Potential prevention of oxaliplatin induced morphological, behavioral and microscopic injury by glutathione in adult albino mice

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ABSTRACT

Objective: To assess the effects of oxaliplatin on gross appearance, behavior and neural tissue of albino mice and to observe prevention against oxaliplatin induced damage by glutathione.

Study Design: Experimental study

Place and Duration: Department of Anatomy, Liaquat University of Medical and Health Sciences Jamshoro in collaboration with Sindh Agricultural University TandoJam from 1st January-30th June 2015.

Methodology: Adult mice (n=36) from both genders were grouped and labeled as Control (Group A), Oxaliplatin treatment (Group B), Oxaliplatin plus glutathione (Group C). The gross features (Weight, hair loss, paw edema) and behavior (heat and cold stimulation test, noise stimulation test, hearing test) of the animals were monitored and animals were sacrificed and brains were collected for the histopathology to see the effects of oxaliplatin and its prevention by glutathione.

Results: The weight of the animals significantly decreased over the entire period of study as compared to control animals. Also a significant decrease was noticed in hair on the skin of front part of the body in group B. In other parameters; paw edema, mental orientation, object recognition, noise stimulation group B exhibit significant difference to control $p<0.05$. Heat and cold stimulation tests significantly increased in group B. Microscopic features of brain tissue also showed inflammatory and ischemic changes in group B. All gross and microscopic features were improved with the addition of glutathione.

Conclusion: The toxic effects of oxaliplatin, on morphology and behavior and brain of adult albino mice were partially reversed with glutathione supplementation.

Keywords: Adult mice, Behavior, Brain damage, Glutathione, Gross Morphology, Oxaliplatin, Neural tissue.

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INTRODUCTION

The cancer, one of the leading causes of the mortality is increasing in frequency with approximately 17 million new cases are expected by 2020[1]. The development of new chemotherapeutic agents is associated with complications which limit their dose and thus the role in the prevention of cancers[2]. The most common drug induced side effect with almost all chemotherapeutic drugs is peripheral neuropathy (CIPN), which has long term effects on the surviving patients even after medicine discontinuation[3].

However the prevalence of this side effect depends with the type of anticancer drug, mode of administration, duration of the therapy and combination of drugs, and ranges from 10 to 100%[4]. This ultimately leads to modification in the regimens with poor compliance and less benefits on the survival ratio[5].

The platinum based oxaliplatin, has been proven as drug of choice in the treatment of ovarian cancers, testicular carcinomas and tumors of colon[6]. This drug can be used alone or with the combination of other groups such as 5-fluorouracil (5-FU) and leucovorin (LV) to treat metastatic cancers of

colon[7], and has also been used against those cancers where other platinium based drugs such as oxaliplatin has been shown resistance to kill cancer cells[8]. The side effects of this drug also increased as the dose advances[9]. Some of the most common side effects associated with this drug are peripheral neuropathy, ototoxicity, gastrointestinal problems, extreme weight loss and fatigue[10].

Previous studies have shown oxaliplatin on drug on peripheral nerves, but very little is known about its targeted effects on CNS. The mechanisms by which these agents produce deleterious effects on nervous system are unknown. However, these drugs are well-known to be responsible for increase oxidative stress and reactive oxygen, nitrogen, or carbonyl species (ROS, RNS, and RCS, respectively), and may be responsible for their toxicity. Treatment with antioxidants shown to have reduced the sensory hypersensitivity to the experimental animals and to exhibit some level of protection among patients having CIPN[11]. Preventive therapies include ionic calcium and magnesium infusions, vitamin E, glutathione, glutamine, and N-acetyl cysteine. All these substances are used to reduce neuropathic symptoms in patients with chemotherapy[12].

