ASSESSMENT OF THE ROLE OF ALPHALIPOIC ACID IN PREVENTION OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY.

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Abstract

Introduction: Chemotherapy induced peripheral neuropathy (CIPN) is a common dose limiting side effect of many chemotherapeutic agents. It is considered the second most common acute side effect after hematologic toxicity. It affects ~ 30 % of patients receiving chemotherapy. Causes of CIPN in not exactly known and well understood. However treatments that are used to treat this condition have been found to be ineffective and have many undesirable side effects. Alpha Lipoic acid (ALA) is a physiological anti-oxidant that has been found effective in diabetic neuropathy, but hasn't been investigated thoroughly for the use in CIPN.

Material and Methods: This is a prospective clinical trial conducted at Clinical Oncology Department in Suez Canal University Hospital, where one hundred patients received chemotherapy causing peripheral neuropathy were included in our study; they were divided into two equal groups, study and control group. Study group received ALA 600 mg three times daily for 12 weeks from the start of chemotherapy, control group received no treatment. Assessment was done before starting treatment and after each cycle by using FACT/GOG-Ntx score.

Results: A total of 100 patients were included in this study, 83% were females and 17% were males. 62% of patients had breast cancer and 17 % had GIT cancer.65% of patients received single neurotoxic agent causing peripheral neuropathy while 35% received combined agent causing peripheral neuropathy. 96% patients completed the study (12 weeks). There was a statistically significant difference between the ALA and the control groups for FACT/GOG-Ntx scores.

Conclusions: CIPN is one of the most severe adverse effects of chemotherapy; with a significant impact on the Quality of life .This strategy of oral ALA administration was effective at preventing neurotoxicity.ALA as a neuroprotective agent has shown some promise. Future studies to explore ALA as a neuroprotective agent should take heed of the barriers confronted in this study.
Introduction:
Chemotherapy induced peripheral neuropathy is considered a common dose limiting side effect of many chemotherapeutic agents. It is considered the second most common acute toxicity after hematologic toxicity (Windebank & Grisold, 2008). It affects about 30% of patients treated by chemotherapy. Although it is not a life threatening complication but it affects the quality of life and daily activities e.g. buttoning a shirt (Seretny et al., 2014). CIPN manifests clinically as deficits in motor, autonomic, sensory or less likely, functions. The incidence mainly related to the dose and the used chemotherapeutic agent and it also affected if there is preexisting nerve damage from other causes (such as diabetes mellitus, previous exposure to neurotoxic drugs). Also motor manifestations may occur in the form of weakness of the extremities (such as foot drop), and autonomic manifestations may occur in the form of orthostatic hypotension (Kaley & DeAngelis, 2009).

Dose reduction or alteration of a potentially curative chemotherapeutic agent usually occurs due to this side effect. However treatments to this condition (such as amfostine, anti-depressant drugs…) have been found to be ineffective and have many side effects. The most common used CIPN agents include (platinum drugs, taxanes, vinca-alkaloids, thalidomide, bortezomib, interferon, methotrexate, fluorouracil, cytarbine) (Simão DAdS et al., 2015).

Alpha Lipoic acid is a physiological anti-oxidant that has been found effective in diabetic neuropathy, but isn't investigated thoroughly for the use in CIPN. ALA is easy to be transported across all membranes as it is a fat- and water soluble, and exerts its antioxidant activity inside and outside of cells (Guo et al., 2014).

Materials and Methods:
It was a prospective clinical trial conducted at Clinical Oncology Department in Suez Canal University Hospital, done to assess role of alpha lipoic acid in prevention of CIPN where one hundred patients received chemotherapy causing peripheral neuropathy were included in our study. The target population included adult patients who attended clinical oncology department in Suez Canal university hospital, they were divided into two equal groups, study and control group where 50 of eligible patients were assigned to each of the 2 groups.

Group (A): The Study group: Patients who received chemotherapeutic drugs causing peripheral neuropathy received alpha lipoic acid 600 mg three times daily for 12 weeks from the start of chemotherapy.

Group (B): control group, Patients who received chemotherapeutic drugs causing peripheral neuropathy but didn't take alpha lipoic acid.

Inclusion criteria:
Patients planned to receive chemotherapy known to cause peripheral neuropathy (vincristine, taxanes and platinum derivatives), any stage of the disease, adult patients (aged between 18 and 65 years old), expected survival of the patients more than one year and patients have normal liver and renal function.

