Section: Physiology

Original Research Article

DETERMINING THE TIME OF ONSET OF PERIPHERAL NEUROPATHY IN PATIENTS RECEIVING CISPLATIN CHEMOTHERAPY BY DOING ELECTROPHYSIOLOGICAL STUDY

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ABSTRACT

Background: Cancer is the leading cause of death in developed countries and second leading cause of death in developing countries. The burden of cancer is increasing because of aging population, family history of cancer and cancer associated lifestyles such as smoking, alcohol, physical inactivity and westernized diet. The treatment of cancer is therefore a vital component. Cancer treatment includes surgery, chemotherapy, radiation therapy, and immune-therapy. Chemotherapy is the treatment of cancer with antineoplastic drugs. It is used in the management of advanced or metastatic disease and following failed surgery. Chemotherapy has a lot of adverse effects that depends upon the type of drug used, dosage and the duration of drug administration. Among the side effects, neurotoxicity is the most common. The neurotoxic effect can appear immediately or shortly after administration of drug. Symptoms are predominantly sensory or sensorimotor neuropathy. **Materials and Methods:** Our study included thirty patients with stage II gastric carcinoma receiving cisplatin 100mg/m2. They were subjected to nerve conduction study before and after second, fourth and sixth cycles of chemotherapy. **Result:** The study results showed significant decrease in nerve conduction velocity of median nerve – sensory component. Nerve conduction velocity was reduced after the end of sixth cycle (after 18 weeks). There was no significant difference in nerve conduction velocity of median nerve – motor component at the end of sixth cycle. **Conclusion:** From this study by knowing the time of onset of peripheral neuropathy, we can supplement the neuro-protective agents along with cisplatin, to reduce or prevent the toxic effects of cisplatin induced peripheral neuropathy.

INTRODUCTION

Cancer is the leading cause of death in developed countries and second leading cause of death in developing countries. The burden of cancer is increasing because of aging population, family history of cancer and cancer associated lifestyles such as smoking, alcohol, physical inactivity and westernized diet. The treatment of cancer is therefore a vital component. Cancer treatment includes surgery, chemotherapy, radiation therapy, and immune-therapy. Chemotherapy is the treatment of cancer with antineoplastic drugs. It is used in the management of advanced or metastatic disease and following failed surgery. Chemotherapy has a lot of adverse effects that depends upon the type of drug used, dosage and the duration of drug administration. Among the side effects, the neurotoxicity is the most common. The neurotoxic effect can appear immediately or shortly after administration of drug. Symptoms are predominantly sensory or sensorimotor neuropathy. Our study included thirty patients with stage II gastric carcinoma receiving cisplatin 100mg/m2. They were subjected to nerve conduction study before and after second, fourth and sixth cycles of chemotherapy.

Aim and objective

To determine the time of onset of peripheral neuropathy in patients receiving cisplatin chemotherapy by doing electrophysiological study

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MATERIALS AND METHODS

This study was conducted in a tertiary care centre. Thirty male patients with biopsy proved stage II gastric carcinoma (according to TNM staging) in the age group between 30 – 55 years were included in the study. All patients received 6 cycles of cisplatin. Each cycle is given at an interval of 3 weeks (21 days), with cisplatin 100mg/m2/cycle. All the patients were informed about the study, and written consent was obtained from them. Patients were subjected to nerve conduction study before starting cisplatin chemotherapy (0 day). Nerve conduction study was done by using Recorders Medicare System – EMG EP Mark –II Equipment. Nerve conduction tests of median nerve (motor and sensory component) were performed. Only those patients with normal base line nerve conduction parameters were included in this study. After starting chemotherapy, nerve conduction study is repeated after the end of second cycle (after 6 weeks), fourth cycle (after 12 weeks) and sixth cycle (after 18 weeks) and each of these values were compared with their base line values (0 day).

Inclusion Criteria

- Male, age group between 30 and 55 years.
- Biopsy proved stage II gastric carcinoma (according to TNM staging).
- Normal Base line nerve conduction parameters.