As, the oxidative stress and inflammation performs the main role in the mechanism of action of neurotoxicity occurred due to the cisplatin. Glutathione is a very powerful antioxidant which has got the anti-aging /anti-inflammatory properties. Therefore, this study was aimed to observe the effects of oxaliplatin on central and peripheral nervous system in adult Albino mice and to detect the possible preventive effects of antioxidant glutathione in oxaliplatin induced neurotoxicity.

METHODOLOGY

This experimental study was conducted at Department of Anatomy, Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, in collaboration with Sindh Agricultural University Tando Jam. Study was conducted from 1ST January to 30th June 2015 after approval from institutional ethical committee. All 36 adult mice of 8 to 16 weeks' age (female and male) with average body weight of 30-35 gm were included in this study. Animals were housed in stainless steel cages about 4-6 per cage in a temperature controlled room (22± 20C) and humidity (55%±5%), and a 12-h light/dark cycle. The animals were given free access to food and water. The researchers performed this study were remained blind to the treatment being administered. Pre-approved proforma was used to collect and document all data during research. All chemicals used (Oxaliplatin, Glutathione) were purchased through NIMRA hospital Jamshoro.

The Oxaliplatin was purchased in powder form and was dissolved in 50 ml 5% dextrose to make concentration of 10mg/50ml. Glutathione was purchased in capsule form (500mg) and was dissolved in the mice feeding.

The mice were divided in three groups each comprised of 12 animals. They were labelled as:

Control group (Group A): This group was given normal diet and drinking water

Oxaliplatin treated animals (Group B): This group was given oxaliplatin 0.02mg/kg/sc

Oxaliplatin + glutathione (Group C): This group was given oxaliplatin 0.02/kg/day and glutathione (1gm) in diet orally.

In Group A or control group mice were given distilled water orally along with normal diet for six weeks. In Group B, low dose oxaliplatin was given for 6 weeks in five divided doses. The mode of oxaliplatin administration was subcutaneous. The oxaliplatin solution was dissolved in 5% dextrose water. The drug was prepared freshly before administration. Mice were given the drug for five days followed by five days of rest up till the period of six weeks.

In Group C, in addition to low dose oxaliplatin *(administered subcutaneously)* with glutathione was given orally in the diet.

Gross examination: The animals were weighed before and after administration of the drugs using an electronic weight measuring machine. Other gross features mentioned in table 1 were monitored and scoring criterion was made to examine different parameters.

Behavioral studies: In order to further examine the effects of oxaliplatin on central nervous system and any protection brought about by antioxidants, behavioral studies were performed. All the experiments were observed by at least two observers and were conducted in quiet atmosphere[13,14].

Pain stimulation test: This test was performed to examine the pain sensations in the animals. The hind and front paws of animals of all groups were pricked with the help of 1cc syringe needle and effects were observed. If the animals withdrew their paws immediately the pain was counted as instant otherwise not instant. All readings were taken after every five days of rest.

Heat Stimulation Test: This test was performed to examine the thermal sensations in the animals. Animals were kept on hot gels with constant heat measured with the help of a thermometer. The time was noted for the mice to be moved away from the heat pad. The mouse was thrown on the hot pack gel and the time was assessed till the mouse moved away from the hot pack gel. All readings were taken after every five days of rest.

Cold Stimulation Test: This test was performed to examine the cold sensations in the animals. Animals were kept on cold gels with constant temperature measured with the help of a thermometer. The time was noted for the mice to be moved away from the cold pad. The mouse was thrown on the cold pack gel and the time was assessed till the mouse moved away from the cold pack gel. All readings were taken after every five days of rest.

Response to noise and Hearing Test: Hearing sensations of all animals were assessed by making noise through clapping or whistling near the ears of the animals. Animal's response to noise was assessed and noted. Any noisy movement like clapping or playing pinch will be performed near the ears of mouse and the noise reaction was observed. All readings were taken after every five days of rest.

Mental Orientation and Object Recognition Test: Higher mental functions were examined by examining the confusion

level of the animals. First animals were made habitual of different objects like their feeding bowls and water bottles, in their cages and after treatment the objects were moved to different places other than the original place. Mice were observed to recognize the objects and results were noted.