Exclusion criteria:
Patients known to have diabetes, preexisting neurologic condition that would complicate interpretation, presence of peripheral nerve damage due to other disease or treatment, patients received previously neurotoxic chemotherapeutic drugs, patients already on treatment for neuropathy, patients known to have spinal cord compression or brain lesion, and patients known to be allergic, patients refused to be included the study.

Assessment was done before starting treatment and after each cycle. Neuropathy was measured by the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) scale (Wampler, 2016).

| Summary |
|-------------------|-----------------------------|
| Functional Assessment of Cancer Therapy/Gynecologic Oncology Group Neurotoxicity (FACT/GOG-Ntx) (v4) | • An 11-item patient self-report tool that describes CIPN symptom severity and functional consequences. |
|                    | • 0-44 points, a lower score indicates better quality of life |
Demographic data:
Age, sex, residence, performance using ECOG-PS score, educational level of the patient.

Data related to disease:
Pathology of primary disease, presence of bone metastasis that would cause numbness, presence of pre-existing neurologic disease, presence of any other metastasis.

Data related to Management:
Onset, severity of neuropathy and efficacy of treatment in CIPN.

Post management: Outcome was rated using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) scale.

Results:
Table 1: Sociodemographic characteristics of study population

| Variable          | Total N= 100 (%) |
|-------------------|------------------|
| Gender            |                  |
| Male              | 17 (17%)         |
| Female            | 83 (83%)         |
| Residence         |                  |
| Rural             | 20 (20%)         |
| Urban             | 80 (80%)         |

Table 2: Pathology distribution of study population

| Group                          | Total N=100 (%) | Control N=50 (%) | Study N=50 (%) |
|--------------------------------|-----------------|------------------|---------------|
| Breast cancer                  | 62%             | 30 (60%)         | 32 (64%)      |
| lymphomas                      | 6%              | 4 (8%)           | 2 (4%)        |
| GIT tumor                      | 17%             | 8 (16%)          | 9 (18%)       |
| Genitourinary cancer           | 5%              | 5 (10%)          | 0             |
| Metastatic adenocarcinoma      | 3%              | 1 (2%)           | 2 (4%)        |
| Lung cancer                    | 7%              | 1 (2%)           | 5 (10%)       |

Table 2: shows distribution of primary tumor among our enrolled patients, where breast cancer was 60% in control group and 64% in study group, lymphomas were 8% in control and 4% in study group, and the remaining were genitourinary, lung and metastatic adenocarcinoma.

Table 3: Chemotherapy types of study population

| Variable                          | Total N=100 (%) | Control N=50 (%) | Study N=50 (%) |
|-----------------------------------|-----------------|------------------|---------------|
| Chemotherapy                      |                 |                  |               |
| Single agent causing CIPN         | (65)            | 32 (64%)         | 33 (66%)      |
| Taxanes                           | 43%             | 22 (44%)         | 21 (42%)      |
| Platinum compounds                | 18%             | 9 (18%)          | 9 (18%)       |
| Vincristine                       | 4%              | 1 (2%)           | 3 (6%)        |
| Combined therapy causing CIPN     | 35%             | 18 (36%)         | 17 (34%)      |

Taxanes; taxol, taxotere - platinum compounds; cisplatin, oxaliplatin, carboplatin - Combined therapy; Taxanes/ platinum.

Table 3 shows the types of chemotherapy that was used in the enrolled patients, in the control group single agent causing CIPN was used in 64% of patients while 36% of them had combined therapy causing CIPN, the most commonly used were Taxanes. In the study group single therapy was used in 66% of patients, the most common
used medications were Taxanes which was used in 42% of patients and Platinum compounds which was used in 18% of patients.

Table 4: Association between both groups and FACT/GOG-Ntx score at each session of chemotherapy

| Variable          | Total    | Control | Study    | p-value |
|-------------------|----------|---------|----------|---------|
|                   | Mean ± SD| Mean ± SD| Mean ± SD|         |
| Baseline          | 0.6 ± 1.3| 0.7 ± 1.5| 0.5 ± 1  | 0.53    |
| 1st Follow-up     | 4.1 ± 5.9| 5 ± 6.6  | 3.2 ± 4.9| 0.11    |
| 2nd Follow-up     | 7.3 ± 6.3| 10.7 ± 6.4| 3.1 ± 2.7| <0.001* |
| 3rd Follow-up     | 7.2 ± 6.4| 10.9 ± 6.4| 2.6 ± 2.2| <0.001* |

*P-values are based on Mann-Whitney U test. Statistical significance <0.05.

