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INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/11213

DOI URL: <http://dx.doi.org/10.21474/IJAR01/11213>



RESEARCH ARTICLE

ROLE OF VITAMIN E IN PREVENTION OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY

Dr. Asif Riaz Khan, Dr. Fauzia Abdus Samad, Dr. Syed Abdus Samad, Dr. Anum Khan, Dr. Sharmin Arif
and Dr. Rimsha Zahid

Medical Oncology Department, Fauji Foundation Hospital Rawalpindi, Pakistan 46000.

Manuscript Info

Manuscript History

Received: 20 April 2020

Final Accepted: 25 May 2020

Published: June 2020

Abstract

Background: Chemotherapy induced peripheral neuropathy (CIPN) is one of the commonest and disabling side effect of chemotherapy drugs like taxanes, platinum compounds, vinca alkaloids, thalidomide and bortezomib. It often leads to dose reduction and discontinuation of treatment. Many agents like Vitamin E, glutathione, glutamate, acetyl L carnitine have been evaluated for their role in prevention of CIPN without any significant success. Hence, CIPN is an important area of research due to lack of effective agent to prevent CIPN. Methodology: Un-blind double arm interventional study

Results: Forty patients were distributed in two groups; intervention (vitamin E supplemented n=20) and control (n=20) arms. The TNSn scores were comparable at baseline and immediately after chemotherapy among both groups. However, after 3 months of chemotherapy the mean TNSn was comparatively low in the intervention arm (0.95 versus 1.64) which was not statistically significant. In subset analysis of Paclitaxel-Cisplatin combination chemotherapy subgroup, TNSn scores of two arms immediately post chemotherapy and at 3 months showed maximum difference between the arms (p-value, <0.001). In subset of Paclitaxel group, TNSn score at baseline and after chemotherapy were comparable. However, TNSn score measured after 3 months of chemotherapy in Intervention arm normalized, in contrast to non-intervention arm which still had a mean TNS of 1 with a p-value of 0.001

Conclusions: Our study showed a protective role of vitamin E profoundly in patients receiving single agent paclitaxel followed by paclitaxel and cisplatin regimen where the recovery from CIPN was much better as compared to control arm.

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Introduction:-

Chemotherapy induced peripheral neuropathy (CIPN) is one of the commonest and disabling side effect of cytotoxic medicines like taxanes, platinum compounds, vinca alkaloids, thalidomide and bortezomib.^[1] It is one of the dose limiting side effects and often leads to dose reduction and discontinuation of treatment.^{[2][3][4]} CIPN may be seen after treatments of cancers like ovary, breast, colorectal and hematological malignancies in approximately up to 40 % of patients.^{[3][5][1][6]} CIPN is mostly reversible but it can persist in one third of the patients.^[7]

CIPN symptoms are largely sensory in nature including pain, tingling and numbness in gloves and stocking distribution.^{[7][8][9][5][1][10]} Motor symptoms are less common than sensory symptoms and include distal muscle weakness, muscle cramps, loss of deep tendon reflexes in ankle and gait dysfunction. Autonomic symptoms are least common in their presentation and include postural drop in blood pressure, diarrhea and constipation, anhidrosis, dryness of eyes and mouth.^{[9][10][8]}

The exact mechanism of taxane induced neuropathy is not known. It is hypothesized that Taxanes lead to alteration of micro-tubulin structure of neurons resulting in reduced transportation of nutrients within the nerves resulting in dying back neuropathy.^{[8][11]} The longest neurons in body are of hand and feet which is the reason CIPN affects in gloves and stocking distribution.^[8] Other possible mechanism of taxane induced neuropathy is toxic effects on mitochondria in afferent neurons leading to interruption of axonal energy supply leading to sensory neuropathy.^{[8][11]} Cisplatin and carboplatin affect dorsal root ganglia as their main target structure causing accumulation of platinum in neural tissue.^{[8][11]}

Agents like Vitamin E, glutathione, glutamate, acetyl L carnitine have been studied to prevent of CIPN.^[6] Antioxidants like Vitamin E has been evaluated and are thought to act by affecting cellular metabolism.^[9] It protects neurons by inhibiting DNA damage and toxins accumulation. Vitamin E in doses ranging from 300 mg to 600 mg per day which has been tolerated well by patients in various studies and no therapy related adverse outcomes were reported.^[12] Moreover, it has not been reported to affect the antitumor activity of chemotherapeutic agents.^[13]

CIPN symptoms are usually difficult to describe and quantify. Of all available neuropathy assessment scores, the total neuropathy score (TNS), developed by Johns Hopkins University, is one of the most comprehensive score.^[12] TNS assesses sensory, motor and autonomic signs and symptoms along with quantitative assessment of vibration and perception threshold.^[14] TNS has different versions like reduced (TNSr), modified (mTNS), clinical (TNSc) and nurse (TNSn). We used TNSn for the assessment of peripheral neuropathy after getting permission from the author to utilize TNS for assessing CIPN, as it has been validated as sensitive tools for assessment of CIPN.^{[11][15]} TNS values range from 0-20 for TNSn. Two point change is considered as significant in TNS score.^[12]

The aim of the study was to study the role vitamin E in preventing or minimizing the severity of CIPN.

