J Nephropharmacol. 2018; 7(2): 126–130.

http://www.jnephropharmacology.com

Journal of Nephropharmacology

doi: 10.15171/npj.2018.04

Frequency of electrolyte imbalance associated with cisplatin in oral cancer patients; a tertiary care experience from Pakistan

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ARTICLEINFO

Article Type:
Original

Article History:
Received: 9 May 2018
Accepted: 2 July 2018
ePublished: 28 July 2018

Keywords:
Chemotherapy
Cisplatin
Hyponatremia
Hypokalemia
Hypocalcemia
Hypomagnesemia

ABSTRACT

Introduction: Electrolyte imbalance associated with cisplatin is quite prevalent, and increase morbidity in cancer patients.
Objectives: To determine the frequency of electrolyte imbalance associated with cisplatin in oral cancer patients.
Patients and Methods: Oral cancer patients of more than 16 years of age, who received cisplatin-based cancer chemotherapy, were monitored for electrolyte imbalance (Na, K, Ca and Mg). Patients who were as the known cases of kidney disease (acute or chronic) or those having electrolyte imbalance prior to start of chemotherapy were excluded. Primary outcome was to determine electrolyte imbalance.
Results: Among 98 patients, 90 patients developed electrolyte imbalance to cisplatin chemotherapy. The observed electrolyte imbalance included hyponatremia, hypokalemia, hypomagnesemia and hypocalcaemia. Hypokalemia is found to be the most common electrolyte to be affected in the patients (91.8%), whereas hypocalcemia in 88.7%, hypomagnesemia in 67.34% is also observed. Mild hyponatremia is also observed less frequently in 67% of patients.
Conclusion: Cisplatin-based chemotherapy has a high potential to cause electrolyte imbalance. Most of the abnormalities were of milder nature and not associated with symptoms. The common electrolyte abnormalities such as hypokalemia, hypocalcemia and hypomagnesemia were statistically significant, but hyponatremia was not statistically significant.

Original

Implication for health policy/practice/research/medical education:
Chemotherapeutics, on the one hand, has changed the concept of cancer treatment and on other hand causes various effects which increases morbidity of patients. Cisplatin is effective in treating oral cancers but associated electrolyte imbalance is the main concern.
Please cite this paper as: Gulzar K, Ahmed M, Junejo AM. Frequency of electrolyte imbalance associated with cisplatin in oral cancer patients; a tertiary care experience from Pakistan. J Nephropharmacol. 2018;7(2):126-130.

Introduction

Platinum based chemotherapeutics like cisplatin, carboplatin, oxaliplatin, satraplatin, and picoplatin are in use for treating the solid organ malignancies since 1978 (1). Platinum based chemotherapeutics induces apoptosis by cross linking DNA. Cisplatin, (cisplatinum, or cis–diamminedichloroplatinum) is the first class of platinum based chemotherapeutics, a known therapeutic option in multi-technique treatment of oral cancers (2-4). Oral cavity and oropharynx malignancies are third most prevalent after stomach and cervical cancers, constitute around 2 to 5% of head and neck cancers (5). Approximately, 450 000 new case of oral cancers reported in 2017 worldwide (6). Bhurgri et al (Pakistan) reported 4.1 and 4 oral cancer cases per 100 000 population per year in males and females respectively (7).

Platinum based chemotherapeutics have common side effects such as nephrotoxicity, neurotoxicity, ototoxicity, nausea, vomiting and electrolyte imbalance and myelosuppression principally like thrombocytopenia (1). Side effects profile of carboplatin is better than cisplatin especially in children (8). Early reports indicate that nephrotoxicity might occur in 50 to 75 % of patients receiving cisplatin (9). However, reversible nephrotoxicity was generally noted between doses of 50 and 75 mg/m^2, while doses more than 100 mg/m^2 were frequently followed by acute renal failure in 47% of cases (10).

Electrolyte imbalance is also quite common in cisplatin patients such as hypomagnesaemia (60%-90%), hypocalcaemia (70%-90%), hypokalemia (70%-95%) and

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hyponatremia (60%-80%) (9). Injury to proximal tubules by cisplatin leads to decrease absorption and persistent excretion of magnesium, potassium and calcium (11). Hence, the deranged renal function or electrolyte imbalance associated along with cisplatin therapy increases the morbidity and mortality of patients.

Objectives

Nephrotoxicity and electrolyte imbalance associated with cisplatin has a significant impact on patient's morbidity. Thus, its frequency determination in our population is important to reduce the burden of nephrotoxicity. This study aimed to determine the frequency of electrolyte imbalance associated with cisplatin in oral cancer patients.

