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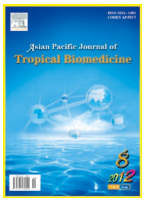

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Science behind cisplatin-induced nephrotoxicity in humans: A clinical study

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ABSTRACT

Objective: To investigate the relationship between serum electrolyte changes and cisplatin induced nephrotoxicity. **Methods:** We collected data from 18 patients undergoing cisplatin chemotherapy including serum electrolytes, creatinine, blood urea nitrogen (BUN) and urine potassium, sodium and pH levels before and after the cisplatin chemotherapy. All the patients had cancer and were treated with 40-50 mg/day cisplatin. Renal injury was assessed by measuring serum electrolytes, creatinine, BUN levels and urine potassium, sodium and pH levels. **Results:** The five cycles of cisplatin based chemotherapy resulted in hypomagnesia (P=0.029), hypocalcaemia (P=0.001*), hypophosphatemia (P=0.003*), hypokalemia (P=0.001*) and increased serum creatinine (P=0.001*) and BUN (P=0.292*) levels. In urine analysis, decrease in potassium (P=0.024*) was found, except potassium there was no significant changes in sodium and urine pH. **Conclusions:** The present study demonstrates that, acute nephrotoxicity was observed in patients with different types of cancers undergoing cisplatin based chemotherapy due to electrolyte disturbances, when no corrective measures were initiated.

1. Introduction

Cancer is a class of disease characterized by uncontrolled cell division and these cells have the ability to invade other tissues either by invasion or migrating to distinct sites by metastasis[1]. Global burden of cancer is high and it is growing still larger, worldwide each year more than 11 million people are diagnosed with cancer. By 2020, the number is expected to increase to 16 million. In addition, cancer causes more than 8 millions deaths per year worldwide[2]. The most common types of cancers include testicular, ovarian, bladder, cervix, prostate, breast, head and neck cancer. The occurrence of toxicities in patients with cancer chemotherapy is found to be grave concern, the elimination of side effects and possible toxicities become a major problem during chemotherapy[3].

Cisplatin is a co-ordinate metal complex with significant antineoplastic activity and the side effects including acute and chronic renal insufficiency, renal magnesium wasting, electrolyte disturbances like hypomagnesia, hypocalcaemia, hypophosphatemia and hypokalemia are common with cisplatin treatment. So routine monitoring of magnesium in plasma is recommended to avoid tetany[4]. The electrolyte disturbances and renal damage may be associated with focal necrosis at major parts of nephron.

The present study was aimed to evaluate the pre- and post-cisplatin medication monitoring of electrolyte balances, thereby allowing supplementation of deficient electrolyte without discontinuing therapy.

2. Materials and methods

2.1. Study design

The prospective, randomized, open labelled study was conducted at Curie Centre of Oncology, St. John's Medical College Hospital campus, Bangalore, India during July 2007 and February 2008. This study was approved by the Institutional Human ethic committee of Curie Centre of Oncology, Bangalore, India.

2.2. Patient selection

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All the patients who were admited to this hospital and were histologically confirmed as invasive squamous cell carcinoma, aged between 30–75 years with more than IIA TNM (Tumour node metastatis) stage and 0–2 performance status were included in the study. Patients with renal failure, HIV (Human immuno deficiency virus)/HbS Ag +ve (Hepatitis–B–antigen), bone marrow suppression, pregnants, peripheral neuropathy, allergic to platinum compounds, were excluded from the study.

2.3. Study material

A total of 18 various types of cancer patients of either sex, who satisfies the criteria and were schedulled for cisplatin chemotherapy at the Curie centre of Oncology, Bangalore, India were enrolled into the study, after the nature of the study were explained to them and written consent was obtained. All the demographic details such as name, sex, age, occupation, education, clinical data such as diagnosis and therapeutic data such as name of the drug, dose, route, frequency, duration of the therapy and other relevant details were collected from treatment charts, case notes and laboratory investigation reports. Complete blood count, histopathological confirmations, chest X–ray, serum creatinine and BUN, urine Na^+, K^+, pH, and albumin, CT scan/MRI–head and neck, serum electrolyte analysis was done using VITROS Ortho–Clinical Diagnostics kits.

2.4. Chemotherapy

Serum electrolytes, creatinine, BUN, urine protein, urine sodium, potassium and pH were evaluated before and after the completion of 5 cycles of cisplatin–based chemotherapy. Chemotherapy was administered weekly and concurrently with radiotherapy with linear accelerator (6MV X–rays) in conventional fraction (1.8 Gy/ fraction), once a day, 5 fractions per week using shrinking field technique. Cisplatin 40–50 mg/m^2 was administered once a week after pre–medication with Dexamethasone 16 mg *i.m.*, Granicetron 3 mg *i.v.*, Ranitidine 50 mg *i.v.* thrice a day, Frusemide 20 mg *i.v.* Mannitol 20%, 100 mL over 15 min, along with multielectrolyte intravenous infusion of Isolyte E and multivitamin infusion (MVI), slowly for 60minutes.