![Figure 1](image)

Figure 1: Comparison between both groups and FACT/GOG-Ntx score

Table 4 & Figure 1. shows statistical significance difference in mean FACT/GOG-Ntx score of neuropathies in 2nd and 3rd follow up between both control and study groups, (p-value<0.001) where study group had a lower mean score than control group.

Discussion:

CIPN is considered one of the most debilitating side-effect of chemotherapy and mostly worsening the patients' quality of life and if severe enough leads to decrease dose or change the type of the used curative chemotherapy (Hausheer et al., 2006).

Alpha lipoic acid has strong chelating, antioxidant activity, and neuroprotective and neurotrophic properties; therefore, it can eliminate the free radicals produced by chemotherapy, re-activate the normal axonal flow and reduce the neuropathic anticancer therapies effects (Bilska, A. et al., 2005).

In this trial, we investigated ALA to determine if its use decreases the severity of peripheral neuropathy and if it improves the quality of life after patients' exposure to twelve weeks of chemotherapy.

The study was conducted at clinical Oncology department in Suez Canal university hospital over a period of one year. Our study included 100 eligible patients which was more than the number of patients found in a study done in Italy where the number of patients were 25 adult treated at the Radiation Oncology Unit of the Careggi University.
Hospital (Desideri et al., 2017) and more than another study done in Austria where the total number of included patients were 14 adults treated at University of Vienna (Gedlicka et al., 2003).

Regarding age of the studied population, the mean age of the study participants was 45.8 ± 11.4. This was less than the study done in Careggi University Hospital where the mean age was 64 (40–76) (Desideri et al., 2017) and also less than study done by (Guo et al., 2014) where the mean was 55 ± 11.

However there was no statistically significant difference in mean age between two groups in our study.

The dose of ALA that was tested in our study was 600 mg capsule three times daily that was used among study group that showed a statistical significance difference between the study and the control group among different sessions (baseline, 1st session, 2nd session and 3rd session).

The mean score in control group was increasing across chemotherapy session in contrast to the score of the study group which was decreasing across chemotherapy session and this proves effectiveness of ALA use in reducing neurotoxicity. Although both ALA group and control group exhibits worsening of neuropathic symptoms at week 12 compared to baseline, but the overall neuropathy score between the two groups were statistically significance.

This was nearly similar to results by (Gedlicka et al., 2002) where ALA was co-administered with oxaliplatin, in patients with advanced colorectal cancer, and this was able to counteract cumulative effect of oxaliplatin-related PNP; in 53% of patients who received ALA. This was also comparable to the results of (Gedlicka et al., 2003) where patients with gastric cancer receiving docetaxel/cisplatin showed the effectiveness of ALA in reducing peripheral neuropathy caused by them.

An in vitro study by (Melli et al., 2008) also showed effectiveness of alpha lipoic acid as a neuroprotective agent in preventing neurotoxicity induced by taxanes, through a mitochondrial action, while randomized control study by (Guo et al., 2014) evaluated the effectiveness of alpha lipoic acid in prevention of neuropathy caused by platinum-based chemotherapy where patients were randomized to either receive oral alpha lipoic acid 1800 mg daily or placebo, CIPN was measured by the 11-item Gynecologic Oncologic Group-Neurotoxicity component of FACT at week 24, no statistical differences were found between the two groups.

Conclusion:-

CIPN is one of the most severe adverse effects of chemotherapy, with a significant impact on the QOL of affected patients, mostly because the long-term effects of the persistence of symptoms/signs cannot be estimated and its treatment remains difficult.

One hundred patients were recruited in this study during period of twelve weeks, randomly assigned to either receive ALA (study group) or no treatment (control group), and 95 % of the study group was compliant to the dose of ALA prescribed to them. Males account 15 % of the patients while females were 85 %. The mean age of them was 45±12.45%. Sixty two % of the patients had breast cancer, while GIT cancer each was 17 %. There was statistical significance between study and control group in the follow up. Where study group had less severe symptoms.

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