Objective:-

The Objective of this study is, To evaluate the effect of Vitamin E supplementation on the incidence and severity of chemotherapy induced peripheral neuropathy (CIPN) in patients treated with cytotoxic agents known to cause it.

Operational Definition:

Chemotherapy induced peripheral neuropathy: Chemotherapy induced peripheral neuropathy is development of sensory, motor or autonomic neuropathy secondary to the use of different chemotherapy agents.^[9]

TNS Score:

Total Neuropathy Score is a tool to detect neuropathy by assessing five parameters; sensory, motor, autonomic, pain sensitivity and vibration threshold.^[14]

Material and Methods:-

It was an open label two arm interventional study, conducted at Oncology Department, Fauji Foundation Hospital, Rawalpindi. Total duration of study was 12 months. We included 40 patients based on our parent study data. Patients were randomized into two arms, interventional and non-interventional, based on consecutive non-probability sampling technique. Patients included in our study met following criteria;

1. Patient aged ≥ 18 years
2. Treatment with cisplatin, carboplatin, paclitaxel, containing chemotherapy regimens
3. Performance status 0-2

Patients with following features were excluded from our study;

1. Patients who had already received chemotherapy.
2. Diabetes with end organ damage
3. Pre-existing peripheral neuropathy

4. History of CVA
5. Pregnancy

Chemotherapy regimens included Paclitaxel, Cisplatin or Carboplatin either alone or in combinations. Patients were recruited from both outpatient and inpatient departments after taking an informed consent. After detailed history and examination, staging workup was done as indicated for respective cancers. Patients in intervention arm were given vitamin E (400 mg/day) prior to starting chemotherapy till one month after completion of chemotherapy cycles. TNSn was used to assess CIPN. TNSn assessed five components. Among these sensory, motor and autonomic components were assessed by questionnaire. Pin sensitivity was gauged by neuropen and vibration sensibility was measured by Rydel-Seiffer calibrated tuning fork. The original TNSn questionnaire was used after taking written permission from the licensing body which is attached as annex "A". The two instruments required were specifically imported from England, on the recommendation of licensing body. Patients in the control arm were not given vitamin E. TNSn score was calculated at baseline before chemotherapy, immediately after the completion of chemotherapy and 3 months later for patients in both intervention and control arms.

SPSS version 23 was utilized to analyze data. Descriptive analysis included means and standard deviations for quantitative variables like, age and TNSn Score. Frequencies and percentages were calculated for categorical variables like tumor types, proportions of intervention arm and different chemotherapy regimens. Inferential statistics included the comparison of mean TNS score among vitamin E intervention and non-intervention groups at baseline, at the end of chemotherapy regimen and 3 months after last cycle of chemotherapy. Our data was normally distributed and Independent student's t-test was used to compare these means. The p-value of <0.05 was considered significant. ANOVA was used to compare the TNSn scores between different chemotherapy groups.

Results:-

In this study a total of 40 patients were distributed in two groups; intervention (vitamin E supplemented with n=20) and control (n=20) arms. Overall, the mean age of patients was 49.2 ± 7.9 years. Commonest diagnosis was ovarian carcinoma (14 patients, 35.0%), breast cancer (13 patients, 32.5%), carcinoma cervix (7 patients 17.5%) and endometrial cancer (6 patients 15%). Majority of the patients 17 (42.5%) were given Paclitaxel and Cisplatin combination chemotherapy, followed by paclitaxel alone in 12 patients (30%) and paclitaxel-carboplatin combination in 11 patients (27.5%) (Table 1).

As per study objective TNSn score was determined in both vitamin E and control arm. The baseline TNSn level was 0.15 ± 0.36 in vitamin E group and 0.30 ± 1.12 in the control group. The post therapy TNSn level was comparable among intervention and control group, however, after 3 months of chemotherapy the mean TNSn was comparatively low in the intervention (0.95 versus 1.64) which was not statistically significant (Table 2). Based on these findings further subset analyses were conducted.