Sample collection and staining: After gross examination the animals were sacrificed after 24 hours of last dose. After euthanizing the mouse by cervical dislocation the mouse was placed on table with face upside down. Limbs were made fixed with the help of tape on the table. Once fixed the skin of the neck region was held with the forceps and was removed from head region up to the nose with the help of scissors.

A cut was given at the base of the skull and brain was exposed by cutting cranial bones. Brain was harvested, weighed and collected in 10% formalin after labeling. The formalin fixed tissues were processed and slides were made with 5µm thick brain tissues and were stained with Hematoxylin and eosin dye.

Table-I: Morphological scoring based on certain variables

Morphological features	Grade 1	Grade 2	Grade 3	
Hair loss	Gross hair loss observed (hair loss on front and back)	Moderate hair loss observed (hair only present on the back)	No Hair Loss observed	
Paw edema	Edema of both front and hind paw	Edema of either hind or front paw	No edema	
Weight reduction	More than 50 % weight loss		Less than 50% weight loss	No weight loss
Mental orientation	Extremely confused/no response to stimulus		Less active/ late response to stimulus	Active
Respond to noise	No response to stimulus		Late response to stimulus	Response to stimulus
Object recognition	No recognition		Recognize objects slowly	Recognize objects quickly

Data Analysis: The data was entered and analyzed in SPSS (statistical program for social sciences) version 22.0. Numerical variables were presented as Mean ± Standard Deviation and ANOVA (Analysis of variances) "*t*" test was applied to compare the mean (2 tailed) between the groups. P value $\leq$ 0.05 was considered as significant level for all the comparisons.

RESULTS

A total of 36 mice were equally divided in two groups

Hair Loss: Group B mice exposed to 0.02mg/day (diluted in 5% dextrose water/ subcutaneously) dose of oxaliplatin over the period of six weeks in divided doses with five days of continuous exposure followed by five days of resting period. During that period, the mice exhibit gross abnormalities in morphological features. The scoring was done according to the criteria in table 1. Different morphological features were analyzed as Mean ± SEM. Statistical analysis showed no difference in hair loss of animals before start of the drug dose. However gross difference in the mean hair loss of group B oxaliplatin treated mice (1.714±0.3595) and control group A mouse (3±0) p< 0.05 was observed over the period of exposure. Although group C exhibit hair loss over the time but is not significantly different to group A p >0.05 during initial phases but overall the hair loss was same as control (3±0). Table-II, Graph-1

Paw Edema: Regarding Paw edema statistical analysis showed no difference before start of the drug dose. However gross difference in the mean weight of group B oxaliplatin treated mice (1.571±0.297 and control group A mouse (3±0) p< 0.05 was observed over the period of exposure. Although group C exhibit less paw edema over the time but is not significantly different to group A p $\geq$ 0.05 during initial phases but overall the edema was less than control (1.714±0.359) as shown in Table-II, Graph-1.

Weight of the Animals: Statistical analysis showed no difference in weight of animals before start of the drug dose. However gross difference in the mean weight of group B oxaliplatin treated mice (1.857±0.340 and control group A mouse (3±0) p< 0.05 was observed over the period of exposure. Although group C exhibit weight loss over the time but is not significantly different to group A p $\geq$ 0.05 during initial phases but overall the weight was less than control (2.429±0.202) as shown in Fig-1

