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Research Article

Incidence and spectrum of electrolyte disturbances in cisplatin based chemotherapy

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ABSTRACT

Background: Cisplatin, one of the most commonly used chemotherapeutic agents, has electrolyte imbalances as one of its most important adverse effects. We conducted this study to characterize the spectrum of its electrolyte abnormalities.
Methods: In this observational study, all patients who received chemotherapy containing cisplatin either as single agent or in combination of not more than 2 drugs were included. After baseline investigations, serum electrolytes were recorded, before each cycle of chemotherapy. The incidence and grade of electrolyte abnormalities were analyzed Median dose and cycle at which each of the electrolyte abnormality first occurred was analyzed with Kaplan Meir survival analysis.
Results: The most common individual abnormality was hypomagnesaemia, which was seen in 91.8% of patients, followed by hyponatremia 88.2%. Hypocalcaemia 70.6% and hypokalemia 27.1%. The median dose of Cisplatin at which half of the patients had hyponatremia (critical dose) was 195mg and occurred in cycle 2 while the critical dose for potassium was 560mg which occurred in cycle 7. Similarly critical dose and cycle for calcium and magnesium were 240mg at cycle 3 and 160mg at cycle 2 respectively. Majority of electrolyte abnormalities were grade 1 for all the four electrolytes. Grade 3 (15.3%) and Grade 4 (2.4%) was seen predominantly for sodium. There were no grade 3 or 4 hypomagnesaemia.
Conclusions: Cisplatin chemotherapy is associated with hypomagnesaemia in a highly significant percentage of patients. Incidence increases with increase in cumulative dose of cisplatin. Frank clinical manifestations associated with this abnormality are rare.

Keywords: Cisplatin, Chemotherapy, Hypomagnesaemia, Hyponatremia, Hypocalcemia

INTRODUCTION

Cisplatin is one of the most important chemotherapeutic agents, which has a central role in cancer chemotherapy, despite its toxicity. Chemically it is a co-ordinate metal complex containing platinum[1]. It is being used in treatment of head and neck, lung, ovary, gastric and testicular malignancies[2]. The main adverse effects are nephrotoxicity[3]and electrolyte imbalances. The most common electrolyte abnormality associated with cisplatin is hypomagnesemia[4] due to renal magnesium wasting. Others include hyponatremia,[5] hypokalemia, hypocalcaemia and hypophosphatemia.

The available data shows different electrolyte abnormalities, the incidence of which varies significantly between studies. Cisplatin being a commonly used antineoplastic agent with significant nephrotoxicity, accurate evidence regarding the incidence of electrolyte abnormalities is essential, and thus the relevance of this study.

METHODS

Study design

This prospective observational single-arm study was conducted in the Department of Radiotherapy and Oncology, Medical College Thiruvananthapuram, Kerala, India. The study population consisted of patients registered in the Department during the period of January to March 2014. The study was approved by the Institutional Human Ethics Committee of Government Medical College, Thiruvananthapuram.

Inclusion criteria

Patients having a histological diagnosis of cancer aged 18 years and older and receiving cisplatin based chemotherapy as single agent or combination with not more than two drugs in the combination regime including cisplatin.

Exclusion criteria

1) Patients having altered renal, liver dysfunction (above the upper limit of normal).
2) Patients already having altered electrolytes as baseline value.
3) Patients with documented cardiac and any neurological ailments which may alter the electrolyte function.
4) Patients already on any nephrotoxic drugs.
5) Patients who did not complete at least three cycles of the chemotherapy either due to death or drop out from the study.

Procedure

Patients fulfilling the inclusion criteria were included in the study. A written informed consent was taken from each patient. Baseline investigations including complete blood count (CBC), renal function tests (blood urea and serum creatinine), liver function tests, serum electrolytes including sodium, potassium, calcium and magnesium were routinely done for all patients prior to each cycle of the chemotherapy.

Cisplatin was administered at varying doses based on the schedules for each individual malignancy which ranged from 70 to 120 mg. The inter-cycle interval varied from weekly cycle to every 3 weekly cycle as per the protocol. Cumulative dose of cisplatin was recorded each cycle along with the values of basic laboratory investigation and serum electrolytes. All the investigations were done in the Central Diagnostic Laboratory of Government Medical College Hospital, Trivandrum. The electrolyte abnormalities were graded as per the Common Toxicity Criteria (CTC) version 3 of WHO.

