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Medicine

# Vincristine Induced Peripheral and Autonomic Neuropathy

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**ABSTRACT** Vincristine is a common therapeutic agent used in the treatment of various malignant diseases with other oncolytic agents in treatment of Acute Lymphoblastic Leukemia, Non-Hodgkin's Lymphoma. This study conducted was conducted from Jan 2000 to Jan 2002. Patients with Acute Lymphoblastic leukemia, Chronic Lymphoblastic leukemia & Non-Hodgkin's lymphoma were included in this study. Those patient who were diagnosed as acute myeloid leukemia were taken as control. Various test were performed on both group of patients. The study shows the main dose limiting side effect of Vincristine is chronic axonal sensorimotor neuropathy, autonomic neuropathy.

**KEYWORDS :**

**Aims & objectives**

To detect clinical & subclinical incidence of involvement of peripheral neuropathy & autonomic neuropathy who have received Vincristine as a part of their therapy for Acute Lymphoblastic Leukemia & lymphoma.

**Materials & Methods**

Patients who were diagnosed as Acute Lymphoblastic Leukemia & Non-Hodgkin's lymphoma were included in this study. Those diagnosed as Acute Myeloid leukemia were taken as control.

**Inclusion criteria**

Study: patients with Acute Lymphoblastic Leukemia & Non-Hodgkin's lymphoma
Control: Acute Myeloid Leukemia

**Exclusion criteria:**

Patients who had other causes of peripheral neuropathy were excluded like Diabetes, Vitamin B12 deficiency, Underactive Thyroid, Renal Failure, Alcoholism, Guillain Barre Syndrome, Chronic Inflammatory demyelinating Polyradiculopathy.

**Investigation done** for each patients were as follows.

Complete blood count, renal function test, Liver function test, serum Electrolyte, X-ray chest.

ECG: Long lead II was taken for each of the patients. ECG was taken during deep inspiration & expiration & expiration/inspiration ratio was calculated .E/I ratio <1.2 was considered abnormal. ECG during Valsalva maneuver was taken & Valsalva ratio was calculated. Valsalva ratio <1.1 is abnormal.

Indirect Laryngoscopy: Patients were also referred to the ENT dept for indirect laryngoscopy to rule out Vincristine vocal cord paralysis.

Nerve Conduction Studies: Based on the nerve conduction studies patients were considered whether they were diagnosed to have vincristine induced peripheral neuropathy.

Patient was tested for autonomic involvement:

1. Response of blood pressure to change in posture
2. Response of heart rate to change in posture
3. Variation of heart rate with respiration
4. Valsalva ratio
5. Hand grip test
6. Cold pressor test

Each test was done thrice & mean of all reading were taken to determine if patient had autonomic involvement or not. Patients were also observed for clinical symptoms such as constipation, vague abdominal pain, any urinary complaints, weakness, tingling numbness, sensory loss, dysphagia, hoarseness of voice, jaw pain.

Patients detailed neurological examination done including: Mental status examination, Motor, sensory system & cranial examination, Gait. All cranial nerves were examined.

**Observations & results**

**Table 1: Frequency of Peripheral Neuropathy (PN) & Autonomic Neuropathy (AN)**

| | Frequency | PN | AN | PN + AN |
|---|---|---|---|---|
| Case | 25 | 4 | 1 | 1 |
| Percentage | 100 | 16 | 4 | 4 |
| Control | 10 | | | |
| Total | 35 | 4 | 1 | 1 |

PN: Peripheral Neuropathy AN: Autonomic Neuropathy

**Table 2: Age**

| Age (yrs) | Frequency | study | control | PN | AN | PN +AN |
|---|---|---|---|---|---|---|
| 8-17 | 13 | 13 | - | 2 | 1 | 1 |
| 18-27 | 10 | 7 | 3 | 2 | - | - |
| 28-37 | 5 | 1 | 4 | - | - | - |
| 38-47 | 6 | 4 | 2 | - | - | - |
| 48-57 | 1 | - | 1 | 2 | - | - |

**Table 3: Sex**

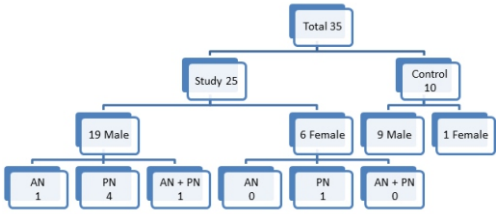


**Table 4 : Total dose**

| Total dose mg | Total No of Patients (25) | PN | AN | PN + AN |
|---|---|---|---|---|
| 8-10 | 3 | 1 | - | - |
| 11-12 | 1 | - | - | - |
| 13-14 | - | - | - | - |
| 15-16 | 11 | 1 | 1 | - |
| 17-18 | 2 | 1 | - | - |
| 19-20 | 2 | 1 | - | - |
| 21-22 | 1 | - | - | - |
| 23-24 | 4 | - | - | 1 |
| 25-26 | - | - | - | - |
| 27-28 | 1 | - | - | - |

