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Electrolyte Abnormalities in Patients Undergoing Concurrent Chemoradiation with Cisplatinin Head and Neck Malignancy

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ABSTRACT

INTRODUCTION: Head and Neck cancer accounts for 18.8% of total cancer burden India.Cisplatin based chemoradiation treatment is one among the standard treatment options for locally advanced head and neck cancer.Howeverciaplatin is associated with ototoxicity,nephrotoxicity and electrolyte abnormalities.The most common electrolyte abnormalities associated with cisplatin chemotherapy include hypomagnesemia, hyponatremia, hypokalemia, hypocalcemia and hypophosphatemia.Electrolyte abnormalities are frequent cause of hospital admissions and poor compliance to treatment.This study intends to find out the electrolyte abnormalities occurring with cisplatin in our clinical practice.

AIM: The aim of this study was to find out the electrolyte abnormalities occurring in radical chemo radiation with Cisplatin in head and neck malignancies treated at Malabar cancer Centre.

MATERIALS AND METHODS: This was a retrospective study of patients who underwent radical chemo radiation treatment with cisplatin for locally advanced carcinoma oropharynx, larynx, nasopharynx and hypopharynx.27 patients underwent radical chemo radiation with cisplatin during the study period.The study was carried out in the department of Radiation oncology Malabar Cancer Centre. The study Period was from May 2018 to July 2018 and the study population was the patients treated from January 2017 to December 2017.Case records and radiation charts were reviewed and necessary data was collected. Electrolyte abnormalities were graded according to Common Terminology Criteria for adverse events (CTCAE version4.0).

RESULTS: A total of 27 patients underwent radical chemo radiation with high dose cisplatin during the study period. Hyponatremia was the commonest electrolyte abnormality detected in the study group.20 out of 27 patients developed some grade of hyponatremia during the entire treatment period.Hyponatremia followed by hypomagnesaemia was the most common electrolyte abnormality encountered in our practice.Grade 4 Hyponatremia occurred in one patient which was medically managed and subsequent cycles could not be given.Grade 3 and grade 4 toxicities occurred mainly during second and third week of chemotherapy.No treatment related mortality occurred.

CONCLUSION: Cisplatin at a dose of 100mg/m2 appears preferable for definitive radio chemotherapy of locally advanced Squamous cell carcinoma head and neck. However, this regimen given every 3 weeks is associated with considerable acute toxicity including electrolyte abnormalities. Patients receiving this regimen needs close monitoring and timely supportive care.

KEY WORDS: Cisplatin, Head and neck malignancy, Electrolyte abnormality

I. INTRODUCTION

Head and Neck cancer accounts for 18.8% of total cancer burden India[1].In 2019 it is estimated that about 64,690 new cases of oral cavity, pharyngeal, and laryngeal cancers will occur[2]. Squamous cell carcinoma is the histologic type in more than 90% of these tumors.

ETIOLOGY AND RISK FACTORS

Alcohol and tobacco abuse are common etiologic factors in cancers of the oral cavity, oropharynx, hypopharynx, and larynx. Because the entire aero digestive tract epithelium may be exposed to these carcinogens, patients with head&neck cancers are at risk for developing second primary neoplasms of the head

&neck, lung, esophagus, and other sites.Smoking is identified as an independent risk factor in 80% to 90% of patients[3-5].Tobacco users have a fivefold to 25-fold higher risk of oral cavity and oropharyngeal cancer[6].Cessation of smoking is associated with a decline in the risk of cancer of the oral cavity. Abstaining from the use of cigarettes results in a 30% reduction in the risk of cancer in those who quit after 1 to 9 years; the risk is reduced by 50% in those who quit for more than 9 years[5].In India the habit of chewing betel nut leaves rolled with lime and tobacco which results in prolonged carcinogen exposure to the oral mucosa, is thought to be the leading cause of oral cancer.The practice of "reverse smoking" (smoking with the lighted end of the cigar in the mouth, also known as Chutta), peculiar to certain parts of India, is associatedwith an increase in cancer of the hard palate. The combineduse of alcohol and tobacco may have a synergistic effect on carcinogenesis[6].