Statistical Analysis

Data was entered in Microsoft Excel 2007 and analysis done with SPSS 17.0 statistical software. The incidence and the grade of electrolyte abnormalities in terms of CTC toxicity criteria were expressed as percentages. The median dose and the number of cycle at which each of the electrolyte abnormality first occurred, was analyzed using the Kaplan Meir survival analysis.

RESULTS

A total of 85 patients satisfied the inclusion criteria. The age of the patients ranged from 21 years to 89 years (57.6+/- 10.2). Male to female ratio was 3:1.There was no significant variation of the values of haemoglobin, total WBC count and platelet count between cycles of chemotherapy.

Table 1: Mean electrolyte values of all chemotherapy cycles.

Electrolyte	Mean	SD	Mediam	Minimum	Maximum
Na	132.0	3.5	133	116.0	138.0
K+	3.9	.6	4	2.4400	5.1000
Ca	8.2	.9	8	5.0000	10.4000
Mg	1.6	.2	2	1.1000	2.1000

Table 2: Incidence of the individual electrolyte abnormalities.

Electrolyte abnormality	Frequency	Percent
Na +	75	88.2
K+	23	27.1
Ca	60	70.6
Mg	78	91.8

The mean values of each of the electrolytes in all cycles of chemotherapy together are as shown in table1.

Among all cycles of chemotherapies taken, the most common individual abnormality was of magnesium which was seen in 91.8% of patients, followed by hyponatremia of 88.2%. Hypocalcaemia incidence was 70.6% and hypokalemia was further rare at 27.1% (Table 2).

All the electrolyte values remained normal only in 1 patient (1.2%). All abnormalities occurred in 20% of patients, whereas the most common constellation of abnormalities was that of sodium, calcium and magnesium together (38.8%). It may also be noted that the incidence of potassium abnormality is lowest as individual or in combination with other electrolytes (Table 3).

Table 3: Incidence of electrolyte abnormalities as combinations.

Abnormal	Frequency	Percent
No abnormalities	1	1.2
Mg	2	2.4
Ca	2	2.4
Mg & Ca	4	4.7
Mg, Ca & K	1	1.2
Na	1	1.2
Na & Mg	17	20.0
Na & Ca	2	2.4
Na, Ca & Mg	33	38.8
Na, K, Mg	4	4.7
Na K Ca	1	1.2
All abnormalities	17	20.0

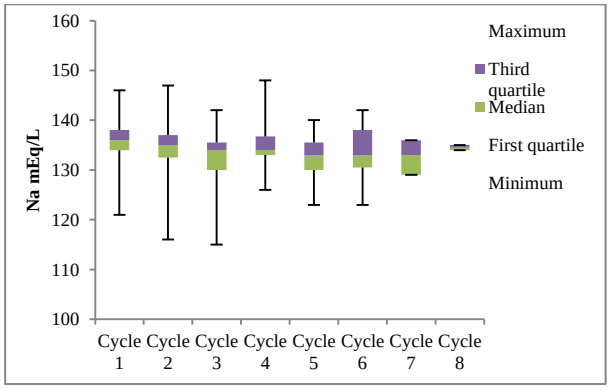

Figure 1: Forest plot depicting the range of sodium values in each chemotherapy cycle.

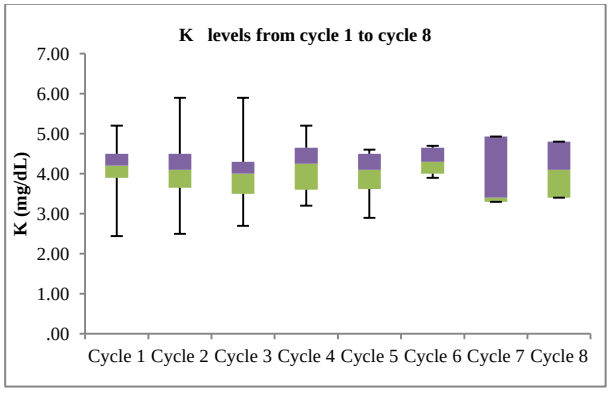

Figure 2: Forest plot depicting the range of potassium values in each chemotherapy cycle.

