



Cisplatin Induced Nephrotoxicity- An Assessment Based on Calculated Creatinine Clearance

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Cancer is a group of more than 100 different diseases that are characterized by uncontrolled cellular growth, local tissue invasion, and distant metastases. Cisplatin is the most widely used anti-neoplastic agent for most of the tumors like lung cancer, gastric cancers, ovarian cancer, penile cancer, cervical cancer and many other. Nephrotoxicity is the main side effect of cisplatin.

Aim: To determine the incidence and evaluate the risk factors of cisplatin induced nephrotoxicity.

Methods: A prospective-observational study was conducted in the Department of Radio Therapy in a tertiary care hospital for 6 months from February 2015 to July 2015.

Results: Incidence of nephrotoxicity was high in male patients in other studies. But in our study more female patients are affected with nephrotoxicity, it may be due to inclusion of pelvic Malignancy cases in our study. Few patients also had co-morbid conditions like hypertension and diabetes mellitus.

Conclusion: Female sex was a risk factor for cisplatin induced nephrotoxicity although the cancer type may also contribute to increase in nephrotoxicity.

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1. INTRODUCTION

Cancer is a group of more than 100 different diseases that are characterized by uncontrolled cellular growth, local tissue invasion, and distant metastases [1]. Different types of cancer treatment include: surgery, radiation, chemotherapy, hormonal therapy and immunotherapy [2]. The era of modern cancer chemotherapy was born in 1941, when Goodman and Gilman first administered nitrogen mustard to patients with lymphoma. Since then, numerous antineoplastic agents have been developed, and a variety of chemotherapy regimens have been investigated in every type of cancer [3]. Chemotherapy is often used as an adjuvant treatment (treatment given after surgery or radiation therapy) to kill any cancer cells that remain. It may also be used as neo-adjuvant therapy (treatment given before surgery or radiation therapy to shrink tumors). For cancers of the blood or lymph system, such as leukemia and lymphoma, chemotherapy may be the only treatment given. More than 100 drugs are available to treat cancer. The drug or combination of drugs—as well as the dose and treatment schedule given to the patient depends on many factors, including the type and stage of cancer; the patient's overall health, age, and ability to cope with certain side effects; the presence of other medical conditions; and previous cancer treatments [4].

Approximately half of all patients who receive anticancer chemotherapy are treated with a platinum drug. The widespread use of platinum agents in the treatment of cancer began with the discovery of the anti-neoplastic activity of cisplatin by Barnett Rosenberg in the 1960. Commonly used platinum based compounds are; cisplatin, carboplatin and oxaliplatin [5]. Cisplatin (cis-diammine dichloro platinum [II]) is a widely used and potent chemotherapy drug used in the treatment of many solid tumors [5]. For more than 30 years, cisplatin has been used as a standard component of combination chemotherapy in several cancers such as ovarian and cervical cancer, testicular cancer, head and neck cancer including nasopharyngeal, and lung Cancer [6]. Cisplatin is generally used in combination with fluorouracil, docetaxel, paclitaxel, and cyclophosphamide for the treatment of various malignancies. The major limiting factor in the use of cisplatin is the side

effects in normal tissues, which include neurotoxicity, ototoxicity, nausea, vomiting, and nephrotoxicity. Nephrotoxicity is found in 28-36% patients who received a single dose (50 mg/m²) of cisplatin [7]. It is recommended that repeated courses of cisplatin should not be given until serum creatinine is < 1.5 mg/dl and/or BUN is <25 mg/dl [8].

Nephrotoxicity is evaluated by GFR and creatinine clearance values using the Modification of Diet in Renal Disease (MDRD) formula or the Cockcroft-Gault formula, as well as Serum creatinine (SCR) values [9]. The Cockcroft-gault equation provides an estimate of creatinine clearance and is the equation most commonly used to determine drug dosages in patients with impaired kidney function [10].

Creatinine clearance (ml/min)

$CLCr = \frac{[(140 - \text{age (years)}) \times \text{weight (kg)}] / 72 \times \text{serum creatinine (mg/dl)}}{\text{(x 0.85 for women)}} [10]$

2. MATERIALS AND METHODS

2.1 Study Design

A prospective-observational study was conducted in the Department of Radio Therapy in a tertiary care hospital for 6 months from February 2015 to July 2015.