The myelosupression and renal toxicity was evaluated weekly with haemogram, BUN, and creatinine level.

2.10. Statistical analysis

The data collected to evaluate pre and post–cisplatin induced electrolyte imbalance was expressed as Mean ± SEM or as percentage. The comparison of the mean values within the group was done using paired *t*–test.

3. Results

A total of 18 patients were enrolled with age ranging from 30–75 years [60–75 years (56%), 50–59 years (28%) and 30–49 years (16%)]. 56% were female 44% were male. The patients with site of tumor at head and neck, cervix and esophagus ware equally distributed (33.33%), about 78% of patients were found in stage III followed by stage II in TNM staging distribution. Out of 18 patients, most of the patients (12) were found with 0 performance status followed by 1(4) and 2(2) stage.

3.1. Effect of cisplatin treatment on serum and urine electrolyte levels

A significant decrease in serum electrolytes viz., magnesium (–7.18%), potassium (–6.44%), phosphate (–16.44 %) and calcium (–5.94%); significant increase in serum sodium (+1.35%) and chloride (+3.85%) was observed after five cycles of cisplatin treatment compared to pretreatment serum electrolyte levels. The comparison of urine electrolyte levels in pre and post cisplatin treatment have indicated a significant decrease in urine sodium (–24.29 %) and potassium (–18.7 %) when compared to cisplatin pretreatment levels (Table 1).

3.2. Effect of cisplatin treatment on serum creatinine and BUN

A significant increase in Serum creatinine (+ 44.87 %) and a non–significant increase in BUN (+8.71%) was observed after five cycles of cisplatin treatment compare to pre treatment levels (Table 1).

3.3. Gender based comparison of serum and urine parameters

In males there was significant difference in serum components between pre and post treatment of cisplatin. A significant increase in serum sodium (+1.28%), chlorine (2.49%) and creatinine (37.5%); significant decrease in serum calcium (–4.67%) upon five cycles of cisplatin chemotherapy compared to pre treatment levels. In female, there was a significant decrease in serum magnesium (–9.31%), potassium (–6.54%), phosphate (–14.69%) and calcium (–6.87%); significant increase in serum creatinine (50.6%) upon five cycles of cisplatin chemotherapy compared to pre–cisplatin therapy. Results are shown in Table 2.

3.4. Effect of cisplatin treatment on serum and urine components in patients with carcinoma of oesophagus

After five cycle of cisplatin treatment, the patients with oesophagus carcinoma showed a significant decrease in serum potassium (–6.23%), phosphate (–25%), calcium (–5.33%) and bicarbonate (–8.31%); conversely there was a significant increase in serum creatinine (56%), after five cycles of cisplatin chemotherapy compared with pre cisplatin therapy and there was no significant difference in other serum (Magnesium, Sodium, Chlorine and BUN levels) and urine parameters (Table 3).

3.5. Effect of cisplatin treatment on serum and urine components in patients with carcinoma of head and neck

There was a significant increase in serum creatinine (46.66%) and significant decrease in serum potassium (–18.22%), after cisplatin treatment and where as there was no significant difference observed in other serum and urine parameters (Table 4).

3.6. Effect of cisplatin treatment on serum and urine components in patients with carcinoma of cervix

In patients with cervical carcinoma treated with cisplatin, there was a significant decrease in serum magnesium

Table 1
Comparison of serum and urine component levels in cancer patients before and after cisplatin chemotherapy.

Parameters		Before cisplatin treatment	After cisplatin treatment
Serum parameters	Magnesium	2.09±0.40	1.94±0.45*
	Sodium	136.37±3.67	138.21±4.52*
	Potassium	4.35±0.48	4.07±0.52*
	Phosphate	4.31±0.43	3.62±0.91*
	Calcium	9.10±0.70	8.56±0.71*
	Chlorine	98.70±3.87	101.17±6.0*
	Bicarbonate	28.61±3.15	27.39±3.09
	Creatinine	0.78±0.15	1.13±0.17*
	BUN	12.28±3.85	13.35±3.15
Urine parameters	Potassium	36.26±16.94	29.48±14.48*
	Sodium	80.18±49.47	60.71±32.16
	pH	6.41±0.26	6.31±0.64

Values are expressed as Mean±SEM (n=18). Values before cisplatin treatment were compared with values obtained after cisplatin treatment by paired t-test. *P<0.05 is considered as statistically significant.

Table 2
Comparison of Serum and urine component levels in male and female cancer patients.