Exclusion Criteria

Diabetes mellitus, smoking habits, alcohol habits, hypothyroidism, leprosy, obesity, vitamin deficiency, previous chemotherapy, neurodegenerative diseases, H/O neuropsychotropic drugs.

Statistical Analysis

Results were analysed by using Paired't'test. P–value was calculated to test the statistical significance. P = <0.05 means significant. P = <0.01 means highly significant.

RESULTS

Table 1: Nerve conduction velocity of median nerve – sensory component. Before chemotherapy and after second cycle of chemotherapy

NERVE CONDUCTION VELOCITY	MEAN ± SD (ms)	P -VALUE
Before chemotherapy	56.33 ± 3.71	0.967
After chemotherapy (second cycle)	56.33 ± 3.73	

P = >0.05 not significant

There was no significant decrease in nerve conduction velocity of median nerve- sensory component, after second cycle of chemotherapy

Table 2: Nerve conduction velocity of median nerve – sensory component. Before chemotherapy and after fourth cycle of chemotherapy

NERVE CONDUCTION VELOCITY	MEAN ± SD	P -VALUE
Before chemotherapy	56.33 ± 3.71	0.775
After chemotherapy (fourth cycle)	56.26 ± 3.95	

P = >0.05 not significant

There was no significant decrease in nerve conduction velocity of median nerve- sensory component, after fourth cycle of chemotherapy.

Table 3: Nerve conduction velocity of median nerve – sensory component. Before chemotherapy and after sixth cycle of chemotherapy

NERVE CONDUCTION VELOCITY	MEAN ± SD	P –VALUE
Before chemotherapy	56.33 ± 3.71	< 0.001
After chemotherapy (sixth cycle)	54.09 ± 4.40	

P = < 0.01 is highly significant

There was a highly significant decrease in nerve conduction velocity of median nerve - sensory component, after sixth cycle of chemotherapy.

Table 4: Nerve conduction velocity of median nerve – motor component, before chemotherapy and after second cycle of chemotherapy

NERVE CONDUCTION VELOCITY	MEAN ± SD	P -VALUE
Before chemotherapy	57.54 ± 3.82	0.978
After chemotherapy (second cycle)	57.54 ± 3.79	

P = >0.05 not significant

There was no significant decrease in nerve conduction velocity of median nerve- motor after second cycle of chemotherapy.

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Table 5: Nerve conduction velocity of median nerve –motor component, before chemotherapy and after fourth cycle of chemotherapy

NERVE CONDUCTION VELOCITY	MEAN ± SD	P –VALUE
Before chemotherapy	57.54 ± 3.82	0.692
After chemotherapy (fourth cycle)	57.51 ± 3.85	

P = >0.05 not significant

There was no significant decrease in nerve conduction velocity of median nerve-motor component, after fourth cycle of chemotherapy.

Table 6: Nerve conduction velocity of median nerve – motor component, before chemotherapy and after sixth cycle of chemotherapy

NERVE CONDUCTION VELOCITY	MEAN ± SD	P -VALUE
Before chemotherapy	57.54 ± 3.82	0.368
After chemotherapy (sixth cycle)	57.47 ± 3.91	

P = >0.05 not significant

There was no significant decrease in nerve conduction velocity of median nerve- motor component after sixth cycle of chemotherapy.

DISCUSSION

Cisplatin is the most frequently used chemotherapeutic drug, indicated against wide range of solid tumours. Cisplatin exerts its cytotoxic effect by covalently binding to purine DNA bases and cause DNA damage by forming intra-strand crosslinks. This induces apoptotic cell death in a rapidly dividing cancer cell (Huang et al., 1842).

Neurotoxicity is the major dose limiting side effect of cisplatin chemotherapy. About 20% of the patients are unable to complete their full course of cisplatin chemotherapy due to neurotoxicity (Cano et al., 1998; Mc Donald and Windebank, 2002). The spectrum of cisplatin induced neurological damage includes peripheral sensory neuropathy (Boogerd, 1995; Albert and Noel, 1995; Cersosimo, 1989; Hilken and Van den Bent, 1997), optic neuropathy (Cersosimo, 1989), ototoxicity (Smoorenburg et al., 1999), focal encephalopathy, cortical blindness, seizure (Hilken and Van den Bent, 1997; Cersosimo, 1989) and rarely autonomic neuropathy and gastric paresis (cersosimo, 1989). Among all these, peripheral sensory neuropathy is the most common dose limiting toxicity (Hadley et al; 1979; Roelofs et al., 1984).