In subset analysis of Paclitaxel-Cisplatin combination chemotherapy subgroup, TNSn scores of two arms immediately post chemotherapy and at 3 months showed maximum difference between the arms (p-value, <0.001) as shown in table 3. In subset of patients receiving Paclitaxel as single agent only, TNSn score at baseline and after chemotherapy were comparable. However, in this group, TNSn score measured after 3 months of chemotherapy in Intervention arm normalized, in contrast to non-intervention arm which still had a mean TNS of 1. Moreover, this difference was also statistically significant with a p-value of 0.001.

Age (years)	n (%)
< 40	69 (15%)
40 to 50	12 (30%)
51 or above	22 (55%)
Mean \pm SD	49.2 ± 7.9
Diagnosis	
Cervical Cancer	7 (17.5%)
Ovarian Cancer	14 (35%)
Breast Cancer	13 (32.5%)
Endometrial Cancer	6 (15%)
Chemotherapy	
Paclitaxel Cisplatin	17 (42.5%)

Paclitaxel Carboplatin	11(27.5%)
Paclitaxel	12(30%)
Vitamin E intervention	
Yes	20 (50%)
No	20(50%)

Table 1:- Overall baseline characteristics of patients (n=40).**Table 2:-** TNSn score comparison between intervention and non-intervention groups.

TNSn scores (Mean \pm SD)	Vitamin E (n=20)	Control (n=20)	p-value
Baseline	0.15 \pm 0.36	0.30 \pm 1.12	0.57
Post chemotherapy	2.6 \pm 1.14	2.1 \pm 1.41	0.22
3 months Post chemotherapy	0.95 \pm 0.68	1.60 \pm 1.93	0.16

Table 3:- Stratification of TNS score according to chemotherapy regimens in intervention group.

TNS	Chemotherapy Regimen	Mean Std. Deviation	p Value
TNS at baseline	Paclitaxel Cisplatin (n=6)	0.83 \pm 2.04	0.394
	Paclitaxel carboplatin (n=7)	0.14 \pm 0.37	
	Paclitaxel (n=7)	0.00 \pm 0.00	
TNS after Chemo	Paclitaxel Cisplatin (n=6)	3.33 \pm 1.96	0.025
	Paclitaxel carboplatin (n=7)	1.71 \pm 0.75	
	Paclitaxel (n=7)	1.43 \pm 0.53	
TNS 3 months after Chemo	Paclitaxel Cisplatin (n=6)	3.83 \pm 2.29	0.000
	Paclitaxel carboplatin (n=7)	0.29 \pm 0.48	
	Paclitaxel (n=7)	1.00 \pm 0.00	

Table 4:- Stratification of TNS score according to chemotherapy regimens in non-intervention group.

TNS	Chemotherapy Regimen	Mean Std. Deviation	p Value
TNS at baseline	Paclitaxel Cisplatin (n=11)	0.00 \pm 0.00	<0.001
	Paclitaxel carboplatin (n=4)	0.75 \pm 0.50	
	Paclitaxel (n=5)	0.00 \pm 0.00	
TNS after Chemo	Paclitaxel Cisplatin (n=11)	3.36 \pm 0.80	<0.001
	Paclitaxel carbo platin (n=4)	2.00 \pm 0.81	
	Paclitaxel (n=5)	1.40 \pm 0.54	
TNS 3 months after chemo	Paclitaxel Cisplatin (n=11)	1.36 \pm 0.50	<0.001
	Paclitaxel carboplatin (n=4)	1.00 \pm 0.00	
	Paclitaxel (n=5)	\pm 0.00 0.0	

Discussion:-

Cancer survival has improved dramatically due to advancement in treatment modalities.^[16] Cancer survival is quoted to be around 67% in patients above the age of 65 years.^[16] Chemotherapy induced peripheral neuropathy (CIPN) is one of the adverse effects of chemotherapy which substantially affects quality of life among cancer patients.^[8] Paclitaxel and platinum compounds like cisplatin and carboplatin have dramatically improved treatment outcomes at the expense of disabling adverse effect of neuropathy.^[17] So far, there is no known proven therapy which can prevent onset of CIPN.^[18] Hence it is an important area to explore if CIPN can be prevented or minimized to improve the quality of life of patients. With this background, we studied the role of Vitamin E in these patients.