Human papillomavirus (HPV) infection is well-accepted as a cause of squamous cancers of the oropharynx and emerging evidence shows that HPV infection may also be associated with increased risk of squamous cell carcinoma of the larynx[7-9].Patients with HPV-associated head and neck cancer tend to be younger. Oral HPV type16 infection increases risk of oropharyngeal cancer and a strong causal relationship has been established.HPV types 18, 31, and 33are responsible for the vast majority of the remaining fraction.

STAGING

Stage at diagnosis predicts survival rates and guides management in patients with head&neck cancers. The 2017 AJCC staging classification is used for head and neck cancers.[10] In general, stage I or II disease defines are relatively small primary tumor with no nodal involvement. Stage III orIVcancers generally include larger primary tumors, which may invade underlying structures and/or spread to regional nodes. Distant metastases are uncommon at presentation. More advanced stages are associated with worse survival.

DIAGNOSTIC WORK UP

Physical Examination

A complete examination of all mucosal head and neck sites should be performed in any patient with a known or suspected diagnosis of oropharyngeal cancer. This process not only characterizes the primary tumor but also evaluates for other malignancies given the high propensity for second primary upper aerodigestive tract tumors. A thorough physical examination is essential for diagnosis and understanding of the complete extent of disease, and it helps to guide the surgeon on the choice of optimal biopsy site.Careful examination of the neck is also important for staging and management. Palpation of the neck should focus on neck levels defined by standard anatomic relationships.Confirmatory biopsy of the primary site or the regional lymphadenopathy should be performed.

Endoscopy

Panendoscopy allows not only biopsy confirmation of the primary tumor site, but also mapping of the extent of the tumor as well as the ability to survey for synchronous primary tumors.

Computed Tomography

Computed tomography (CT) imaging of the head and neck with intravenous contrast should be performed for all newly diagnosed oropharyngeal cancer patients to assess the extent of primary tumors and to determine the presence or absence of cervical lymph node metastases. Scan slice thickness <5 mm is desirable to optimize the detection of smaller pathologically involved lymph nodes and to provide the best anatomic delineation of both primary and nodal disease. Pathologically involved lymph nodes are characterized on CT imaging as those that are enlarged, enhance with contrast, and have a necrotic center. Primary tumors appear as contrast-enhancing masses, distorting normal anatomic relationships.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) can be a useful imaging tool for oropharyngeal tumors. Squamous cell carcinoma appears as low signal in T1 MRI and corresponding high signal in T2 sequences. The ability of MRI to differentiate tumor from soft tissues is particularly useful when determination of the extent of base of tongue or oral tongue invasion is needed. Additionally, MRI is useful in patients with compromised renal function who are not able to receive iodine-based CT contrast agents.

Positron Emission Tomography

Positron emission tomography (PET) and/or PET/CT imaging incorporating tumor physiology in conjunction with anatomic information is another imaging modality available. From a practical standpoint, PET-based imaging can assess not only the locoregional burden of disease but also detect and quantify distant metastases. Also this can be utilized for radiation treatment planning.

MANAGEMENT APPROACHES

Treatment is complex for patients with head and neck cancers. The specific site of disease, stage, and pathologic findings guide treatment. Single-modality treatment with surgery or radiation therapy (RT) is generally recommended for the approximately 30% to 40% of patients who present with early-stage disease (stage I or II). The two most commonly employed modalities, surgery and RT, result in similar survival in these individuals. The choice of surgery or RT is often based on local institutional expertise and perceived relative morbidity of these treatment options. With evolving techniques of systemic therapy/Radiotherapy and less invasive surgery, morbidity is also a moving target. Combined modality therapy is generally recommended for the approximately 60%of patients with locally or regionally advanced disease at diagnosis.

Surgery

All patients should be evaluated by a surgical oncologist before treatment. In addition, it is critical that multidisciplinary evaluation and treatment be well coordinated. Minimally invasive surgery may be useful for decreasing morbidity. The unresectable tumors densely involve the cervical vertebrae, brachial plexus, deep muscles of the neck, or carotid artery. Tumor involvement of certain sites is associated with poor prognosis (ie, direct extension of neck disease to involve the external skin; direct extension to mediastinal structures, prevertebral fascia, or cervical vertebrae).Patients with resectable tumors who can also be adequately treated without surgery represent a very important group. Definitive treatment with RT alone or RT combined with systemic therapy may represent equivalent or preferable approaches to surgery in these individuals.