2.2 Study Materials

- Patient profile forms.
- Patient consent forms.
- Drug- Cisplatin.
- Blood tests- serum creatinine, serum albumin, hemoglobin, BUN.

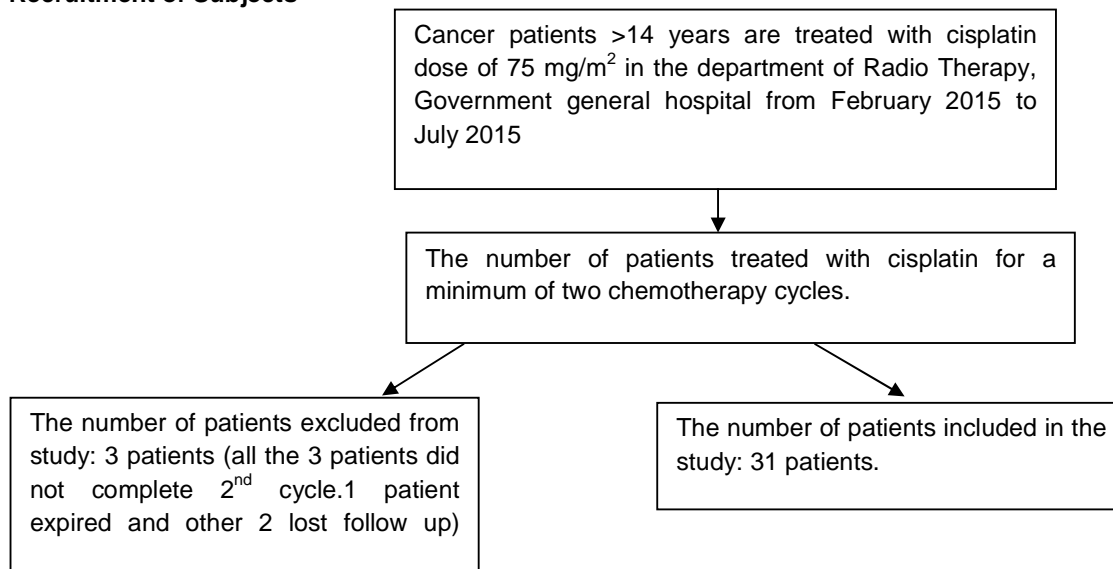
2.3 Eligibility Criteria

We included patients undergoing cisplatin based chemotherapy, patients who were willing to participate in the study were included. Both genders of the patients who were above 14 years were included in the study.

Patients who had received prior radiotherapy to pelvis, and patients with pre-existing renal diseases were excluded from the study.

3. OBSERVATIONS AND RESULTS

Recruitment of Subjects



3.1 Age versus Mean Fall in Creatinine Clearance (In %)

In our study nephrotoxicity was observed in patients who were treated with cis-diamminedichloridoplatinum(II) (CDDP) by calculating creatinine clearance from serum creatinine. Depending on the body surface area (BSA) and creatinine clearance, patients were fixed with the cisplatin dose. The bar diagrams represent the percentage fall in creatinine clearance basing on the age of the patients. On x-axis the three age groups of the patients i.e. 14-40, 41-60 and >60 are taken. Y-axis shows mean decrease in creatinine clearance. From the graph it is shown that there is higher fall in creatinine clearance in older age group i.e. >60 years of age.

3.2 Effect of Nephrotoxicity in Males and Females

In our study there were a total of 31 patients and among them were more males than females. The bar diagrams show the total number of males and female patients and the patients affected with the nephrotoxicity. Among the male and female patients, those who were treated with CDDP, there were more number of females affected by the nephrotoxicity.

3.3 Performance Status versus Nephrotoxicity

Performance status of the patient was examined and the total scoring of the patient was measured and noted based on the Eastern Co-operative Oncology Group (ECOG) scale. The scoring of the scale is based on the health of the patient and the physical condition of the patient. Most of the patients in our study are fit and able to do their work by themselves. Only few patients are weak and are not able to do their work on themselves. In our study there are 20 patients who have performance status (PS) score between 0 and 1 and remaining eleven patients have PS ≥ 2 .

