"AN OBSERVATIONAL STUDY TO ESTIMATE THE INCIDENCE OF ELECTROLYTE IMBALANCES ASSOCIATED WITH CISPLATIN BASED CHEMORADIOTHERAPY AMONG CANCER PATIENTS"

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Abstract

Cancer is a prevalent non-communicable disease (NCD) and a leading cause of global mortality. Combining chemotherapy with radiation therapy is essential for improving loco-regional control and survival rates. Platinum compounds, taxanes, fluoropyrimidines, and other agents are commonly used alongside radiotherapy. However, electrolyte imbalances frequently occur in cancer patients undergoing platinum-based chemotherapy and radiation therapy. This prospective observational study aimed to evaluate the incidence of various electrolyte imbalances associated with cisplatin-based chemoradiotherapy in diverse cancer patients. The study was conducted at the Department of Radiation Oncology, Sri Venkateswara Institute of Medical Sciences in Tirupati, Andhra Pradesh, India. Sixty patients receiving cisplatin-based concurrent chemoradiotherapy were included. Demographic information, including age, gender, and laboratory investigations of serum sodium, potassium, calcium, and magnesium levels, were collected from patient records. The incidence of electrolyte abnormalities was found to be higher during the third cycle of treatment. Moreover, electrolyte imbalances were more prevalent during the delayed phase compared to the acute phase of cisplatin-based chemotherapy. This study highlights the association between platinum-based chemoradiotherapy and various electrolyte imbalances, including hyponatremia, hypokalemia, hypocalcemia, and hypomagnesemia, in patients with cervical and head and neck carcinomas.

Key words: Cisplatin-based chemotherapy, Electrolyte imbalances, radiotherapy.

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Introduction

According to GLOBOCAN 2020, the global cancer burden in 2020 is estimated to be 19.3 million new cases and 10 million deaths. .Electrolyte imbalances are common among cancer patients receiving platinum based chemotherapy concurrently with radiation therapy. Cisplatin, also known as cis-diamine dichloroplatinum; CDDP, is a chemotherapeutic medication. Cisplatin, a platinum-containing chemical, is the most often used chemotherapeutic drug in combination with radiation. Despite its electrolyte imbalance, it has been used to treat a variety of diseases including head and neck cancer, uterine cervix cancer, and lung cancer. Carboplatin is given to patients who have a poor glomerular filtration rate (GFR) [1]

Hyponatremia, hypocalcemia, hypokalemia, hypomagnesemia, and a Gitelman syndrome-like picture characterized by coexisting hypocalciuria and hypokalemic metabolic alkalosis are the most prevalent electrolyte abnormalities encountered in the clinical practice of concurrent chemo radiotherapy.

Hypocalcemia causes tetany, depression, carp pedal spasm, neuromuscular excitability, and cardiac arrhythmias with a longer Q-T interval [2]Tremor, paresthesia, tetany, spasms, and seizures, as well as decreased release and activity of parathyroid hormone (PTH) and reduced synthesis of active vitamin D and its receptors due to hypomagnesemia in the cardiovascular and neuromuscular systems [3] Confusion, behavioral changes, headaches, irritability, nausea, vomiting, lethargy, drowsiness, coma, seizures, and respiratory arrest can all result from hyponatremia [4]

Disruptions in excitable cell electrical activity (cardiac myocytes, skeletal muscle cells, and vascular smooth myocytes), which can have serious consequences, such as life-threatening arrhythmias caused by hypokalemia [5].

Methodology

The present research work follows prospective observational study. This study was conducted in Sri Venkateswara Institute of Medical Sciences, Department of Radiation Oncology, Tirupati Andhra Pradesh India .The study was conducted at a period of 6 months. Histopathologically confirmed cancer patients, Patients from age group 18-65 years, Patients having ECOG Performance status S-02[Eastern cooperative oncology group], Hemoglobin more than equal to 10g/dl, GFR more than equal to 60ml/min, with normal baseline levels of serum electrolytes, Patients who are fit for chemoradiotherapy as per institutional protocol and Patient who signed the approved informed consent form were included. Patient who received prior radiotherapy, chemotherapy, Patient having ECOG performance status issue 3-4, GFR less than 60ml/min, Hb less than 10g/dl, Pregnant women and lactating mother.

Statistical Analysis

Mean values and percentages using Pie Diagrams, Graphs and Bar Diagrams. Continuous variables were analysed using unpaired test and categorical variables were analysed by using Chi-square Test, student's t Test. Statistical significance was taken as $P < 0.05$. The data was analysed using SPSS V26 and Microsoft Excel.