Parameter	Gender	Before cisplatin treatment	After cisplatin treatment
Magnesium	Male	2.03±0.47	1.93±0.46
	Female	2.15±0.35	1.95±0.46*
Sodium	Male	135.61±3.17	137.35±3.60*
	Female	136.98±4.07	138.89±5.23
Potassium	Male	4.24±0.37	3.98±0.37
	Female	4.44±0.55	4.15±0.62*
Phosphate	Male	4.34±0.39	3.56±1.04
	Female	4.29±0.48	3.66±0.85*
Calcium	Male	9.00±0.49	8.58±0.61*
	Female	9.18±0.86	8.55±0.82*
Chlorine	Male	96.6±3.94	99.01±3.87*
	Female	100.38±3.02	102.89±7.00
Creatinine	Male	0.80±0.08	1.10±0.21*
	Female	0.77±0.19	1.16±0.13*
BUN	Male	10.16±3.91	12.81±3.98
	Female	13.98±2.98	13.78±2.44

Table 3
Effect of cisplatin treatment on serum and urine components in patients with carcinoma of oesophagus.

Serum parameter		Before cispaltin treatment	After cisplatin treatment
Serum parameter	Magnesium	2.22±0.27	2.18±0.17
	Sodium	133.33±1.63	135.25±1.20
	Potassium	4.82±0.59	4.52±0.59*
	Phosphate	4.60±0.24	3.45±1.14*
	Calcium	9.75±0.88	9.23±0.61*
	Chlorine	99.48±6.33	104.77±10.78
	Bicarbonate	28.17±2.40	25.83±0.98*
	Creatinine	0.75±0.08	1.17±0.18*
	BUN	10.33±2.30	12.71±3.75
Urine Parameters	Potassium	39.42±16.73	33.15±16.85
	Sodium	70.5±26.64	54.85±25.31
	pH	6.25±0.27	6.00±0.63

Table 4
Effect of cisplatin treatment on serum and urine components in patients with Carcinoma of head and neck

Parameter		Before cisplatin treatment	After cisplatin treatment
Serum parameter	Magnesium	1.92±0.56	1.87±0.55
	Sodium	136.55±4.41	140.25±6.69
	Potassium	4.08±0.35	3.98±0.48
	Phosphate	4.22±0.39	3.85±0.51
	Calcium	8.87±0.53	8.33±0.59
	Chlorine	97.82±2.77	99.43±3.03
	Bicarbonate	28.50±3.21	29.83±3.48
	Creatinine	0.73±0.08	1.07±0.19*
	BUN	13.00±2.69	12.17±4.05
Urine parameters	Potassium	39.53±17.25	32.33±14.11*
	Sodium	93.88±40.97	64.08±21.74
	pH	6.35±0.37	6.83±0.93

Table 5
Effect of Cisplatin treatment on serum and urine components in patients with Carcinoma of cervix.

Parameter		Before cisplatin treatment	After cisplatin treatment
Serum parameter	Magnesium	1.97±0.34	1.73±0.43*
	Sodium	138.35±3.98	137.37±2.87
	Potassium	4.23±0.35	4.00±0.58
	Phosphate	3.87±0.52	3.40±0.86
	Calcium	8.95±0.52	8.48±0.65*
	Chlorine	99.95±3.04	100.75±3.4
	Bicarbonate	27.00±3.09	27.50±3.51
	Creatinine	0.92±0.20	1.22±0.08*
	BUN	15.63±2.41	13.72±1.85
Urine parameters	Potassium	25.65±16.21	19.48±12.39
	Sodium	59.83±23.27	63.17±48.24
	pH	6.50±0.00	6.17±0.52

(−12.19%) and calcium (−5.26%); significant increase in serum creatinine (32.60%), upon cisplatin chemotherapy compared to pre cisplatin therapy (Table 5).

4. Discussion

The present study was undertaken to evaluate the pre and post-cisplatin medication monitoring of electrolyte balances, thereby allowing supplementation of deficient electrolyte without discontinuing therapy.

Cisplatin is one of the most commonly used drug for the treatment of carcinoma of esophagus, carcinoma of head and neck and carcinoma of cervix etc. and it is associated with nephrotoxicity. The exact mechanism of cisplatin-induced nephrotoxicity has not been fully elucidated. Cisplatin may accumulate in the kidney, where it can interact with sulfydryl compounds resulting in an increased membrane fragility and depletion of intracellular glutathione. There is some evidence that, cisplatin can induce apoptosis and necrosis of kidney cells in a dose-dependent manner. Renal damage is associated with several patterns of histological changes, such as acute focal tubular necrosis and dilatation of convoluted tubules and collecting ducts. This damage is clinically manifested as increase in BUN, serum creatinine, disturbances in serum electrolytes and acute renal failure. Present study suggests that these changes have to be reversible, at present, intensive prophylactic hydration and forced diuresis are used for the preservation of kidney function during cisplatin treatment[5].

