

Sample Size

The study included 42 patients was determined to be adequate to detect significant correlations between oxidative stress markers and neuropathy severity, accounting for potential dropouts and ensuring sufficient statistical power.

Data Collection

Baseline Data:

Demographic information: age, sex, BMI and Clinical data: cancer type, stage, chemotherapy regimen, comorbidities.

Neuropathy Assessment:

Neuropathy severity was assessed using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE), specifically the grading of peripheral neuropathy (17).

Blood Sample Collection:

Blood samples were collected at baseline (before the initiation of chemotherapy) and at subsequent

intervals (e.g., every 2 cycles of chemotherapy) to measure serum levels of catalase and malondialdehyde (MDA).

Laboratory Analysis

Catalase Activity:

Serum catalase activity was measured using a spectrophotometric assay. The decomposition rate of hydrogen peroxide (H2O2) by catalase was monitored at 240 nm. Results were expressed in units per milligram of protein (U/mg protein) (18).

Malondialdehyde Levels:

Serum MDA levels were measured using the thiobarbituric acid reactive substances (TBARS) assay. The MDA-TBA adduct formation was quantified spectrophotometrically at 532 nm. Results were expressed in nanomoles per mililiter (nmol/ml)(20).

Results:

The study included 42 patients getting chemotherapy for head and neck tumours. The participants' average age was 58.3 years (SD ± 10.6), with 45.2% being female and 54.8% male. The average BMI was 25.8 kg/m² (SD ± 3.7). All the participant characteristics included in Table-1.

Table: 1 Baseline demographic characteristics of participants in the study

Characteristics	**N = 42**	**Percentage(%)**
Age (years)		
Mean (± SD)	58.3 ± 10.6	
Range	40-75	
Sex		
Male	23	54.8%
Female	19	45.2%
Body Mass Index (Kg/m^2)		
>25	17	40.5%
<25	25	59.5%
Neuropathy Severity (CTCAE)		
No Neuropathy	8	19%
Mild Neuropathy	14	33.33%
Severe Neuropathy	20	47.65%
Malondialdehyde		

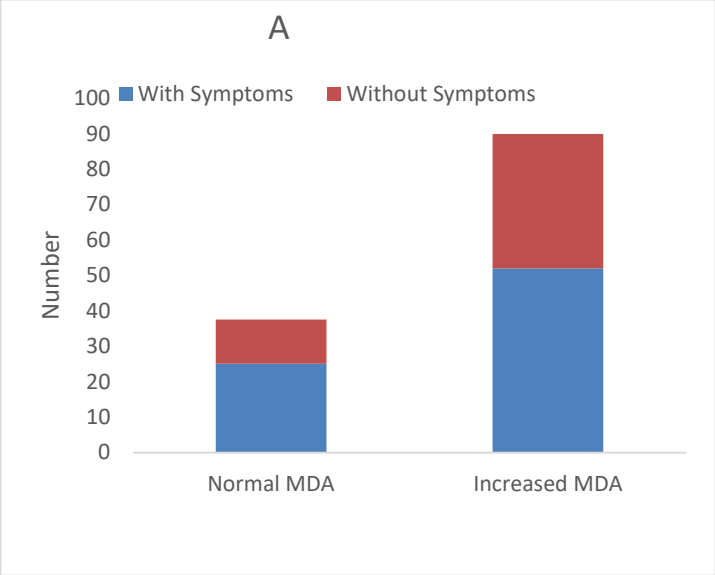
(≤4 nmol/ml)	30	71.4%
(>4 nmol/ml)	12	28.6%
Location:		
Oral cavity	19	45.23%
Oropharynx	7	16.67%
Hypopharynx	6	14.28%
Nasopharynx	6	14.28%
Larynx	4	9.5%
Regime:		
TPF(Docetaxel+Cisplatin+5-Flurouracil)	27	64.28
TIP (Paclitaxel+Ifosfamide+Cisplatin)	9	21.42
PC(Paclitaxel+Carboplatin)	6	14.28

Table- 2 Comparison of CTCAE Score with Melondialdehyde level and Neuropathy symptoms

	CTCAE score	P-value
Melondialdehyde(>4 nmol/ml) N=12	21.53±3.49	<0.0001
Melondialdehyde(≤4 nmol/ml) N= 30	37.10±10.67	
Catalase (U/mg protein)	68.7 ± 12.5	
No neuropathy symptoms	18.45±3.49	0.001
Mild/Moderate neuropathy symptoms	34±10.67	

Among chemotherapy-receiving patients of head and neck cancer, 33.3% of patients had minimal or mild neuropathy (Grades 0-1) according to the CTCAE criteria, 40% had moderate neuropathy (Grades 2-4), and 26.7% had severe neuropathy (Grades 3-4). Catalase activity was highest in patients with mild or no neuropathy (68.7 ± 12.5 U/mg protein), and it gradually decreased as the severity of the neuropathy increased. In patients with moderate neuropathy, it was 54.8 ± 11.3 U/mg protein, and in those with severe neuropathy, it was 45.3 ± 10.2 U/mg protein ($p<0.001$, ANOVA). On the other hand, moderate (5.9 ± 1.3 nmol/ml) and severe neuropathy (7.8 ± 1.5 nmol/ml) groups had considerably higher levels of malondialdehyde (MDA) than the no or mild neuropathy group (4.2 ± 1.1 nmol/ml) ($p<0.001$, ANOVA) Table-2 and figure-1.