Results

This study was attempted to compare the variations in the serum levels of the following electrolytes before and after chemotherapy Serum sodium, Serum potassium, Serum calcium, Serum magnesium. The study included 60 patients who came to the Radiation oncology department and receiving concurrent chemoradiotherapy. The variations in the serum levels of the following electrolytes before and after chemotherapy Serum sodium, Serum potassium, Serum calcium. Serum magnesium Among the 60-study population, majority of subjects were under the age groups of46-55 years (n=25) constituting 41.6% of patients followed with age group of 56-65 years (n=20) constituting 33.4% of patients followed with the age group 36-46 years (n=15) Table 1 and Table 2 constituting 25% of patients as shown in Table 3. In our study most participants were women with 78.30% and 21.70 were male. Based on the gender the subjects have been separated as shown in Table 4.

DISCUSSION

Our study demonstrates the importance of electrolyte imbalances associated with cisplatin-based chemo radiotherapy among various cancer patients. Electrolyte abnormalities in cancer patients remain as one of the distressing side effects of chemotherapy, with the potential for worsening quality of life and nutritional status of patients undergoing chemo-radiotherapy [16]. In our study, every patient received chemotherapeutic agent cisplatin 50mg weekly in chemotherapy treatment cycles. The current study sample was

mostly composed of women with cervical cancer, aged between 36 and 65 years. The incidence of electrolyte abnormalities was higher in 3rd cycle. The incidence of electrolyte abnormalities in the acute phase was lower than the delayed phase, for cisplatin-based chemotherapy [17].

These results were similar with findings of Ignazio Verzicco *et al;* (2020) explained that A vast array of traditional and novel antineoplastic drugs, currently available for cancer treatments, may induce serious and potentially life-threatening derangements in serum electrolyte concentrations, via mechanisms such as nephrotoxic tubular damage, diarrhoea induction, and/or TLS [18].

George Liamis,*etal*;(2016) explained that Platinum-containing drugs are frequently associated with hypomagnesemia, hypokalemia and hypocalcemia, as well as with a Gitelman syndrome-like picture with co-existent hypercalciuria and hypokalemic metabolic alkalosis. Moreover, platinum-containing drugs are associated with hyponatremia, especially when combined with large volumes of hypotonic fluids aiming to prevent nephrotoxicity [19].

Aravindh S. Anand *et al* ; (2015) explained that 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 [20].

CONCLUSION

In the present study we may conclude that various electrolyte imbalances such as hyponatremia, hypokalemia, hypocalcaemia, hypomagnesemia often associated with platinum based chemo radiation therapy among patients with carcinoma cervix and head & neck. Although majority of patients with electrolyte imbalances were apparently asymptomic ,attention should be made towards these subset of patients urge this may lead to potential life threatening complications such as cardiac arrhythmias ,seizures, brain injury and death.

LIMITATION:

- Relatively small sample size.
- Short duration follow up.
- No symptomatic correlation of laboratory parameters of electrolytes.

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References:

1. Mukhi, S., Aramini, J., & Kabani, A. (2007). Contributing to communicable diseases intelligence management in Canada: CACMID meeting, March 2007, Halifax, Nova Scotia. *Canadian Journal of Infectious Diseases and Medical Microbiology*, *18*(6), 353–356. https://doi.org/10.1155/2007/386481
2. Bray, F., Laversanne, M., Weiderpass, E., & Soerjomataram, I. (2021). The ever-increasing importance of cancer as a leading cause of premature death worldwide. *Cancer*, *127*(16), 3029–3030. https://doi.org/10.1002/cncr.33587
3. Ferlay, J., Colombet, M., Soerjomataram, I., Mathers, C., Parkin, D. M., Piñeros, M., Znaor, A., & Bray, F. (2019). Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. *International Journal of Cancer*, *144*(8), 1941–1953. https://doi.org/10.1002/ijc.31937
4. Bittencourt, N. C., Santos, K. A., Mesquita, M. G., Silva, V. G., Telles, A. C., & Silva, M. M. (2021, June 23). Signs and symptoms manifested by patients in palliative cancer care in homecare: Integrative review. *Escola Anna Nery*, *25*(4). https://doi.org/10.1590/2177-9465-ean-2020-0520
5. Sebri, V., Durosini, I., Triberti, S., & Pravettoni, G. (2021, March 1). The efficacy of psychological intervention on body image in breast cancer patients and survivors: A systematic-review and meta-analysis. *Frontiers in Psychology*, *12*, 611954. https://doi.org/10.3389/fpsyg.2021.611954
6. Wu, Z. H., Tang, Y., Yu, H., & Li, H. D. (2021, May 4). The role of ferroptosis in breast cancer patients: A comprehensive analysis. *Cell Death Discovery*, *7*(1), 93. https://doi.org/10.1038/s41420-021-00473-5
7. So, W. K. W., Law, B. M. H., Ng, M. S. N., He, X., Chan, D. N. S., Chan, C. W. H., & McCarthy, A. L. (2021, April). Symptom clusters experienced by breast cancer patients at various treatment stages: A systematic