In the present study, electrolyte disturbances such as hypomagnesaemia (60%), hypocalcaemia (89%), hypophosphatemia (57%), hypokalemia (95%) and elevations in serum creatinine, BUN were observed after cisplatin-based chemotherapy.

Hypomagnesaemia is a well known side-effect in patients receiving cisplatin, the direct injury to magnesium reabsorption in the ascending limb of loop of henle, as well as the distal tubule, is the possible mechanisms behind the cisplatin induced hypomagnesaemia[6].

We studied 18 patients (8 males and 10 females) aged between 30 to 75 years old. The most frequent electrolyte abnormality was significant hypomagnesaemia observed in 11 patients (60%). Significant decrease in the magnesium level in female patients but not in males. Probably the number of male patients in the study were not sufficient to generate significant data, may require detailed study on males. We also observed hypomagnesaemia in patients with carcinoma of cervix. Previous studies suggests that, hypomagnesaemia is a frequent complication to chemotherapy with cisplatin affecting up to 90% of patients[6], but in our study cisplatin chemotherapy affected about 60% of patients with various types of cancers if no corrective measures are initiated.

Hypocalcaemia is another known side effect associated with cisplatin chemotherapy. The possible mechanism behind cisplatin induced hypocalcaemia might be excessive

urinary loss of calcium, decreased renal uptake of calcium due to the proximal tubular damage, due to low tissue response of parathyroid hormone and low serum magnesium levels. In our study significant hypocalcaemia was observed in 16 patients (89%) with various types of cancers. There was significant decrease in calcium level in both female and male patients with carcinoma of oesophagus and cervix after 5 cycles of cisplatin therapy. To prevent this complication, electrolyte monitoring and continuous oral calcium substitution was adviced for patients undergoing cisplatin therapy[7].

Hypokalemia is a common electrolyte abnormality occurred during cisplatin treatment; it is due to increased renal reabsorption capacity observed in response to decreased intestinal absorption of potassium. Further magnesium and potassium metabolism subjected to predicable changes in intestinal absorption and renal excretion with each cisplatin treatment[8]. In present study significant hypokalemia was observed in 17 patients (95%) with various types of cancers, there was significant decrease in potassium level in female patients with carcinoma of oesophagus after cisplatin therapy. Previous studies have suggested that cisplatin therapy have been known to produce hypokalemic paralysis [9], henceforth for the prevention of hypokalemic paralysis, the patients are adviced to undergo regular serum electrolyte measurement for early detection of cation deficiency and appropriate replacement of cations.

The exact cause of cisplatin induced hypophosphatemia and hypobicarbonatemia are not known because these are not frequent complication observed in patients. But in our study significant hypophosphatemia was observed in 12 patients (67%), there was a significant decrease in phosphate levels in female patients with carcinoma of oesophagus. Where as the hypobicarbonatemia was observed only in patients with carcinoma oesophagus.

Hyponatremia is not an uncommon clinical syndrome, in previous studies authors have found that both renal salt wasting syndrome and syndrome of inappropriate antidiuretic hormone secretion have been reported as the underlying mechanism for cisplatin chemotherapy induced hyponatremia[10]. In present study there was significant increase in both serum sodium and chloride levels were observed, it might be due administration of normal saline during each cycle of cisplatin chemotherapy.

In present study we also analyzed serum creatinine and BUN, these are the major parameters to access renal function and excretions of these components are the function of lean body mass in normal person. The serum creatinine concentration is higher in men than in women[6]. In our present study, both of these serum components were increased, but creatinine was increased significantly than BUN after cisplatin treatment may be due to acute nephrotoxicity. We also analyzed some urine components like urine potassium, sodium and pH, there was significant decrease in urine potassium was observed.

In our study the available data indicate that the frequency and severity of cisplatin nephrotoxicity may be reduced by slow intravenous electrolyte infusions and maintaining the hydration; before, during and immediately after the administration of cisplatin. However frequent measurement of serum electrolytes and appropriate replacement are recommended.

From the present study we have found that cisplatin induces nephrotoxicity possibly by disturbing the electrolytes reabsorption mechanism in the renal tubules. Hypomagnesaemia, hypocalcaemia, hypokalemia and hypophosphatemia are frequent complications observed, during and after 5 cycles of cisplatin based chemotherapy, affecting up to 50 to 75% of patients, Significant elevations in serum creatinine and BUN are also observed, if no corrective measures are initiated.

Frequency and severity of cisplatin nephrotoxicity may be reduced by slow intravenous electrolyte infusions and maintaining the hydration; before, during and immediately after the administration of cisplatin.

Conflict of interest statement

We declare that we have no conflict of interest.

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