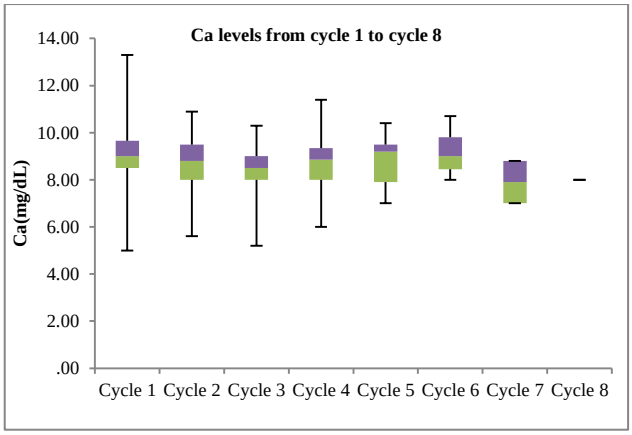

Figure 3: Forest plot depicting the range of calcium values in each chemotherapy cycle.

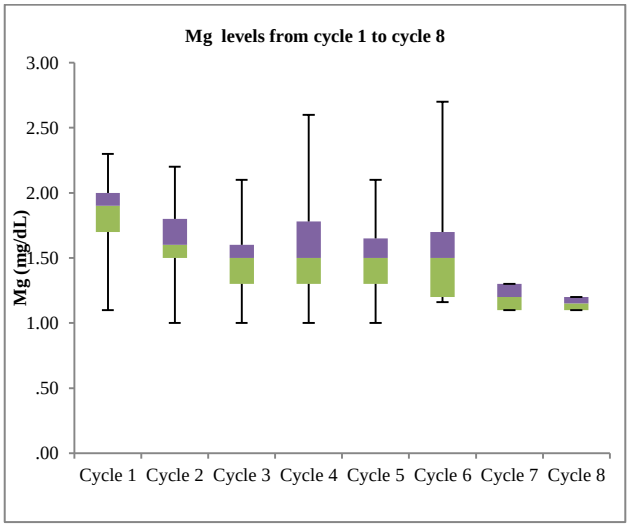

Figure 4: Forest plot depicting the range of magnesium values in each chemotherapy cycle.

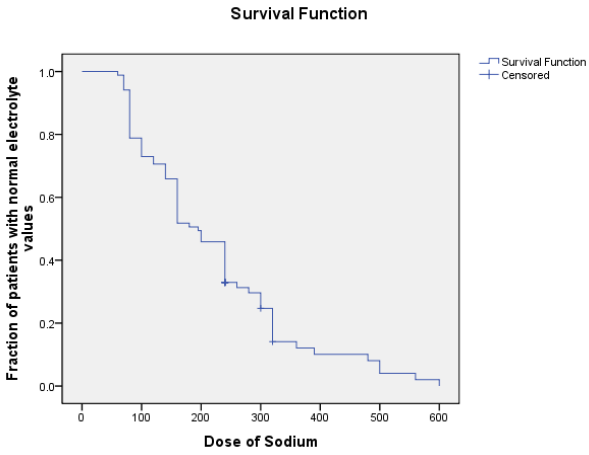

Figure 5: Kaplan Meir Survival Curves depicting the fraction of patients remaining with normal serum sodium levels with increasing dose of cisplatin chemotherapy.

Table 4: Incidence of graded electrolyte abnormalities in each cycle.

