Docetaxel Chemotherapy Induced Peripheral Neuropathy in Breast cancer Patients and its Amelioration by Vitamin E

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ABSTRACT

Background: Chemotherapy is used to treat different types of cancer. Its use is associated with neurotoxicity, the most common of them is peripheral neuropathy. Taxanes are recognized to cause peripheral neuropathy of which Docetaxel is studied.

Aim: To evaluate the neurotoxicity of Docetaxel and assess the protective effect of vitamin E in breast cancer patients.

Methods: In a prospective placebo controlled randomized study, 60 women with breast cancer were selected. Patients had surgery and planned for chemotherapy administration. Chemotherapy protocol used is TAC that includes Docetaxel, Doxorubicin and Cyclophosphamide given every 21 days. They are assessed for neuropathy clinically and by nerve conduction study at the baseline and after completion of chemotherapy. They are divided into 2 groups each composed of 30 patients. The 1st group is given Vitamin E and the second group is given placebo.

Results: showed that the incidence of neuropathy is the same in both groups, but it was less severe in Vitamin E treated group compared to the placebo group.

Conclusion: vitamin E ameliorates the severity of peripheral neuropathy and can be used for this purpose.

Recommendation: We recommend large multicenter studies to be done and using other agents that possibly prevent or ameliorate Docetaxel induced neuropathy in the future.

Introduction

Vitamin E is an antioxidant discovered in 1922 by Katharine Scott Bishop and Herbert McLean Evans [1]. The synthetic form of Vitamin E is lipophilic vitamins called 'all-rac'-α-tocopherol act as strong antioxidant and consists of a set of eight different stereoisomers related tocopherols and tocotrienols [2, 3].This form has the highest bioavailability because it is easily absorbed and metabolized by the body [4].

Vitamin E is a liposoluble molecule dispersed between lipids and proteins in cell membrane. Liver takes up the vitamin E after the various forms are absorbed from the small intestine and then re-secretes only alpha-tocopherol via the hepatic alpha-tocopherol transfer protein [5, 6]. The α-Tocopherol acts as a strong antioxidant to scavenger the free radical and decrease oxidation propagation and prevent further damage to body cells mainly neurological functions [7]. Thus, it plays an important role as neuroprotective if nerve damage caused by neurotoxic agents [8].

Vitamin E is used in clinical practice in dosages vary between 200 and 3600 IU/d, about 400 IU /d is commonly used by many healthy humans, while in special cases such as a betalipoproteinemia, it is prescribed in a dose as much as 14000 IU/d [9]. Vitamin E is administered in a dose of 400 IU two times daily to protect neurological dysfunction that caused by cytotoxic drugs[10,11]. Docetaxel is a new semi-synthetic analogue of paclitaxel extracted from the European yew (Taxus baccata) and prepared as semisynthetic taxoid[12].

The cytotoxic activity of docetaxel and modes of action prevents physiological microtubule depolymerisation. This effect leads to a decrease in free tubulin and as a result reduces microtubule formation that prevents further cancer cell progeny through inhibition of mitotic process of malignant cell multiplication [13]. The pharmacokinetic behavior of docetaxel if given in a dose of <115 mg/m2 over 1 h, it behave as linear dose schedules, characterized by strong tissue uptake and about > 90% of it binds to plasma proteins14. Docetaxel is metabolized by hepatic P-450 cytochrome enzymes, mainly excreted through feces. About 70%–80% of total dose of docetaxel administration is mainly deposited in animals tissue while the remaining amount (<10%) is excreted through the kidney [15].

Docetaxel induced peripheral neuropathy (DIPN) occurs due to their oxidative effects in the body tissue. The fact that they produce harmful production called reactive oxygen

species (ROS). The symptoms of DIPN are commonly mild to moderate and uncommon severe toxicity but these symptoms predominantly sensory. Sensory neuropathic symptoms are symmetrical, usually started distally as abnormal sensory sensation within well-defined area at extremities in form of glove-and-stocking distribution. These neurological symptoms are found according to nerve fiber insult, if large fibers are affected the changes occur in proprioception and vibration, while if small fibers are affected, the abnormal changes were in pin prick and temperature sensation.