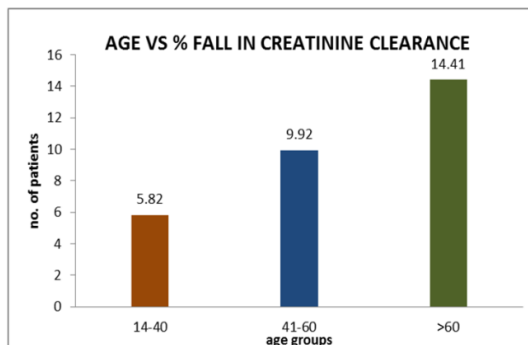


Fig. 1. Relationship between age and decrease in creatinine clearance

3.4 Cisplatin Induced Nephrotoxicity versus BSA

Body surface area (BSA) is the measured surface area of a human body. Chemotherapy drugs are administered based on the BSA of the patient. In our study the average BSA of the patient's was 1.5 m². The above figure shows that there were more number of patients with BSA above 1.5 m² and among them few patients were affected with CDDP induced nephrotoxicity.

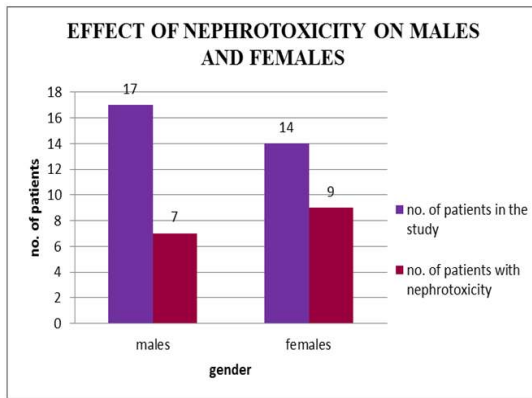


Fig. 2. Relationship between cisplatin induced nephrotoxicity (CIN) and sex distribution

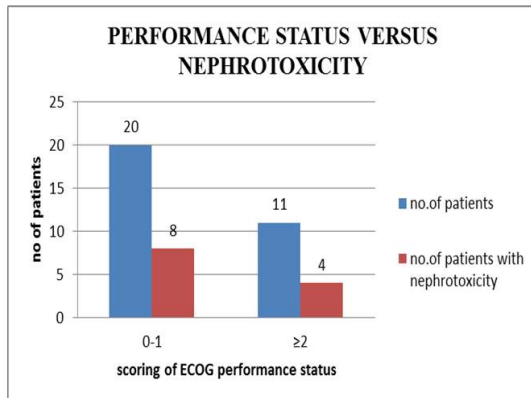


Fig. 3. Association of CIN and ECOG performance status

3.5 Co-morbidities versus CDDP Induced Nephrotoxicity

In our study few patients having co-morbidities such as hypertension, diabetes mellitus and asthma were included. No patient had asthma or any past renal disease in included subjects. In

total patients, those with hypertension were 6 and diabetes mellitus were 4. Patients with nephrotoxicity among hypertensive patients were 4 and among diabetes mellitus were 3 in number. The x-axis shows the co-morbid conditions and the y-axis shows the number of patients affected with the co-morbid condition.

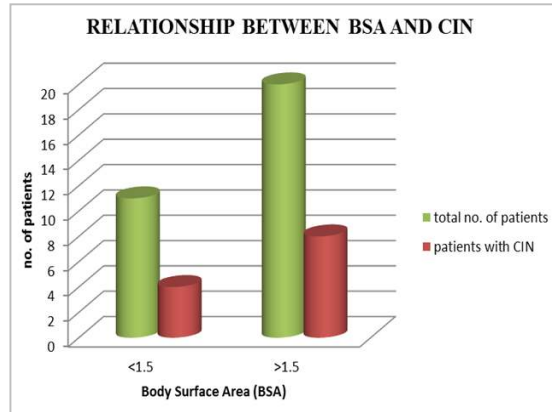


Fig. 4. Relationship between BSA and CIN

3.6 Non-steroidal Anti Inflammatory Drugs Nsaid's Use versus Decrease in Creatinine Clearance

Non-steroidal anti inflammatory drugs (NSAIDs) are the most commonly used over the counter (OTC) medication and is used by most of the patients. Among the total 31 patients, twenty four patients use NSAIDs for various purposes. Dividing the patients into 3 groups based on their ages, there are 5 patients among 14-40 years of age who use NSAIDs and in them 2 patients have decrease in creatinine clearance. In 41-60 years of age 14 patients use NSAIDs and 7 patients show nephrotoxicity. In >60 years of age 5 patients use NSAIDs and 4 patients have fall in clearance.