The overall incidence of cisplatin induced neuropathy was 47% irrespective of the grade of severity, and incidence in long survivors was 61 % (Vander Hoof, 1998). Clinically the patients present with numbness, paraesthesia in the stocking and glove distribution, loss of tendon reflexes, impaired vibration and joint position sense (Quasthoff and Hartung, 2002). Motor power remains normal (Boogerd, 1995; Hilkens and Van den Bent, 1997). The neuropathy worsens with continued treatment and the symptoms may progress even up to four months after cessation of drug (Albert and Noel, 1995; Schattschneider, 2001). Recovery is usually incomplete and 30 to 50 % of cases are irreversible even after stopping the chemotherapy (Albert and Noel, 1995; Strumberg et al., 2002).

In our study 30 patients with stage II gastric carcinoma treated with cisplatin were followed by performing nerve conduction study to evaluate the time of onset of neuropathy. All these patient received six cycles of cisplatin chemotherapy, with a dose of 100mg/m2 per cycle. Each cycle is given at an interval of 3 weeks (21 days).

In our study the nerve conduction parameters of median nerve (sensory and motor component) were studied. Nerve conduction velocities were assessed before cisplatin chemotherapy, and then after the end of second, fourth and sixth cycle of chemotherapy.

In the present study, sensory conduction of median nerve showed a statistically significant decrease in nerve conduction velocity after 6th cycle of cisplatin chemotherapy. From the above finding it was found out that there is sensory involvement after cisplatin therapy which was supported by other studies done by Boogerd, 1995; Albert and Noel, 1995; Hilken and Van den Bent, 1997. The levels of cisplatin were found to be higher in Dorsal Root Ganglion (Gregg et al., 1992). The anatomical sites that are capable of being affected are dorsal root cell body, supporting cells within dorsal root ganglia, the axon and the peripheral nerves (Roelofs et al., 1984).

The sensory neuropathy of cisplatin is related to damage to the DNA in the dorsal root ganglia neurons and satellite cells leading to apoptosis (McDonald and Windebank, 2002; Fischer et al., 2001). It also disrupts the intra and extra-neuronal transport and tropic function of satellite cells. The damage to the sheath of satellite cells, which is the only protective barrier for dorsal root ganglia neurons, also facilitates the neuronal damage (Corsetti et al., 2000; Sugimoto et al., 2001). This results in morphological alteration in Dorsal Root Ganglion neurons such as shrinkage of cell nucleus particularly the nucleolar size, shrinkage of cell cytoplasm (Muller et al., 1990; McKeage et al 2001). All these changes lead to damage to myelinated sensory fibers.

In the present study, nerve conduction velocity of median nerve (motor component) did not show any significant difference after chemotherapy.

CONCLUSION

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The study included thirty patients with stage II gastric carcinoma receiving cisplatin 100mg/m2. They were subjected to nerve conduction study before and after second, fourth and sixth cycles of chemotherapy.

The study result showed significant decrease in nerve conduction velocity of median nerve – sensory component. Nerve conduction velocity was reduced after the end of sixth cycle (after 18 weeks).

There was no significant difference in nerve conduction velocity of median nerve – motor component at the end of sixth cycle.

From the above findings it was concluded that cisplatin causes peripheral sensory neuropathy. From this study by knowing the time of onset of peripheral neuropathy, we can supplement the neuro-protective agents along with cisplatin, to reduce or prevent the toxic effects of cisplatin induced peripheral neuropathy.

The further study is intended to supplement the patients receiving cisplatin with neuro-protective agents, and to evaluate them with NCS. This would give way to know the other mechanism involved in pathogenesis of neurotoxicity and throw light to design newer neuro-protective agents. This will improve the quality of life in patients receiving cisplatin chemotherapy.

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