Symptoms are manifested as paresthesias (such as burning, pricking, itching or tingling); numbness; sensory loss; weakness in hands and feet. Many patients suffered from disability due to have clumsiness, loss of fine skill and un-ability to get normal gait [16]. The mainstay of assessment of CIPN is a clinical evaluation, which includes the taking of complete history and clinical examination of various sensory modalities (vibration, touch, joint position sense, pinprick, warm and cold), various motor modalities (muscle strength, flexion and extension of wrists, walking on heel and toe especially those of distal muscles, testing of deep tendon reflexes, Babinski sign, fine motoric function e.g., buttoning) and balance, e.g. Romberg's test, walking along straight line[17]. Several neurotoxicity assessment score system and neurophysiological studies have been developed to score the severity of CIPN:

1-Modified 5-Item reduced total neuropathic score (5-ItemTNSr) Score [18, 19]. This composite tool represents structural validity of a more clinically utilitarian and contains five neurologic components to quantify subjective symptoms, strength, tendon reflexes, pin prick and vibration test, these components would group together to form a neuropathy factor [20].

2- Nerve conduction studies (NCS), the comprehensive tool for the measurement of CIPN is a clinical neurophysiological studies of nerve conduction velocity [21]. It is comprehensive assessment of both subjective and objective neurologic components and a gold standard approach to detect signs that cannot be confirmed by history and neurologic examination [22]. The aim of the current study is to assess the incidence of chemotherapy induced peripheral neuropathy among patients with breast cancer given docetaxel and to evaluate the preventive and ameliorative effect of vitamin E on chemotherapy induced peripheral neuropathy..

Methods

A prospective placebo controlled clinical study was carried out at the Department of oncology in Al-Sadr Medical City in Najaf governorate from 1st February to the 30th of November 2014. The study population consisted of 60 patients who were attending the department of oncology with newly diagnosed breast cancer, treated surgically, and referred by the surgeons for chemotherapy. From those patients the study samples were selected. The study protocol was approved by the ethical committee of the medical college in Kufa University. Patients in groups A and B were additionally informed that they will receive vitamin E capsules or placebo medications twice daily for 4 months. Informed written consent for participants was obtained prior to participation. Patient's data were coded with a serial number and did not contain the name of participant.

Patients were underwent full history taking, including clinical characteristics, data sheet and complete physical examination. Also, laboratory investigations were performed for all patients to exclude abnormal findings associated with peripheral neurological diseases. Performed investigations were renal function tests (Blood urea, and serum creatinine), thyroid function tests (T3, T4 & TSH), and complete blood count and screening for diabetes mellitus (fasting blood sugar & HbA1c). Patients with the following criteria were excluded from the study:

1-Chemotherapy induced peripheral neuropathy if was given previously.

2-Patients who use any vitamin preparation or herbal remedies in the last three months.

3-Concomitant diseases that cause peripheral neuropathy such as diabetes mellitus, hypothyroidism, and chronic renal failure.

4-Concomitant neurologic conditions that would complicate interpretation.

5-Treatment with antiepileptic drugs, antidepressants and major analgesics.

6-The presence of peripheral neuropathy due to medications, e.g. alcohol abuse, statins, isoniazid, metronidazole & cimetidine.

7-Patients who currently had hypersensitivity to vitamin E.

Patients were received chemotherapy medications consisting of a combination, usually for periods of 4 months. The regimen is known as "TAC" protocol (Docetaxel, doxorubicin & cyclophosphamide). Each course consists of doxorubicin (Adriamycin) 50mg/m^2 intravenous infusion over 15

minutes, cyclophosphamide 500mg/m2 intravenous infusion over 1 hour followed by docetaxel (Taxotere) 75mg/m2 intravenous infusion over 1 hour on day1. This is repeated every three weeks for 6 cycles. Taxotere-80 Aventis, Pharma S.A. France, Batch No 4F116A is used in the present study during the treatment for breast cancer.