3.7 Relationship between Type of Cancer and Nephrotoxicity

There are various types of cancers and the most commonly seen in our study are lung cancer, gastric cancer, head and neck cancer and ovarian cancer. Classifying the cancer types into lung, gastric, head and neck and others, and by plotting a graph for the type of cancer and the patients affected with nephrotoxicity. The bar diagram shows higher number of patients with other type of cancer and lower for the gastric cancer. In all types of cancers, the patients are affected with nephrotoxicity.

3.8 Hypoalbuminemia (<3.5 mg/dl) versus Decrease in Creatinine Clearance

Hypoalbuminemia is a condition where the albumin levels in the blood falls below 3.5 mg/dl. It is also a risk factor in patients treated with cisplatin chemotherapy. Hypoalbuminemia is observed in most of the patients above sixty years of age. The bar diagram shows that in patients who had hypoalbuminemia also had decrease in creatinine clearance. In the age group 14-40 years, there are 3 patients with hypoalbuminemia but there is fall in creatinine clearance only in one patient among them. In 41-60 years of age, 3 patients had hypoalbuminemia and 1 had fall in clearance. In 60 years of

age four patients had hypoalbuminemia and among them 3 had decrease in creatinine clearance.

3.9 Combination Drug versus Nephrotoxicity

There are many drugs that are used in combination with cisplatin. The most widely used drugs in our study in combination with cisplatin are 5-fluorouracil, etoposide, cyclophosphamide and paclitaxel. Nephrotoxicity is observed among all types of combination drugs. The graph shows the incidence of nephrotoxicity with each combination drug.