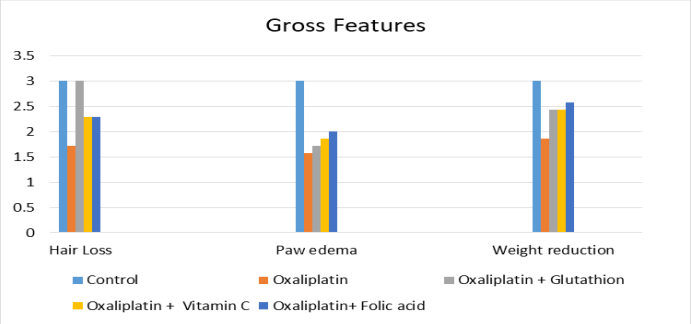

Fig-1: Mean of Gross features (Weight loss, hair loss and Paw edema) of animals based on the scoring criteria in table-I (N=36)

Mental Orientation: Statistical analysis showed animals in all groups were mentally active before the administration of experimental drugs. However, the level of mental orientation decreased as the time advanced in group B animals (1.857±0.340) p<0.05. While Group A animals were remained active throughout the time period (3±0). Group C (2.571±0.202) exhibit no confusion and was not significantly different to group A as shown in Table-III.

Response to hearing stimuli: Statistical analysis showed animals in all groups responded to noise before the administration of experimental drugs. However, group B animals (2.286±0.286) were insensitive to noise as compared to group A (3±0) after third dose p $\leq$ 0.05. However, administration of antioxidants in group C (3±0) group reversed the effects of 0xaliplatin and responded well to noise as shown in Table-III.

Novel Object Recognition: Statistical analysis showed animals in all groups were able to recognize the object before the administration of experimental drugs. However, Group A (3±0) animals were able to recognize throughout duration of study

while their ability to recognize decreased significantly in group B (2.143±0.340) p< 0.05. In Group C (2.571±0.202) and D (3±0) ability to recognize was better as compared to group B animals as indicated in Table-II.

Table-II: Assessment of animal behavior by level of mental orientation, response to noise and object recognition based on the scoring criteria in Table-I (N=36)

	Control	Oxaliplatin	Oxaliplatin + Glutathion	Oxaliplatin + Vitamin C	Oxaliplatin+ Folic acid
Mental orientation (Mean±SEM)	3	1.857±0.340	2.571±0.202	3	2.571±0.202
Response to noise (Mean±SEM)	3	2.286±0.286	3	3	2.429±0.202
Object recognition (Mean±SEM)	3	2.143±0.303	2.571±0.202	3	2.714±0.184

Heat Stimulation Test: Statistical analysis showed that Group A (7±2.854) animals were responding to heat stimulus throughout duration of study while their ability to respond decreased significantly in group B (20.667±0.615) $p \leq 0.05$. In Group C (19.833±6.949) ability to response was better as compared to group B animals group were comparable less ability as control $p \geq 0.05$ as indicated in Fig-2.

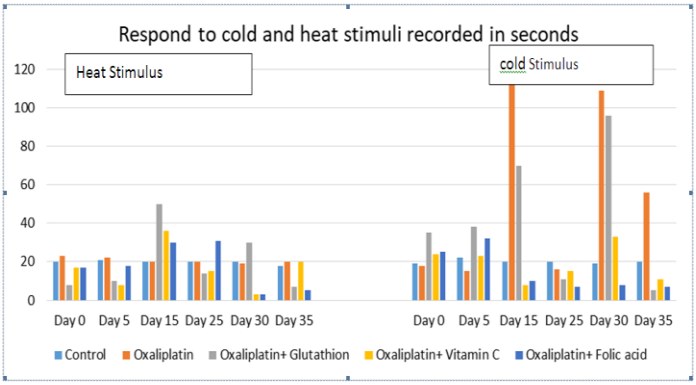

Fig-2: Ability of animals in different treatment groups to respond to heat and cold stimulus recorded in seconds (N=36)

Cold Stimulation Test: Statistical analysis showed animals in all groups were able to recognize the object before the administration of experimental drugs. However, Group A (20±0.447) animals were response to heat stimulus throughout duration of study while their ability to response decreased significantly in group B (54.667±19) $p \leq 0.05$. In Group C (42.5±14.252) ability to response was better as compared to group B group were comparable less ability as control p> 0.05 as indicated in fig 2.