According to the design of the of the study, breast cancer patients were followed up for 4 months and divided randomly into two groups: group A (N=30): received chemotherapy and vitamin E capsule twice daily after meals , vitamin E capsule 400 IU (T&D pharma GmbH/Germany). The control group B (N= 30): received chemotherapy and placebo capsules twice daily after meals.

The patients were randomly assigned to each group. The randomization was achieved by categorization of patients in group A, the subsequent patient in group B. These sequences were followed until the last patient of the study and the sample size was reached. From the sixty enrolled patients, 55 patients reached the end of the study while 5 patients withdrew (one patient from group A, and four patients from group B).

Patients were underwent clinical examination and nerve conduction study (NCS) at baseline and after 6 cycles of chemotherapy. They were evaluated with a neurologic examination including a standardized history for detection of neuropathic signs and symptoms that were scored for the detection of sensory disturbances (e.g paresthesia, pain, and burning in toes & fingers) experienced by the patients; and assessment of pinprick and vibratory sensations and strength and deep tendon reflexes. The degree of neurotoxicity was expressed according to the Clinical Grading Scales and Nerve Conduction Studies (NCS).

1-The (5-ItemTNSr) Score: This scoring system was used for the assessment of patients regarding the symptom extension (tingling, numbness= PN), pin sensibility, vibration sensibility, and strength and tendon reflexes. The evaluation for each item scored 0-4 according to the response of the patient, and the total score ranged (0–20). Hammer, tuning fork 128Hz, disposable neurotips were used in this scale. This assessment method has a good validity and reliability values.

2- Nerve conduction study: Patients were subjected to nerve conduction study (NCS), which were performed at baseline and at end of study. The test is safe and well tolerated with only minor discomfort and no long term side effects. This examination was conducted by a specialist clinical neurophysiologists at the Middle Euphrates centre of neurosciences

in Al-Sadr Medical City in Najaf, using Micromed® Italy, and machine. Nerve conduction studies involve the stimulation of nerves with small electrical impulses over several points (usually limbs) and measuring the resultant responses. Surface electrodes are used to both deliver and detect the electrical impulses. The basic components of NCS include assessment of sensory and motor nerve conduction velocities and action potential amplitudes, distal latencies [23].

Most patients describe the effects as a 'tingling' or 'tapping' sensation. Patients informed to avoid prior application of topical creams as these may increase skin resistance to the applied current, and therefore require stronger levels of electrical stimulation. In cold environment, the limbs may need warming as cool peripheries (<32°C) may slow the conduction velocity of nerves and the electrodiagnostic tests should be performed in an air-conditioned room at constant temperature. Nerve conduction studies using pairs of electrodes that are used one to initiate the impulse and the other to record the response further along the path of the nerve (distally within the innervated muscle for motor nerves or proximally along sensory nerves).

The data were managed and analyzed using the statistical package for social sciences (SPSS) software for windows version 21, US, IBM, 2013. Descriptive statistics were presented as mean, standard deviation, standard error of mean, frequencies (numbers) and proportions (%). Analysis of variances (ANOVA) and post hoc tests were used to compare means and chi square test was used to compare frequencies. Fisher's exact test was used as an alternative when chi square test was inapplicable. Level of significance, P value, was set at <0.05 as a cut off point for significance.

Results

Table 1 shows the demographic characteristics of the 55 patients who completed the study and represented the two studied groups. As shown in this table, no statistically significant differences were found between the 2 studied groups regarding the demographic characteristics in all comparisons.