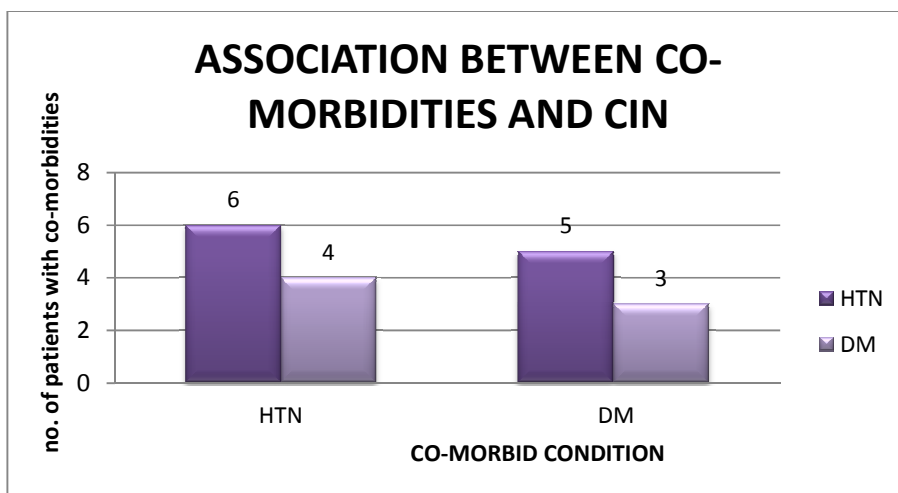


Fig. 5. Association between co-morbidities and CIN

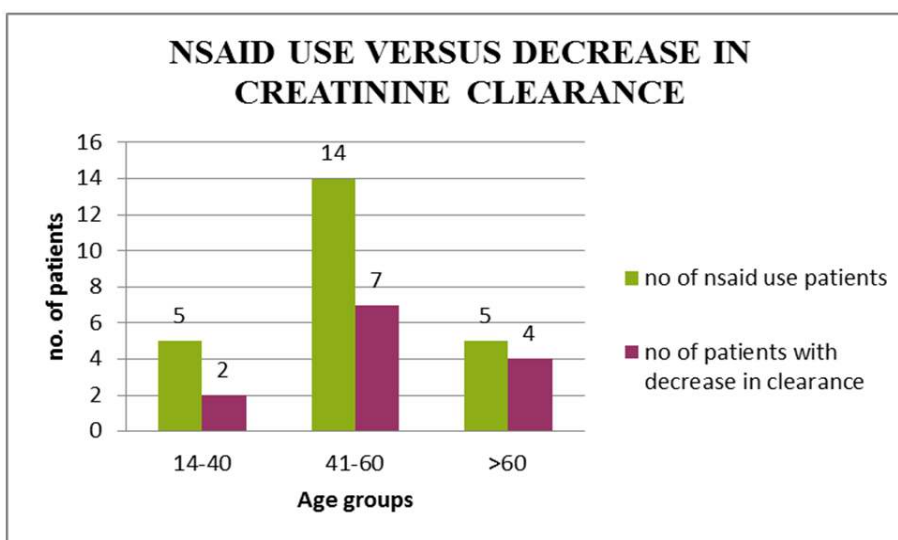


Fig. 6. Relationship between NSAIDs and creatinine clearance

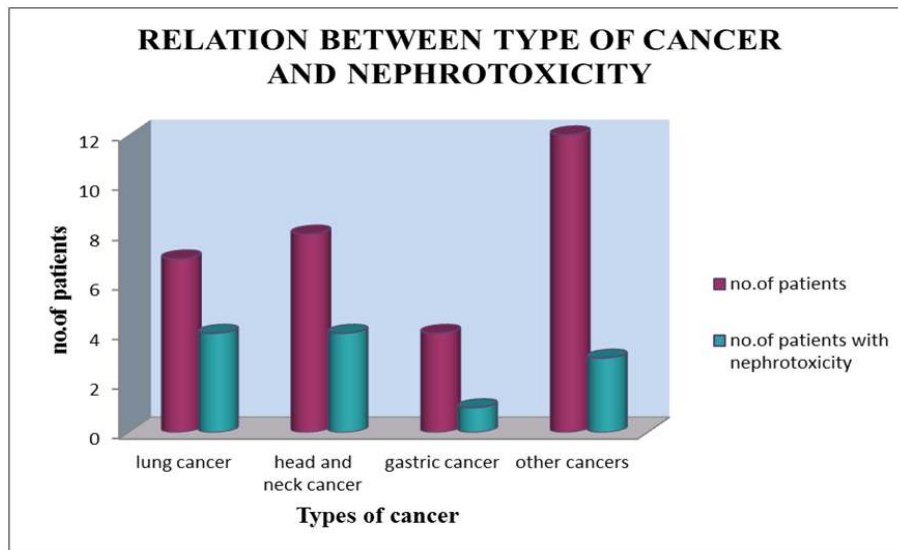


Fig. 7. Relation between type of cancer and CIN

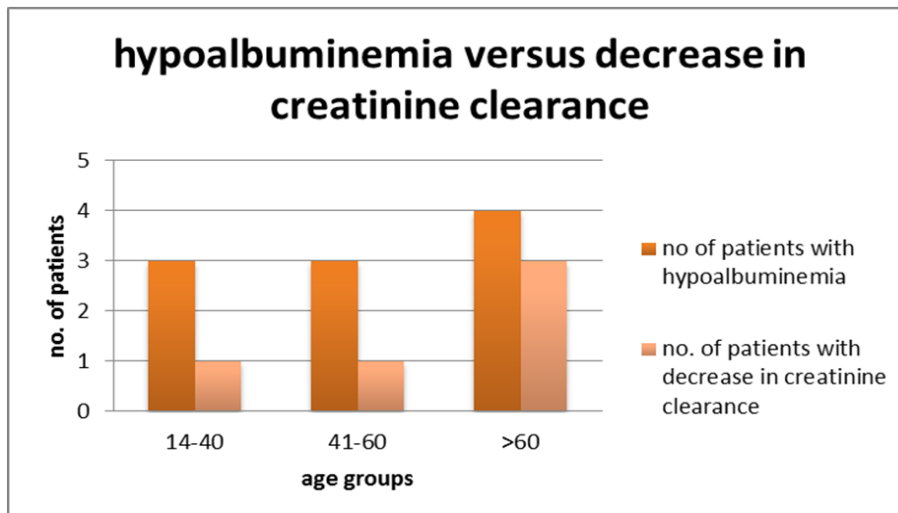


Fig. 8. Hypoalbuminemia versus fall in creatinine clearance

4. DISCUSSION

CDDP is the most widely used antineoplastic agent for most of the tumors like lung cancer, gastric cancers, ovarian cancer, penile cancer and many other. Nephrotoxicity is a major side effect induced by cisplatin in 25 – 42% of patients [11]. In our present study we found that 38% of individuals who received cisplatin at dose of 75 mg/m² developed nephrotoxicity despite of prior treatment with hydration with normal saline and ringer lactate solution. The dose of the drug is fixed based on the creatinine clearance value and body-surface area of the patient. In our study