**Table 5: Dose in mg/m2**

| Dose | Total patients | PN | AN | PN+ AN |
|---|---|---|---|---|
| 1.4 | 10 | 2 | - | - |
| 2 | 15 | 2 | 1 | 1 |

**Table 6: symptoms**

| Symptoms | Dose | No of patients | PN | AN | PN+AN |
|---|---|---|---|---|---|

| | | | | | |
|---|---|---|---|---|---|
| PNS | 2 | 1 | 1 | - | - |
| ANS | 2 | 1 | - | 1 | - |
| Others | - | - | - | - | - |

**Table no 7: On examination**

| | Dose 1.4 | Dose 2 | No of patients | PN | AN | PN + AN |
|---|---|---|---|---|---|---|
| Motor | - | - | - | - | - | - |
| Sensory | 1 | 1 | 2 | 2 | - | - |
| Reflexes | 1 | 1 | 2 | 2 | - | - |
| Cranial | - | - | - | - | - | - |

**Table 8: Autonomic Test**

| Test No | No of patients abnormal | Dose 1.4 | Dose 2 | Total dose | PN only | AN only | AN + PN |
|---|---|---|---|---|---|---|---|
| 1 | - | - | - | - | - | - | - |
| 2 | 1 | - | 1 | 16 | - | ü | - |
| 3 | 1 | - | 1 | 24 | - | - | ü |
| 4 | 2 | - | 1 | 16 | - | ü | - |
| | | | | 24 | | | ü |
| 5 | 2 | - | 1 | 16 | - | ü | - |
| | | | | 24 | | | ü |
| 6 | 2 | - | 1 | 16 | - | ü | - |
| | | | | 24 | | | ü |

1. Response of BP to change in posture
2. Response of HR to change in posture
3. Variation in HR with respiration
4. Valsalva
5. Hand Grip
6. Cold Pressor Test

**Table No 9: Nerve Conduction Studies**

| Involvement | No of patients abnormal | Dose 1.4 mg/m2 | Dose 2 mg/m2 |
|---|---|---|---|
| Sensory | 5 | 2 | 3 |
| Motor | 5 | 2 | 3 |
| Upper limb | 4 | 2 | 2 |
| Lower limb | 5 | 2 | 3 |
| Axonal | 5 | 2 | 3 |
| Axonal + demyelinating | 2 | 1 | 1 |

**Total 10: Dose & duration of last dose of Vincristine & the test performed**

| Sr No | Total dose of Vincristine | Duration between last dose & test done | PN | AN | PN + AN |
|---|---|---|---|---|---|
| 1 | 20 | 1 month | ü | - | - |
| 2 | 8 | 1 month | ü | - | - |
| 3 | 24 | 7 month | - | - | ü |
| 4 | 18 | 1 month | ü | - | - |
| 5 | 16 | 2 month | ü | - | - |
| 6 | 16 | 1 month | - | ü | - |

## Discussion

Vincristine is a common chemotherapeutic agent used in the treatment of various malignant disease with other oncolytic agents. It is available in powder from as well as in fluid solution form for intravenous use. Its usual dose is 2mg/m2 body surface area in children & 1.4mg/m2 in adult. Dose should not exceed 2gm because beyond this dose toxicity is likely to occur. Common side effects are neurotoxicity which is reversible on stopping Vincristine or reducing the dose. Individuals with prior peripheral nervous system disorder should receive less dose as they are more sensitive to even small dose of Vincristine .The main dose limiting side effect is chronic axonal sensorineural neuropathy, autonomic neuropathy & cranial nerve palsy. Loss of deep tendon reflexes is the first sign of toxicity. Vincristine causes autonomic neuropathy. It causes gastrointestinal symptoms like constipation, abdominal pain & paralytic ileus as its major manifestation. Cranial nerves involvement is less common as compared to peripheral & autonomic involvement. It can present as ptosis, opthalmoplegia, loss of corneal reflexes & paroxysmal jaw pain.