Neurotoxicity is dose limiting side effect of paclitaxel with an incidence of up to 60% in patients receiving paclitaxel.^[11] Cisplatin is more neurotoxic than carboplatin.^[11] The incidence of neuropathy is almost 60% in Cisplatin treated patients and combination of paclitaxel and cisplatin has additive effect on the incidence of neuropathy.^[11]

Different drugs and natural compounds have been used for the prevention of CIPN.^{[3][10][18]} Vitamin E has been reported in literature to have some protective role in prevention of CIPN.^{[19][20]} Vitamin E is believed to have protective role in reducing neuronal cell destruction secondary to DNA damage and helps to diminish the accumulation of toxins in dorsal root ganglia.^{[20][13]} Vitamin E was chosen because we could only find six studies about the role of Vitamin E in preventing CIPN during the literature search from first January 2003 till 31st

December 2018. Our literature search included Google Scholar, PubMed and ProQuest. Also, Vitamin E is easily available, with no known interactions with chemotherapy and being well tolerated by patients without any significant adverse effects.^[13] Moreover, no such study has been conducted in Asia-Pacific region.

Argyriou et al studied role of vitamin E in preventing paclitaxel induced neuropathy.^[20] The mean age in his study was 57 years as compared to 49.2 years in our study. Their study included 32 patients with breast, lung and ovarian cancer. While we had 40 patients in our study cohort who had ovarian, breast, cervical and endometrial carcinoma. These authors studied the effect of paclitaxel induced peripheral neuropathy in contrast to our study group where patients receiving chemotherapy regimens including paclitaxel, cisplatin or carboplatin either alone or in combination were recruited. They used vitamin E 300 mg twice daily while we used vitamin E 400 mg once daily dose^[20]. They assessed neuropathy by neurological symptom score (NSS) while we used TNSn score. They found positive role of vitamin E in preventing CIPN, while in our study we could appreciate role in early recovery of the symptoms. In our study both the arms developed almost same severity of neuropathy as demonstrated by mean TNS score after chemotherapy but at 3 months post chemotherapy, intervention arm had complete resolution of CIPN in paclitaxel chemotherapy group. The mean TNSn score in our study was lower in Paclitaxel/Cisplatin arm which shows beneficial effect in cisplatin induced peripheral neuropathy.

Pace et al investigated role of Vitamin E in Cisplatin induced neuropathy.^[19] Their study population was 47 patients as compared to 40 patients in our study. Their study population average age was 58 years as compared to 49 years in our study. This was a two arm study. These authors used Vitamin in a dose of 300 mg/day in intervention arm.^[19] Their study population included patients with lung cancer, ovarian cancer, head and neck cancer, urothelial cancer, gastric and testicular cancer. They reported a lesser incidence and severity of neuropathy in Vitamin E supplemented arm.^[19] Contrary to these results, we did not observe a preventive role of Vitamin E on the incidence of CIPN. However, early recovery of CIPN was evident by low mean TNSn scores 3 months after chemotherapy. This could be explained by use of Paclitaxel and Cisplatin combination in our study which was given to 42.5 % population in contrast to no patient receiving this combination in study of Pace et al. Given the additive effect of Paclitaxel and Cisplatin as causative agents of CIPN, we observed conflicting role of Vitamin E in preventing CIPN.

Contrary to Argyriou et al and Pace et al, Kottschade et al did not report protective role of vitamin E in CIPN. Patients were divided into two age groups with 39% patients in ≤ 50 age group and 61% in ≥ 50 age group.^[10] Our patients had mean age of 49.2 ± 7.90 . Their study population was much bigger ($n=207$) as compared to our 40 patients.^[10] Their study population received taxanes, cisplatin, carboplatin and oxaliplatin either alone or in combination.^[10] Patients were given Vitamin E 400 mg twice a day.^[10] They used patient questionnaire to detect neurotoxicity while we studied neuropathy by TNSn score which gives an objective assessment of CIPN. Most of the patients received single agent chemotherapy and combinations were used in 11 % patients as compared to 42.5 % in our study. The common finding between our study was the early resolution of neuropathy in vitamin E receiving group, suggesting its role in early recovery.^[10]

Conclusion:-

Prevention and treatment of CIPN is a key area of research with cytotoxic agents known to cause it. Our study showed a protective role of vitamin E profoundly in patients receiving single agent paclitaxel followed by paclitaxel and cisplatin regimen where the recovery from CIPN was much better as compared to control arm. This is an exciting finding as early resolution of neuropathy will also improve quality of life. This finding of quicker recovery could be the trigger for further exploring role of nutraceutical in helping mitigate the CIPN. There were some shortcomings in our study including shorter follow up and smaller study size. The study population could be followed up further to see rate of recovery of CIPN in both the arms. We recommend testing these results in larger sample to validate the results of our study. Even larger doses of Vitamin E could be given to see safety and enhanced role in recovery of CIPN.

Conflict Of Interest:

Nil

Funding:

None

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