creatinine clearance was calculated from serum creatinine by Crockcroft-gaultt equation. Creatinine clearance obtained during the first cycle of cisplatin chemotherapy was taken as the baseline value. The clearance values obtained from the second cycle were compared with the baseline value. In our study among 31 patients, we observed nephrotoxicity in twelve patients in the second cycle of chemotherapy. Few patients had nephrotoxicity during fifth-sixth cycles of chemotherapy. Dose modification was done in patients who had fall in creatinine clearance. There was no necessity for the changing of drug regimen in any patient as there was no severe or

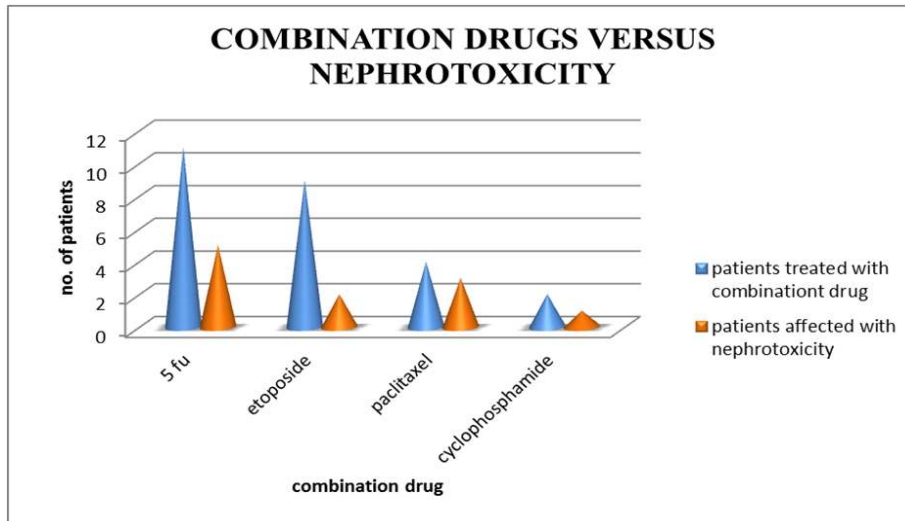


Fig. 9. Relationship between cisplatin combination drug and nephrotoxicity

chronic nephrotoxicity. In our study we showed that there is great fall in the creatinine clearance in patients with age >60 years. Hence there is higher incidence for the occurrence of nephrotoxicity in elderly patients than in younger patients. However, there are more females who have decrease in creatinine clearance in second cycle or fifth cycle of cisplatin chemotherapy compared to the males. Hence in our study there is higher incidence for nephrotoxicity in females than in males. In our study most of the patients had performance status scoring above one. This shows that majority of the patients had good health and better physical ability. For the patients cisplatin dose was calculated based on BSA but the dose was administered to patient based on their creatinine clearance. In our study the patients with hypertension or diabetes mellitus are at risk for nephrotoxicity. The patients with hypertension and diabetes mellitus are also having decrease in creatinine clearance. Hence it shows that the co-morbid condition affects the rate of cisplatin elimination from the body and therefore reduces creatinine clearance. In our study we used cisplatin most frequently with 5 fluorouracil combination. Cyclophosphamide was least used combination drug in our study.

Limitations of our present study include selection of treatment bias which is inevitable in a prospective study and small sample size for patients who received the chemotherapy. The second limitation is lack of measurement of serum magnesium due to inappropriate resources.

5. CONCLUSION

Elderly age group and female sex are more severely associated with cisplatin induced nephrotoxicity. Presence of co-morbidities like hypertension and diabetes contribute to cisplatin induced nephrotoxicity. The decrease in renal function was affected with the dose of cisplatin at 75 mg/m², hence cessation or reduction of cisplatin dose should be done in patients having creatinine clearance below 60 ml/min. Based on the results of this study, calculated creatinine clearance by cock-croft gault equation may be used to modify the dose of cisplatin.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by the ethics committee of Guntur Medical College and Government General Hospital, Andhra Pradesh, India.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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