review. *Cancer Medicine*, *10*(8), 2531–2565. https://doi.org/10.1002/cam4.3794
8. Wang, Y., Huang, P., Wu, Y., Liu, D., Ji, M., Li, H., & Wang, Y. (2022, April 1). Association and mechanism of garlic consumption with gastrointestinal cancer risk: A systematic review and meta-analysis. *Oncology Letters*, *23*(4), 1–6. https://doi.org/10.3892/ol.2022.13245
9. Alshahrani, M. M. (2022, January 15). A glance at the emerging diagnostic biomarkers in the most prevalent genitourinary cancers. *Saudi Journal of Biological Sciences*.
10. Garrido, M. P., Torres, I., Vega, M., & Romero, C. (2019). Angiogenesis in gynecological cancers: Role of neurotrophins. *Frontiers in Oncology*, 9, 913. https://doi.org/10.3389/fonc.2019.00913
11. Pfister, D. G., Spencer, S., Adelstein, D., Adkins, D., Anzai, Y., Brizel, D. M., Bruce, J. Y., Busse, P. M., Caudell, J. J., Cmelak, A. J., & Colevas, A. D. *Head and neck cancers* version 2.2020, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*. (2020, July 1), *18*(7) (pp. 873–898).
12. Ayodele, O., & Razak, A. R. A. (2020, February). Immunotherapy in soft-tissue sarcoma. *Current Oncology*, *27*(s1) Suppl. 1, 17–23. https://doi.org/10.3747/co.27.5407
13. Weniger, M. A., & Küppers, R. (2021, April). Molecular biology of Hodgkin lymphoma. *Leukemia*, *35*(4), 968–981. https://doi.org/10.1038/s41375-021-01204-6
14. Bible, K. C., Kebebew, E., Brierley, J., Brito, J. P., Cabanillas, M. E., Clark, Jr., T. J., Di Cristofano, A., Foote, R., Giordano, T., Kasperbauer, J., Newbold, K., Nikiforov, Y. E., Randolph, G., Rosenthal, M. S., Sawka, A. M., Shah, M., Shaha, A., Smallridge, R., & Wong-Clark, C. K. (2021, March 1). 2021 American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. *Thyroid*, *31*(3), 337–386. https://doi.org/10.1089/thy.2020.0944
15. Papaleontiou, M., Chen, D. W., Banerjee, M., Reyes-Gastelum, D., Hamilton, A. S., Ward, K. C., & Haymart, M. R. (2021, September 1). Thyrotropin suppression for papillary thyroid cancer: A physician survey study. *Thyroid*, *31*(9), 1383–1390. https://doi.org/10.1089/thy.2021.0033
16. Jeppesen, A. N., Jensen, H. K., Donskov, F., Marcussen, N., & Von Der Maase, H. (2010, March). Hyponatremia as a prognostic and predictive factor in metastatic renal cell carcinoma. *British Journal of Cancer*, *102*(5), 867–872. https://doi.org/10.1038/sj.bjc.6605563
17. Berardi, R., Santoni, M., Newsom-Davis, T., Caramanti, M., Rinaldi, S., Tiberi, M., Morgese, F., Torniai, M., Pistelli, M., Onofri, A., Bower, M., & Cascinu, S. (2017, April 4). Hyponatremia normalization as an independent prognostic factor in patients with advanced non-small cell lung cancer treated with first-line therapy. *Oncotarget*, *8*(14), 23871–23879. https://doi.org/10.18632/oncotarget.13372
18. Verzicco, I., Regolisti, G., Quaini, F., Bocchi, P., Brusasco, I., Ferrari, M., Passeri, G., Cannone, V., Coghi, P., Fiaccadori, E., Vignali, A., Volpi, R., & Cabassi, A. (2020). Electrolyte disorders induced by antineoplastic drugs. *Frontiers in Oncology*, *10*, 779. https://doi.org/10.3389/fonc.2020.00779
19. Liamis, G., Liberopoulos, E., Barkas, F., & Elisaf, M. (2014). Diabetes mellitus and electrolyte disorders. *World Journal of Clinical Cases*, *2*(10), 488–496. https://doi.org/10.12998/wjcc.v2.i10.488
20. Anand, A. S., & Nikhil, S. (2015). Incidence and spectrum of electrolyte disturbances in cisplatin based chemotherapy. *International Journal of Research in Medical Sciences, 3* (12), 3824–3829. https://doi.org/10.18203/2320-6012.ijrms20151450