Patients and Methods

Study population

This prospective study was conducted in oncology ward of Jinnah Postgraduate Medical Centre, over a period of 3 months (November 1, 2016 to May 7, 2017). Oral cancer patients of either gender, more than 16 years of age and normal electrolytes before cisplatin therapy were included, whereas patients having derange renal function or abnormal electrolytes before cisplatin were excluded.

Those who fulfil the inclusion criteria were enrolled and informed consent was taken. All the demographic details (name, gender, age, occupation and education), clinical data (diagnosis) and therapeutic data (name of the drug, dose, route, frequency and duration of therapy) were collected from patients' records. Blood count, serum creatinine and blood urea nitrogen (BUN), serum electrolytes, urine electrolytes and albumin, analysis was conducted using VITROS Ortho-Clinical Diagnostics kits.

Before and after the completion of three cisplatin-based chemotherapy cycles, we assessed serum electrolytes, creatinine, BUN, urine protein, urine sodium, potassium and pH. Chemotherapy was given weekly, whereas concurrently radiotherapy with linear accelerator (6MV X-rays) in conventional fraction (1.8 Gy/fraction) was given once a day, 5 fractions per week using shrinking field technique. Each cycle of cisplatin 100 mg/m^2 at day 1, 07 and 22, after premedication with ondansetron 8 mg/IV stat, ranitidine 150 mg/IV, normal saline/IV 1000 mL before and after cisplatin therapy. The electrolyte imbalance associated with cisplatin will be assessed by measuring of pre-cisplatin and post-cisplatin cycle, of parameters such as sodium, potassium, calcium and magnesium.

Ethical considerations

This research was performed following the Declaration of Helsinki principles. Informed written consent was obtained from each patient. All information about individuals was coded and kept confidential. This study was approved by the institutional ethical committee and research oversight committee, Jinnah Post Graduate Medical Center, Karachi, Pakistan.

Statistical analysis

All the analysis will be conducted on Statistical Package for Social Sciences (SPSS) (Release 10.0, standard version). Mean ± standard deviation (SD) will be calculated for continuous variables like age, change in serum potassium, calcium, magnesium, sodium while, frequency distribution will be calculated for categorical variables like gender hypokalemia, hypocalcemia, hyponatremia and hypomagnesemia. Effect modifier will be controlled by stratification of age, controlling co-morbid conditions (diabetes and hypertension), weight, stage of the disease and premedication before cisplatin chemotherapy (IV fluids, antiemetics and antacids), using chi-square test. Accordingly *P* values equal to or less than 0.05 will be considered as statistically significant.

Results

A total of 98 patients were enrolled to the study, with mean age of 44.88 ± 17.28years [<40 years (33 patients, 33.67%), 40-60 years (57 patients, 58.16%), >60 years (08 patients, 08.1%)]. In enrolled patients, number of male (68 patients, 69.38%) were more than female (38, patients 30.61%). The most common histological lesion is squamous cell carcinoma in 82 patients (83.67%) and 78% in stage III followed by 14% in stage II in TNM staging. Most common site of lesions is mucosa of cheek 33 (33.67%), followed by tongue and floor of mouth. Tobacco consumption is observed in 87 (88.77%) of patients (see Table 1).

Effects of cisplatin on serum electrolytes

Hypokalemia is observed in 90 (91.83%), percent decrease

Table 1. Patients characteristics (n= 98)

Variable	No. (%)
Age (y)	
<40	33 (33.67)
40-60	57 (58.16)
>60	08 (08.1)
Gender	
Male	60 (61.2)
Female	38 (38.8)
Oral cancer (histological type)	
Squamous cell cancers	82 (83.67)
Verucous carcinoma	12 (12.24)
Others	4 (4.08)
Site of lesion	
Cheek	33 (33.67)
Tongue	20 (20.40)
Floor of mouth	20 (20.40)
Lips	16 (16.32)
Hard palate	09 (9.18)
Tobacco consumption	87 (88.77)

in potassium is -9.4%, and is more common in male than female, whereas hypocalcemia is reported in 87 (88.77%) of patients while percent decrease is -6.66% (hypocalcemia is more common in male). Hypomagnesemia is reported in 66 (67.34%) of patients (percent change is -7.18%), and hyponatremia was observed in 66 of cases (67.34%), while percent decrease was -3.35% (both are frequent in females than males) (Tables 2, 3 and 4).

Stratification of age shows hypokalemia and hypocalcemia are more frequent among young and middle age group than older patients, whereas hyponatremia is frequent in older age patients and hypomagnesemia more frequent in younger patients (Table 5).