Figure:1 comparison of with symptoms and without neuropathy symptoms among increased Melondialdehyde and normal Melondialdehyde patients



MDA levels showed a positive correlation with neuropathy severity ($r = 0.52$, $p<0.001$), although catalase activity showed a significant negative correlation ($r = -0.46$, $p<0.001$), according to correlation analysis. Additionally, there was an inverse relationship between MDA levels and catalase activity ($r = -0.38$, $p<0.001$). Both catalase activity ($\beta = -0.32$, $p<0.001$) and MDA levels ($\beta = 0.38$, $p<0.001$) were found to be significant independent predictors of neuropathy severity using multiple linear regression analysis. The model explained 47% of the variance in neuropathy severity (Adjusted $R^2 = 0.47$).

Discussion:

The results of the investigation show persuasive evidence that oxidative stress is an important factor in the aetiology of chemotherapy-induced neuropathy (CIPN). Our results specifically demonstrate that elevated levels of malondialdehyde (MDA) and decreased catalase activity are substantially linked to worsened CIPN severity. These findings support the theory that oxidative stress markers could serve as indicators of the severity of neuropathy, hence directing clinical treatment and intervention strategies.

Our findings are consistent with previous two studies that have demonstrated the crucial role of oxidative stress in neuropathy and other neurodegenerative diseases. Ankita Nandi et al. (2019) oxidative Stress in Age-Associated Degenerative Diseases like Parkinson's disease, Alzhaimer disease, etc published in Oxidative Medicine and Cellular Longevity and Qing-Shan Wang et al. (2014) observed that oxidative stress is a major contributor to allyl Chloride caused neuropathy, with increased ROS generation and decreased antioxidant enzyme activity observed in animal models treated with allyl chloride (19-20). Similarly, our result of lower catalase activity in individuals with severe neuropathy is consistent with the findings of A Soliman et al. (2019), who discovered that

impaired antioxidant defence mechanisms increase neuronal damage in CIPN (21).

Elevated MDA levels observed in our study reflect increased lipid peroxidation, corroborating findings from Few studies. Eva Decroli et al. (2019) and Kwong-Han et al. (2022) found that patients with diabetic neuropathy exhibited higher MDA levels, indicating significant oxidative damage. Our results extend these findings to CIPN, suggesting that similar oxidative mechanisms may be involved across different types of neuropathy (22).

Additionally, our study supports the work of Galasso et al. (2021) published in Free Radical Biology & Medicine, who identified a correlation between oxidative stress markers and neuropathy severity in cancer patients undergoing chemotherapy. The significant negative correlation between catalase activity and neuropathy severity, along with the positive correlation between MDA levels and neuropathy severity, observed in our study, further validates oxidative stress as a key factor in CIPN development (23).

The identification of catalase and MDA as potential biomarkers for CIPN has important clinical implications. These markers could be used to stratify patients based on their risk of developing severe neuropathy, allowing for personalized treatment plans. For instance, patients with low catalase activity and high MDA levels could be monitored more closely and may benefit from antioxidant therapies aimed at mitigating oxidative stress.

Our findings also suggest that enhancing antioxidant defenses could be a viable strategy for preventing or reducing CIPN. Antioxidant supplements or drugs that boost catalase activity or reduce lipid peroxidation may help protect against neuronal damage induced by chemotherapy. This aligns with the therapeutic potential suggested by previous studies, such as the work by Bauer et al. (2012), who demonstrated that antioxidants could attenuate CIPN symptoms in cell line models (24).

Despite the strength of our findings, this study has several limitations. The observational nature of the study precludes establishing a direct causal relationship between oxidative stress markers and CIPN. Longitudinal studies are needed to confirm these associations and determine whether changes in catalase activity and MDA levels precede the onset of neuropathy or are a consequence of it.

Additionally, our study did not control for all potential confounding factors, such as nutritional status, genetic predispositions, and the use of other medications that could influence oxidative stress. Future research should incorporate these variables to provide a more comprehensive understanding of CIPN pathogenesis.

Moreover, while our study focused on catalase and MDA, other oxidative stress markers and pathways may also play significant roles in CIPN. Exploring a broader range of biomarkers could yield more detailed insights into the mechanisms underlying neuropathy and identify additional therapeutic targets.

Conclusion

In conclusion, our study demonstrates that oxidative stress markers, specifically catalase activity and malondialdehyde levels, are significantly associated with the severity of chemotherapy-induced neuropathy. These findings underscore the importance of oxidative stress in CIPN and suggest that catalase and MDA could serve as valuable biomarkers for assessing neuropathy risk and severity. The

results align with and extend previous research on oxidative stress in neuropathy, highlighting the potential for antioxidant-based therapeutic strategies to mitigate CIPN and improve the quality of life for cancer patients undergoing chemotherapy. Further research is warranted to explore these strategies and validate the use of oxidative stress markers in clinical practice.

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