As shown in table 2, the majority of the patients had lower score zero at each item of this scoring system; 18 (62.1%) of the patients in group A and 15 (57.7%) of the control group B. From another point of view, as summarized in the same table, there were significant differences in symptoms and sign reduction within (5-ItemTNSr) components between group A and group B (P= 0.016) in

symptoms extension (tingling , numbness, PN) and (P = 0.038) in tendon reflex. Regarding the vibration sensibility, pin sensibility and Strength scale, despite the clinical differences that were observed between the studied groups, the differences were found to be statistically insignificant. The incidence rates of DIPN according to the 5-ItemTNSr in the A & B groups were estimated to be 41.4 % and 46.2 % respectively, with no statistically significant difference in the incidence rates (Table 3).

The nerve conduction study at the second visit revealed that sensory axonal PN was evident in 10 (34.5%) patients of group A and 3 (11.5%) of group B. Additionally, sensori-motor axonal PN was found in 2 (6.8%) patients of group A and 8 (30.8%) of group B, with a statistically significant difference. Group B was more likely to have mixed sensory motor PN than group A. Also, it was found that a significant difference existed according to severity of nerve insult between groups A &B (p= 0.006) (Table 4 and Figure1).

The incidence rate of CIPN obtained according to the NCS, was demonstrated to be 41.4% in group A and 42.3% in group B, where the lower rate reported in group A. However, the difference was not statistically significant (Table-5).

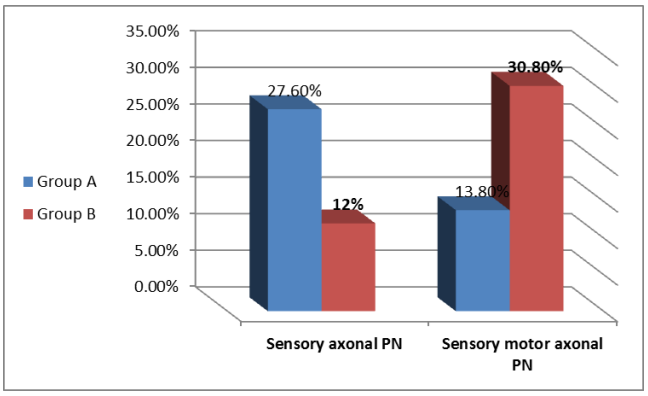

Fig. (1): Comparison of abnormal findings of the NCS assessment of the patients in the two studied groups.

Discussion

The current study revealed statistically insignificant differences in the demographic characteristics of the patients of the three studied groups. These insignificant differences in the demographic characteristics are necessary to exclude the possible effect of these variables in the development of peripheral neuropathy.

Smith et al (2008), reported important challenges that prevent oncology professionals from adequately assessing CIPN such as: patients are unable to report or describe neuropathy and related neuropathic pain24. This was reported by many authors25, 26. There is no specific comprehensive CIPN measurement tool valid and reliable that can easily be used in daily oncology practice and this was revealed by

Smith et al. [24]. According to these challenges, a grade scale is used to measure the severity of neurotoxicity and this measurement was assigned on the basis of clinical signs and symptoms in addition to nerve conduction study.

The 5-Items TNSr score revealed that patients supplemented with vitamin E showed a statistically significant decrease in signs and symptoms of peripheral neuropathy in score components mainly within symptom extension (tingling, numbness, PN) and tendon reflex. The measurement of CIPN by this score components was in agreement with that obtained by Smith et al, who reported that the (5-ItemTNSr) score can be used to measure these constructs24. Furthermore, the NCS assessment of DIPN indicated a significant decrease of neurotoxicity among patients received vitamin E compared with those of group B at the second visit. The overall incidence of chemotherapy induced peripheral neuropathy was determined to be 45.2% in group B of patients. This finding was in agreement with that obtained by Wilkes (2007), who reported that the incidence rate of peripheral neuropathy due to Docetaxol (DIPN) use was about 20–58% and of a sensory motor type [27].

Vitamin E was illustrated to cause significant amelioration of the symptoms and signs of DIPN. This finding was in agreement with that obtained by Argyriou et al. (2005) who concluded that vitamin E supplementation was well tolerated, safely and effectively protects patients with cancer against taxane induced peripheral neuropathy8. Furthermore, in 2006, in a randomized controlled clinical trial conducted by Argyriou etal., It has been highlighted the effectiveness of vitamin E supplementation and protection of patients with cancer against taxane induced peripheral neuropathy[28].