Stratification according to type of oral cancer revealed that in squamous cell carcinoma, the most frequent electrolyte abnormality associated with cisplatin was hypokalemia (93.9%) and least common is hyponatremia (68.2%), whereas hypocalcemia (91.6%) is most common and hypomagnesemia (16.6%) is least common cisplatin associated electrolyte abnormality in verrucous type (Table 6).

Stratification according to staging of oral cancer is given in Table 7. Table 7 shows that in stage III, hypokalemia (94.6%) and hypomagnesemia (80.35%) are more frequent. In stage II, hypocalcemia (93.3%) is more frequent, whereas in stage IV, hyponatremia is the least frequent and the rest three are equally frequent (83.3%).

Table 2. Frequency of electrolyte imbalance

Electrolyte imbalance	Yes No. (%)	No No. (%)
Hypokalemia	90 (91.83)	8 (8.17)
Hypocalcemia	87 (88.77)	11 (11.23)
Hypomagnesemia	66 (67.34)	32 (32.66)
Hyponatremia	66 (67.34)	32 (67.34)

Discussion

This study was conducted to detect electrolyte imbalance after cisplatin cycles, thereby allowing supplementation of deficient electrolytes without disrupting the chemotherapy cycles.

Cisplatin is known for its effectiveness in the treatment of oral cancers, however, nephrotoxicity associated with cisplatin is reported for years. The exact mechanism has not been fully understood. It may increase membrane fragility and deplete intracellular glutathione while interacting with sulfhydryl compound. Additionally, cisplatin can induce apoptosis and necrosis of kidney cells in a dose dependent fashion. Cisplatin associated nephrotoxicity

Table 3. Change in electrolytes pre-cisplatin and post-cisplatin therapy

Serum electrolyte	Pre-cisplatin	Post-cisplatin	Decrease in electrolytes	*P* value
P (mEq/dL) (n = 90)	4.02±0.30	3.13±0.31	0.63±0.15	0.002
Ca (mg/dL) (n = 87)	9.12±0.46	8.02±0.32	0.76±0.32	0.03
Mg (mg/dL) (n = 66)	2.26±0.34	1.39±0.28	0.45±0.12	0.003
Na (mEq/dL) (n = 66)	141.6±4.9	130.2±3.1	5.82±1.06	0.6

Table 4. Stratification of electrolyte imbalance as per gender

Electrolyte Imbalance	Male (n=60)		Female (n=38)		*P* value[a]
	Yes No. (%)	No No. (%)	Yes No. (%)	No No. (%)	
Hypokalemia	57 (91.6)	03 (08.4)	33 (78.9)	05 (21.1)	0.001
Hypocalcemia	53 (88.3)	07 (11.7)	34 (89.4)	04 (10.6)	0.001
Hypomagnesemia	36 (60)	24 (40)	25 (65.8)	13 (34.2)	0.025
Hyponatremia	38 (63.3)	22 (36.7)	28 (73.7)	10 (26.3)	0.01

[a] Chi square test.

Table 5. Stratification of electrolyte imbalance as per age

Electrolyte Imbalance	<40 years (n = 33)		40-60 years (n = 57)		>60 years (n = 8)		*P* value[a]
	Yes No. (%)	No No. (%)	Yes No. (%)	No No. (%)	Yes No. (%)	No No. (%)	
Hypokalemia	29 (87.8)	4 (12.2)	55 (96.4)	2 (03.6)	6 (75)	2 (25)	0.001
Hypocalcemia	27 (81.8)	6 (18.2)	53 (92.8)	4 (07.2)	7 (87.5)	1 (12.5)	0.005
Hypomagnesemia	24 (72.7)	9 (27.3)	37 (64.9)	20 (35.1)	5 (62.5)	3 (37.5)	0.001
Hyponatremia	19 (57.6)	14 (42.4)	41 (71.2)	16 (28.8)	6 (75)	2 (25)	0.1

[a] Chi square test.

Table 6. Stratification of electrolyte imbalance as per type of carcinoma

Electrolyte Imbalance	Squamous carcinoma (n = 82)		Verrucous carcinoma (n = 12)		*P* value[a]
	Yes No. (%)	No No. (%)	Yes No. (%)	No No. (%)	
Hypokalemia	77 (93.9)	05 (06.1)	09 (75)	03 (25)	0.001
Hypocalcemia	72 (87.8)	10 (12.2)	11 (91.6)	01 (08.4)	0.004
Hypomagnesemia	62 (75.6)	20 (24.4)	02 (16.6)	10 (80.4)	0.07
Hyponatremia	56 (68.2)	26 (31.8)	07 (58.3)	05 (41.7)	0.1

[a] Chi square test.