In this study conducted, patients of Acute Lymphoblastic Leukemia, Chronic Lymphoblastic Leukemia & Non-Hodgkin's Lymphoma were included. Those diagnosed with Acute Myeloid Leukemia were taken as control. The control group has received Cytosine Arabinoside & Daunorubicin as a part of their chemotherapy. Arabinoside & daunorubicin causes neurotoxicity within their therapeutic range. All our controls patients as well as the study group of patients had received cytosine & Daunorubicin as a part of their chemotherapy. All Our study & control group had similar course during their chemotherapy such as use of blood, blood products & plasma products, febrile neutropenia, use of broad spectrum antibiotics, etc. None of the patients in control group developed any symptoms of peripheral or autonomic neuropathy. The nerve conduction studies done in control group were also normal. Out of 25 study patients, 5 patients had developed peripheral neuropathy & one patient had developed autonomic neuropathy & one had developed both peripheral as well as autonomic neuropathy in these patients.

Patients of different age group were studied. The youngest patient was age 8 yrs. & oldest patient was 54 yrs old. The maximum incidence of peripheral & autonomic neuropathy was found in the first age group ranging from 8-17 yrs.(Table no 2).Two patients developed peripheral neuropathy, one developed autonomic & peripheral neuropathy both. Though only two patients had symptoms of paresthesia & abnormal sweating individually, both of these patients showed evidence of peripheral neuropathy & autonomic neuropathy on nerve conduction studies & test for autonomic neuropathy. William wood et al (2) studied similar incidence of involvement of autonomic & peripheral involvement in children ranging from age group 3 months to 16 months. In these patients, 7 had developed Vincristine induced peripheral neuropathy in 10 – 40 days from the chemotherapy with an average of 22 days.

Maximum Number of patients had received the total dose ranging from 15-20 mg (Table no 4). There were three patients reported to have abnormal nerve conduction studies suggesting peripheral neuropathy & one developed autonomic neuropathy. The minimum dose with which patient developed was 8 mg & maximum dose with which another patient developed peripheral & autonomic neuropathy was 24mg.

When the total dose/m2 was taken into consideration it was observed that 1 patient had developed peripheral neuropathy with a minimum dose of 5 mg & maximum dose was 20 mg. Thus Vincristine induced neuropathy was independent of its course.

On Examination, only two had depressed reflexes & vibration & position sense depressed, both these patients had peripheral neuropathy which was proved on the basis of nerve conduction studies. Autonomic test were done for all the patients. (Table no 8)Test no 1 was normal in all the patients. Test no 2 was abnormal in one patient. Test no 3 was abnormal in one patient. Test no 4, 5, 6 was abnormal in two patients. Thus test no 4, 5, 6 were considered more sensitive in detecting autonomic neuropathy.

Nerve Conduction studies were done in all the patients. Only 5 patients were reported to have abnormal nerve conduction studies. Vincristine causes primary sensorimotor axonal neuropathy. In our study all 5 patients had both sensory & motor involvement & 4 patients had upper limb involvement as well.

Vincristine causes predominately, axonal involvement but in our study 2 patients had both the axonal & demyelinating neuropathy. (Table no 9). The reason for demyelinating lesions could not be explained. One possible explanation can be considered that these patients had received Intrathecal Methotrexate injection which could cause a local axonal involvement. However with this only the lower limb would be involved but in our patients had both upper limb & lower limb involvement. Therefore it is unlikely to be due to Methotrexate injection. Also radiation is one of the cause for demyelinating peripheral neuropathy but our patients had received cranial radiation & no spinal; radiation was given .In our study one of the patients was 14 yrs old & other was 44 yrs old & none of these patients had any other cause of demyelinating lesion such as alcohol, diabetes. Though it would be helpful if the nerve conduction test was done before & after giving Vincristine. It was not possible for us to get test before & after giving Vincristine. But since other causes of demyelinating lesions were ruled out, it can be stated that Vincristine was a cause of demyelinating lesion in our patients.

## Conclusion

In our study we could demonstrate that 6 out of 25 patients i.e. 16% had the evidence of neuropathy either peripheral or autonomic or both.

These features were demonstrable 1-7 months after discontinuation of Vincristine therapy.

In the age & sex group, that we studied we did not find any difference in the occurrence of neuropathy in children or adults, males or females neither was it dose dependent.

The tradition clinical signs used to check the presence of neuropathy were found in only 2 patients & hence only a clinical examination is not enough to diagnose a neuropathy.

We had an unusual finding that is two out of five patients with peripheral neuropathy had electrophysiological evidence of demyelination. This is an extremely unusual form of neuropathy with Vincristine & to the best of our knowledge has not been reported.

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