Histopathological findings: Examination revealed that animals of Group A (control) shows no histopathological finding in the brain sections of the animal. There is normal structure of cerebral cortex, parts of diencephalon, corpus callosum and cerebellum. The hippocampus areas are normal without any necrotic and lymphatic infiltrations Figure 3-A and 3-B.

Group B animals showed necrotic changes such as; diffuse and focal area of lymphatic infiltration and gliosis within the corpus callosum, hippocampus, cerebral cortex and cerebellum Figure 3-C.

Additional treatment of anti-oxidant glutathione with oxaliplatin in Group C shows normal architecture of cerebral cortex, corpus callosum and hippocampal areas with few lymphatic infiltration and gliosis figure 3-D. Although anti-oxidant proved to have reverse the toxicity which is produced by oxaliplatin such as in Group B; but still there was no complete cure of the chemotherapeutic agents.

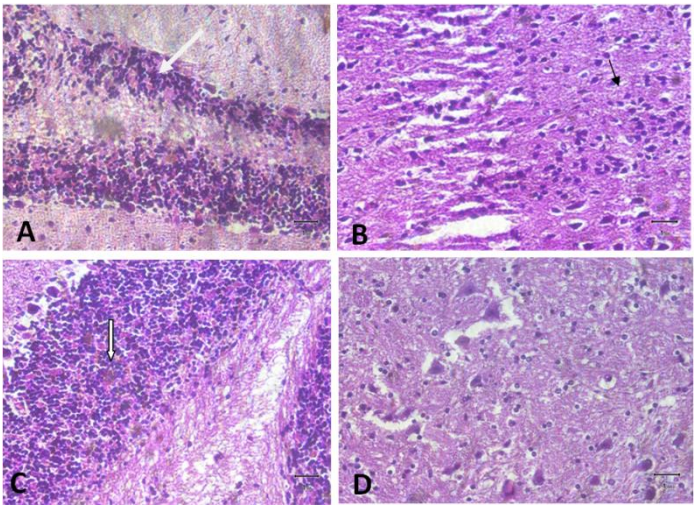

Fig-3

A: Photomicrograph Showing Histological section of control mice of the pyramidal layer of hippocampus, indicated by white arrow (H&E x 100).

B: Photomicrograph Showing Histological section of normal appearance Oligodantrites indicated by arrow.(H&E x 100).

C: Photomicrograph Showing Histological section of Oxaliplatin Lymphocytic infiltration, Gliosis and area of Necrosis in hippocampus (H&E x 100).

D: Photomicrograph Showing Histological Section showing diffuse lymphocytic infiltration in rat treated with oxaliplatin and glutathione

DISCUSSION

The most common factor which limits the dose of certain chemotherapeutic agents is toxicity with their pharmacological dose[2]. One of the deleterious side effect related to almost all platinum based Chemotherapeutic drugs is neuropathy which compromises the long-term quality of life[3]. Due to this fact various approaches have been tried to prevent its side effects on neurotoxicity. This study was conducted to assess side effects of oxaliplatin on physical and mental status of the body and particularly on the gross and histological appearance of nervous system of the mice model. The mice were chosen as animal model due to their easy availability, relatively cheaper cost and easy to handle. Moreover, the genome of mouse resembles closely with human genetic framework which makes it ideal model for biomedical research[15].

In our study, control mice showed no or minimal changes in

the weight over the entire study period. In contrast, the weight of the oxaliplatin treated group started to decrease significantly, the other three groups also showed some weight loss but was not significant. This indicates some protection provided by antioxidants. Glutathione showed better improvement. The significant reduction in the weight of the experimental animals may be due to less food intake and more catabolic activity of the body. Studies mention that glutathione when administered in cancer patients decreased the oxidative stress whereby halts the process of cancer associated cachexia, and improves the body's immune system[16]

Oxaliplatin treated animals had obvious hair loss throughout body[16]. However, the animals treated with glutathione had no hair loss, which was seen on front and back of the body. This indicates the ability of antioxidants to reduce hair loss if given as supplement during chemotherapy.