Conclusion

The overall incidence of docetaxel induced peripheral neuropathy was not affected by vitamin E. Docetaxel induced peripheral neuropathy was usually mild and predominantly sensory. Vitamin E significantly ameliorated chemotherapy induced peripheral neuropathy with well tolerance.

Recommendation

Vitamin E can be used for the amelioration of Docetaxel-induced peripheral neuropathy. More studies with large sample size are recommended to confirm the effect of vitamin E on chemotherapy induced peripheral neuropathy.

Table 1

Demographic characteristics of the patients of the studied groups

Variable	Group				P value
	Vitamin E (A)		Control (B)		
	No.	%	No.	%	
Age groups					
≤ 30	4	13.8	0	0.0	0.27
31–40	6	20.7	6	23.1	
41- 50	11	37.9	11	42.3	
> 50	8	27.6	9	34.6	
Mean ±SD*	44.5±7.9		46.4±6.6		0.25
Range	22–65		31 - 58		
Marital status					
Married	27	93.1	25	96.2	*0.61*
Single	2	6.9	1	3.8	
Education					
Illiterate	10	34.5	12	46.2	0.54
Read and Write	4	13.8	2	7.7	
Primary	6	20.7	2	7.7	
Intermediated	3	10.3	5	19.2	
Secondary	4	13.8	2	7.7	
Institute and college	2	6.9	3	11.5	
Occupation					
Employed	5	17.2	3	11.5	0.54
Not employed	24	82.8	23	88.5	
SE status **					
Low	2	6.9	1	3.8	0.15
Medium	27	93.1	22	84.6	
High	0	0.0	3	11.5	
Hypertension	3	10.3	2	7.7	1.0

*SD; standard deviation, **SE; socioeconomic

Table 2

The incidence of MEE in relevance to NG insertion

		Group				P value
		Vitamin E (A) (N=29)		Control (B) (N=26)		
		No	%	No	%	
Symptoms extension (tingling, numbness & PN)	0	18	62.1	15	57.7	0.016*
	1	7	24.1	1	3.8	
	2	3	10.3	4	15.4	
	3	1	3.4	6	23.1	
Pin sensibility	0	17	58.6	14	53.8	0.059
	1	11	37.9	7	26.9	
	2	1	3.4	5	19.2	
Vibration sensibility	0	17	58.6	14	53.8	0.38
	1	9	31.0	7	26.9	
	2	3	10.3	5	19.2	
Strength	0	27	93.1	23	88.5	1
	1	2	6.9	3	11.5	
Tendon reflex	0	17	58.6	15	57.7	0.038*
	1	2	6.8	2	7.7	
	2	9	31.0	3	11.5	
	3	1	3.4	6	23.1	

Table 3

Incidence of Peripheral neuropathy according (5-ItemTNSr) score of patients in the studied group

Group	PN		No PN		P value
	No.	%	No.	%	
Vitamin E (A)	12	41.4	17	58.6	0.72
Control (B)	12	46.2	14	53.8	
Total	24	43.6	31	56.3	

Table 4

NCS findings of the neuropathy for the patients in the three studied groups

NCS	Group				P value
	Vitamin E (B) (N=29)		Control (C) (N=26)		A vs B
	No.	%	No.	%	
First visit					
Normal	29	100.0	26	100.0	
Second visit					
Normal	17	58.6	15	57.7	
Sensory Axonal PN	10	34.5	3	11.5	0.006*
Sensory Motor axonal PN	2	6.9	8	30.8	

Table 5

Incidence of Peripheral neuropathy according to Nerve conduction study

Group	PN		No PN		P value
	No.	%	No.	%	
Vitamin E (A) (N=29)	12	41.4	17	58.6	0.94
Control (B) (N=26)	11	42.3	15	57.7	
Total	24	43.8	32	58.1	

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