		Grade 0		Grade 1		Grade 2		Grade 3		Grade 4	
		N	%	N	%	N	%	N	%	N	%
Na	Cycle 1	62	72.9	20	23.5			3	3.5		
	Cycle 2	50	58.8	26	30.6			7	8.2	2	2.4
	Cycle 3	37	43.5	34	40.0			13	15.3	1	1.2
	Cycle 4	15	46.9	16	50.0			1	3.1		
	Cycle 5	5	29.4	9	52.9			3	17.6		
	Cycle 6	3	33.3	5	55.6			1	11.1		
	Cycle 7	1	33.3	1	33.3			1	33.3		
	Cycle 8	1	50.0	1	50.0						
K+	Cycle 1	81	95.3	3	3.5					1	1.2
	Cycle 2	76	89.4	7	8.2			2	2.4		
	Cycle 3	73	85.9	10	11.8			2	2.4		
	Cycle 4	28	87.5	4	12.5						
	Cycle 5	15	88.2	1	5.9			1	5.9		
	Cycle 6	9	100.0								
	Cycle 7	1	33.3	2	66.7						
	Cycle 8	1	50.0	1	50.0						
Ca	Cycle 1	65	76.5	12	14.1	4	4.7	3	3.5	1	1.2
	Cycle 2	55	64.7	14	16.5	12	14.1	3	3.5	1	1.2
	Cycle 3	43	50.6	29	34.1	10	11.8	2	2.4	1	1.2
	Cycle 4	19	59.4	6	18.8	6	18.8	1	3.1		
	Cycle 5	11	64.7	2	11.8	4	23.5				
	Cycle 6	7	77.8	2	22.2						
	Cycle 7	1	33.3			2	66.7				
	Cycle 8			2	100.0						
+Mg	Cycle 1	57	67.1	27	31.8	1	1.2				
	Cycle 2	27	31.8	54	63.5	4	4.7				
	Cycle 3	13	15.3	64	75.3	8	9.4				
	Cycle 4	8	25.0	21	65.6	3	9.4				
	Cycle 5	3	17.6	13	76.5	1	5.9				
	Cycle 6	2	22.2	6	66.7	1	11.1				
	Cycle 7			2	66.7	1	33.3				
	Cycle 8			1	50.0	1	50.0				

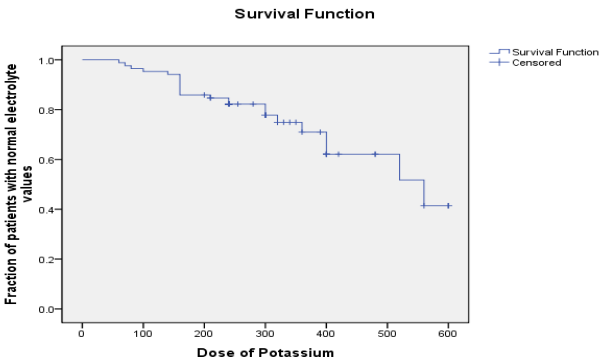

Figure 6: Kaplan Meir Survival Curves depicting the fraction of patients remaining with normal serum potassium levels with increasing dose of cisplatin chemotherapy.

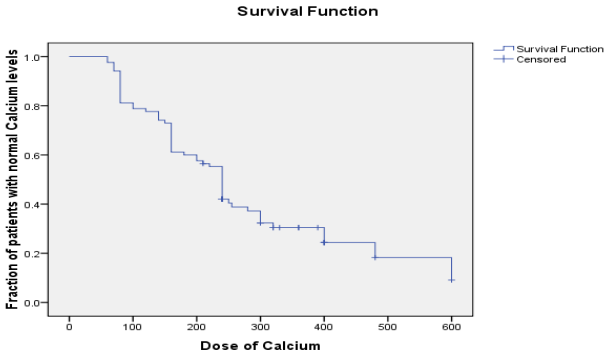

Figure 7: Kaplan Meir Survival Curves depicting the fraction of patients remaining with normal serum calcium levels with increasing dose of cisplatin chemotherapy.

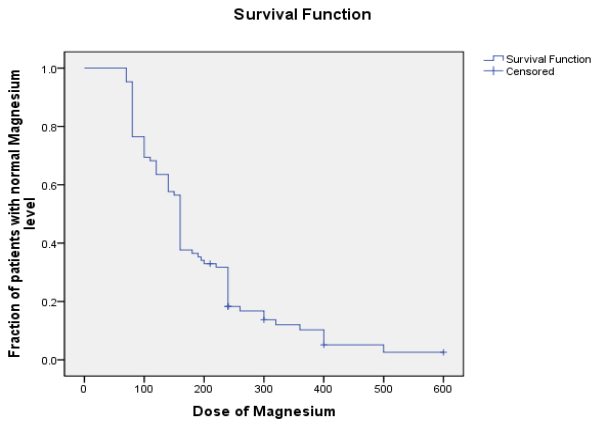

Figure 8: Kaplan Meir survival curves depicting the fraction of patients remaining with normal serum magnesium levels with increasing dose of cisplatin chemotherapy.