Table: 1 Age wise percentage distribution

Age group	Female	Male	Total	Percentage
36-45	13	2	15	25
46-55	19	6	25	41.6
56-65	15	5	20	33.4

Table: 2 Gender wise distribution

Gender	Percentage (%)
Male	21.70
Female	78.30
Total	100.00

Table: 3 Electrolytes analysis by using ANOVA

Electrolytes		Sum of Squares	Degree of freedom (df)	Mean Square	ANOVA-Value (F)	Significance(P – value)
Na	BetweenGroups	47.546	3	15.849	1.323	0.267
	Within Groups	2826.35	236	11.976		
	Total	2873.896	239			
K	Between Groups	5.373	3	1.791	5.381	0.001
	Within Groups	78.544	236	0.333		
	Total	83.917	239			
Ca	Between Groups	14.205	3	4.735	13.300	0.000
	Within Groups	84.024	236	0.356		
	Total	98.23	239			
Mg	Between Groups	2.496	3	0.832	6.334	0.000
	Within Groups	30.994	236	0.131		
	Total	33.489	239			

Table-4 Post Hoc Tests- Electrolytes mean difference by Multiple comparisons

Electrolytes	(I) GROUPS	(J) GROUPS	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Na	Baseline	F1	0.717	0.632	0.669	-0.918	2.351
		F2	0.833	0.632	0.552	-0.801	2.468
		F4	1.233	0.632	0.209	-0.401	2.868
	F1	Baseline	-0.717	0.632	0.669	-2.351	0.918
		F2	0.117	0.632	0.998	-1.518	1.751
		F4	0.517	0.632	0.846	-1.118	2.151
	F2	Baseline	-0.833	0.632	0.552	-2.468	0.801
		F1	-0.117	0.632	0.998	-1.751	1.518
		F4	0.4	0.632	0.921	-1.235	2.035
	F4	Baseline	-1.233	0.632	0.209	-2.868	0.401
		F1	-0.517	0.632	0.846	-2.151	1.118
		F2	-0.4	0.632	0.921	-2.035	1.235
K	Baseline	F1	-0.067	0.105	0.921	-0.339	0.206
		F2	0.1	0.105	0.778	-0.173	0.373
		F4	.3283*	0.105	0.011	0.056	0.601
	F1	Baseline	0.067	0.105	0.921	-0.206	0.339
		F2	0.167	0.105	0.391	-0.106	0.439
		F4	.3950*	0.105	0.001	0.122	0.668
	F2	Baseline	-0.1	0.105	0.778	-0.373	0.173
		F1	-0.167	0.105	0.391	-0.439	0.106
		F4	0.228	0.105	0.135	-0.044	0.501
	F4	Baseline	-.3283*	0.105	0.011	-0.601	-0.056
		F1	-.3950*	0.105	0.001	-0.668	-0.122
		F2	-0.228	0.105	0.135	-0.501	0.044
Ca	Baseline	F1	0.272	0.109	0.063	-0.01	0.554
		F2	.4133*	0.109	0.001	0.131	0.695
		F4	.6733*	0.109	0	0.391	0.955
	F1	Baseline	-0.272	0.109	0.063	-0.554	0.01
		F2	0.142	0.109	0.564	-0.14	0.424
		F4	.4017*	0.109	0.002	0.12	0.684
	F2	Baseline	-.4133*	0.109	0.001	-0.695	-0.131
		F1	-0.142	0.109	0.564	-0.424	0.14
		F4	0.26	0.109	0.082	-0.022	0.542
	F4	Baseline	-.6733*	0.109	0	-0.955	-0.391
		F1	-.4017*	0.109	0.002	-0.684	-0.12
		F2	-0.26	0.109	0.082	-0.542	0.022
Mg	Baseline	F1	-0.035	0.066	0.952	-0.206	0.136
		F2	0.118	0.066	0.281	-0.053	0.29
		F4	.2233*	0.066	0.005	0.052	0.395
	F1	Baseline	0.035	0.066	0.952	-0.136	0.206
		F2	0.153	0.066	0.097	-0.018	0.325
		F4	.2583*	0.066	0.001	0.087	0.43

	F2	Baseline	-0.118	0.066	0.281	-0.29	0.053
		F1	-0.153	0.066	0.097	-0.325	0.018
		F4	0.105	0.066	0.388	-0.066	0.276
	F4	Baseline	-.2233*	0.066	0.005	-0.395	-0.052
		F1	-.2583*	0.066	0.001	-0.43	-0.087
		F2	-0.105	0.066	0.388	-0.276	0.066