Table 7. Stratification of electrolyte imbalance as per stage of carcinoma

Electrolyte imbalance	Stage II (n = 30)		Stage III (n = 56)		Stage IV (n = 12)		*P* value[a]
	Yes No. (%)	No No. (%)	Yes No. (%)	No No. (%)	Yes No. (%)	No No. (%)	
Hypokalemia	27 (90)	3 (10)	53 (94.6)	3 (5.4)	10 (83.3)	2 (16.7)	0.001
Hypocalcemia	28 (93.3)	2 (6.7)	49 (87.5)	7 (12.5)	10 (83.3)	2 (16.7)	0.001
Hypomagnesemia	14 (46.6)	16 (53.4)	45 (80.35)	11 (19.65)	7 (58.3)	5 (41.7)	0.4
Hyponatremia	26 (86.6)	4 (13.4)	30 (53.5)	26 (46.5)	10 (83.3)	2 (16.7)	0.1

[a] Chi square test.

manifest clinically as rise in BUN, creatinine, disturbance in electrolytes and acute renal failure. Furthermore, cisplatin associated nephrotoxicity histologically manifests with acute focal tubular necrosis, convoluted tubule and collecting duct dilatation. The present study suggests that these changes must be reversible. At present, to avoid renal impairment and electrolyte imbalance, hydration and forced dieresis are administered as prophylaxis (12).

In the present study, we observed hypokalemia (91.83%), hypocalcemia (87.75%), hypomagnesemia (67.34%) and hyponatremia (67.34%) after three cycles of cisplatin therapy (Table 2). In our study population, hypokalemia is the commonest electrolyte abnormality, observed in 90 patients (91.83%, $P=0.002$). A significant decrease in potassium level was observed in males, especially in younger and middle age groups (Tables 3 and 4), whereas Arunkumar et al (13) observed in 92% of their patients. Increased renal absorption capacity, in response to decreased absorption of intestinal potassium is a possible explanation behind it. Furthermore, magnesium and potassium are subjected to change in intestinal absorption and renal excretion with each cisplatin treatment (14). Previous studies have suggested that cisplatin is known to produce hypokalemic paralysis (15) however, we had not paralysis in our study population.

Hypocalcemia is also quite common side effect of cisplatin chemotherapy. In our study population, 87 patients suffered from hypocalcemia (88.77%, $P=0.03$; Table 2), whereas Arunkumar et al (13) found in 80% of their study population. Furthermore, in our observation both genders are significantly affected. Additionally hypocalcemia affects younger patients more as compared to others (Tables 3 and 4). The possible mechanism behind this complication is excessive urinary loss of calcium in urine, decreased renal tubular reabsorption of calcium due to tubular damage, due to low tissue response to parathormone, and low serum magnesium levels (16). Electrolyte monitoring and continuous oral calcium substitution is advised for patients undergoing cisplatin therapy.

Hypomagnesemia is a well-known side effect of cisplatin treatment. In our study, 67.34% of patients developed this complication. Female suffer more as compared to male (66, $P=0.003$; Tables 2 and 5), In contrast, Markman et al (17) reported the incidence of cisplatin-induced hypomagnesemia in 89% of ovarian cancer but their sample size was small. Direct injury to renal magnesium reabsorption in ascending loop of Henle, and distal tubule, is the possible mechanism behind the cisplatin-induced hypomagnesemia (18).

Hyponatremia is not uncommon in patients on cisplatin chemotherapy. Renal salt wasting and syndrome of inappropriate antidiuretic hormone are possible mechanisms behind cisplatin-induced hyponatremia (19). Cisplatin-induced hyponatremia was observed in 67.34 % (Tables 2 and 5) of our study population. Cisplatin-induced hyponatremia was more common in females and patients with older age group (Tables 3 and 4). Hamdi et al (18) reported 69% incidence of cisplatin-induced hyponatremia, on contrary Arunkumar et al (13) reported an increase in serum sodium level. They concluded that, opined that this may be due to infusing normal saline before cisplatin chemotherapy. 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

Conclusion

Our study concluded that electrolyte abnormalities are

hypokalemia, hypocalcemia, hypomagnesemia and hyponatremia, which were observed after three cycles of cisplatin. Hypokalemia, hypocalcemia, hypomagnesemia were statistically significant, but hyponatremia was not statistically significant.

Limitations of the study

One of the limitations of the study is the number of patients attending chemotherapy clinic. Larger studies in this regard are necessary.

Authors' contribution

KG participated in the data collection and main draft. MA and AMJ contributed to intellectual input and critical revision. All authors read and signed the final paper.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

This study was conducted with collaboration of department of nephrology and oncology, supported by Jinnah Postgraduate Medical Centre.

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