The median critical dose and number of chemotherapy cycle

The critical dose at which half of the patients had hyponatremia (median dose) was 195mg (SE 16.46, 95% CI 162.73- 227.27). This occurred in cycle 2 (SE 0.23, 95% CI 1.55- 2.45).

The median critical dose of potassium was 560mg (SE 101.56, 95% CI 360.95 – 759.05) and occurred in cycle 7 (SE 0.82, 95% CI 5.39- 8.61).

Similarly median critical dose and cycle of calcium and magnesium are 240mg (SE 8.14, 95%CI 224.05- 255.96) at cycle 3 (SE 0.323, 95% CI 2.37- 3.63) and 160mg (SE 2.79, 95% CI 154.53- 165.47) at cycle 2 (SE 0.14, 95% CI 1.73- 2.27) respectively.

Grading of electrolyte abnormalities

The significant portion of all the abnormalities detected were grade 1 in general for all four electrolytes. Grade 4 abnormality was seen only with sodium (2.4%). Grade 3 hyponatremia was maximum in the third cycle, seen in 13 patients (15.3%). The grade 3 abnormalities of calcium and potassium were only a meagre 3 to 5%. It is noteworthy that although magnesium was the most common individual or combination abnormality, there was no grade 3 or 4 hypomagnesaemia (Table 4).

DISCUSSION

The incidence of electrolyte abnormalities reported varies between studies. The direct injury to magnesium absorption in the ascending loop of Henle, as well as the distal tubule is the possible mechanisms behind the cisplatin induced hypomagnesaemia.[6] The incidence of hypomagnesaemia reported to be 80 to 100% in some studies.[7] The results of other studies have been absolutely contrasting with incidence as low as 3% reported by some.[8] In our study the incidence was 91%, both grade 1 and 2 together.

Few other studies in this regard has demonstrated significant and progressive decline in the serum magnesium levels with each cycle of chemotherapy, but not to the level below the lower limit of normal.[8,9] One of the studies showed no decrease in magnesium levels with cisplatin therapy.[10] In our study, though hypomagnesaemia was the most common abnormality, none of the patients had significant clinical signs or symptoms suggestive of hypomagnesaemia. Grade 3 and 4 hypomagnesaemia were non-existent, similar to the findings in previous studies.[11]

Kazem Anvari et al[6] compared the magnesium levels in a group of patients supplemented with magnesium intravenous in each chemotherapy cycle with a control group who did not receive magnesium supplementation. It was found that there was a progressive decline in magnesium levels with each chemotherapy cycle, and that the decrease was greater in the control group.

Studies published in paediatric age group including one study in infants showed incidence of hypomagnesaemia to be 40 to 45%.[13,14] It is noteworthy that in a study in infants,[14] there has been a progressive decline in serum magnesium over the courses of chemotherapy, and thereafter during follow up till 5 years.

Hyponatremia was the second most common abnormality (88.2%) in our study. It has been reported to be a common abnormality in many studies.[14,15] In a study,[9] hyponatremia (22.9%) was the only abnormality. Serum sodium increased by 1.35% in one study, but other electrolytes showed moderately decreased levels.[16] This was attributed to adequate hydration with normal saline during each cycle of chemotherapy. In an Indian Tertiary care hospital based study,[17] hypocalcaemia was the only abnormality.

In our study the least frequent and late appearing electrolyte abnormality was hypokalemia, and is consistent with previous studies. Rodriguez M et al[18] describes case studies in which hypokalemia was refractory until the hypomagnesaemia was corrected. This demonstrates an association of a refractory potassium depletion and magnesium deficiency.

CONCLUSION

Cisplatin chemotherapy causes hypomagnesaemia in a highly significant percentage of patients. Incidence increases with increase in the cumulative dose of cisplatin. Frank clinical manifestations associated with this abnormality are rare. This may be due to the low grade of hypomagnesaemia which may be asymptomatic

or only subtle changes. Since clinicians fail to monitor it, it is commonly underestimated. Due to the high incidence and also being a correctable cause, it must be always kept in mind and monitored regularly. This become significant when associated with other electrolyte abnormalities as well.

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