In this study oxaliplatin treated mice show peripheral neuropathic effects such as increased pain threshold, heat stimulus and less response to cold stimulus. Similar results were observed previously, where mice showed oxaliplatin treatment results in chronic pain phenotypes in mice, with evidence of mechanical allodynia and heat hyperalgesia. The main reason of this neuropathy may be due the suppression of ability of peripheral nervous system to regenerate and protects itself. Many anti-cancer drugs initiate sensory neuropathy[17,18]. Symptoms vary from painful sensations to paresthesia. The onset is usually sudden start immediately with start of therapy and persists for the rest of the life, even after discontinuation of drug, which poses great impact on the quality of life.

In addition, mice with oxaliplatin treatment also show mental disorientation, they were extremely confused and were not able to recognize object. These findings indicate effects of this platinium based drug on central nervous system as well. Although antioxidants were able to partially attenuate these effects complete protection was not observed. This might be the fact that other mechanisms are involved in oxaliplatin induced nervous system damage[19,20].

This study also reveals that the oxaliplatin treated mice have less ability to respond to noise as compared to control. Animals treated with antioxidants were able to respond but not comparable to control. These results are in line with other studies which showed ototoxicity when oxaliplatin was administered in mice[21,22].

Although numerous researches have elucidated the effects of this drug on spinal cord and peripheral nerves, but very little is known about its targeted effects on CNS. The mechanisms by which these agents produce deleterious effects on nervous system are unknown. However, these drugs are known to increase oxidative stress and reactive oxygen, nitrogen, or carbonyl species (ROS, RNS, and RCS, respectively), which might be responsible for their toxicity[23,24]. Treatment with antioxidant substances has been shown to reduce sensory hypersensitivity in experimental animals and to exhibit some degree of protection in patients with CIPN[11,25]. Preventive therapies such as glutathione, vitamin C and folic acid, with the target of decreasing neuropathic symptoms in patients who undergo antitumor therapy. These effects are dose dependent and may limit the dose and discontinuation of the treatment regimens[26].

For the microscopic examination of brain structure, sections were observed under microscope to detect the effects of this anti-cancer drug on CNS and any protection brought about by addition of antioxidants. The histopathological slides showed that control group showed normal arrangement of cells in all areas of the brain, however oxaliplatin group showed diffuse and focal infiltration of lymphocytes, focal area of necrosis and gliosis, suggesting mitochondrial damage, whereas oxaliplatin glutathione group showed few lymphocytic infiltrations. Here again it matches the data of previous studies which demonstrate that the oxidative stress is considered as a pathological marker for the production of neuropathy caused by platinum based drugs[27]. The organelles which maintain the cellular redox balance are mitochondria and peroxisomes, and their balance is the key element in the maintenance of oxidative homeostasis. Many randomized control trials have showed neuroprotective effects of glutathione and vitamin C[28,29].

Our study shows that the glutathione supplementation is proved partially helpful in reversing the toxic effects of Oxaliplatin on central and peripheral nervous system in adult Albino mice and glutathione is also partially helpful in preventing oxaliplatin induced neurotoxicity. In future, more studies are required to investigate the benefits of glutathione.

CONCLUSION

The toxic effects of oxaliplatin, on morphology and behavior and brain of adult albino mice were partially reversed with glutathione supplementation.

AUTHOR'S CONTRIBUTION

Shaikh P: Conceived idea, Designed research methodology
Memon SG: Data collection and compilation
Bano U: Data collection, Literature review
Shahani MY: Manuscript writing, Data interpretation, Statistical Analysis.
Memon S: Final critical review of the manuscript.
Shahani SB: Data collection, Data analysis

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