Head and Neck Radiation Therapy

Radiation Therapy for head and neck cancers has grown increasingly complex. The availability and technical precision of techniques such as intensity-modulated RT (IMRT) has markedly increased, perhaps beyond our ability to estimate the location of small sub sites of microscopic disease. A thorough understanding of natural history, anatomy, clinical circumstances, and imaging continue to guide the use of radiation as primary or adjuvant treatment.

Radiation Doses

Selection of radiation total dose depends on the primary tumor and neck node size, fractionation, and clinical circumstances, including whether to use concurrent systemic therapy. Target definition and delineation is crucial, and imaging should be used to ensure accurate radiation delivery.

When using conventional definitive fractionation, high risk sites like the primary tumor and involved lymph nodes generally require a total of 66Gy to 70Gy (2.0Gy/fraction)[11-13]. For doses greater than 70Gy fractionation should be slightly less than2.0Gy/fraction to minimize toxicity. External-beam radiation doses exceeding 72Gy using conventional fractionation (2.0 Gy/fraction) may lead to unacceptable rates of normal tissue injury. When using hyperfractionation, high-risk sites generally require up to 81.6Gy (1.2Gy/fraction)[11,6].In contrast, elective irradiation to low-risk and intermediate-risk sites requires 44Gy to 63Gy depending on the estimated level of tumor burden, and on whether 3D conformal RT(3DCRT) or IMRT(Intensity Modulated Radiotherapy) is used.

Fractionation in Concurrent Chemo radiation

Most published studies have used conventional fractionation (at 2.0Gy/fraction to a typical dose of 70Gy in 7 weeks) with single-agent high-dose cisplatin (given every 3 weeks at 100 mg/m2).Other fraction sizes (eg, 1.8 Gy, conventional), other dosing schedules of cisplatin, other single agents, multiagent systemic therapy, and altered fractionation with systemic therapy have been evaluated alone or in combination.

CISPALTIN

Cisplatin or cis-diamminedichloroplatinum is a highly effective chemotherapeutic drug whose anticancer activity was accidentally discovered by the physicist-biologist Barnett Rosenberg. Then, it has been used as a major antineoplastic drug for the treatment of diverse solid tumors[14]. Cisplatin is similar to the bifunctional alkylating agents. It covalently binds to DNA and disrupts DNA function. After cisplatin enters the cells, the chloride ligands are replaced by water molecules. This reaction results in the formation of positively charged platinum complexes that react with the nucleophilic sites on DNA. These platinum complexes covalently bind to DNA bases using intra-strand and inter-strand cross-links creating cisplatin-DNA adducts thus preventing DNA, RNA and protein synthesis. This action is cell cycle phase-nonspecific. Cisplatin also has immunosuppressive, radiosensitizing, and antimicrobial properties.However, the efficacy of cisplatin is limited by severe side effects, dose dependent, such as renal toxicity, Electrolyte imbalance, hematologic toxicity and emetogenicity.The molecular structure of cisplatin is shown in figure 1.

FIGURE NO:1

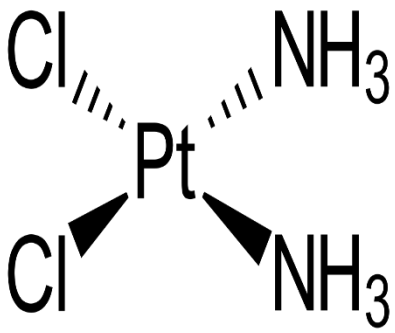

Figure no 1: Structure of cisplatin

ELECTROLYTE ABNORMALITIES IN CISPLATIN CHEMOTHERAPY

The most common electrolyte abnormalities associated with cisplatin chemotherapy include hypomagnesemia, hyponatremia, hypokalemia, hypocalcemia and hypophosphatemia.Normal adult values are given in Table No 1.

TABLE NO:1

	Normal range
Calcium	9-11g/dL
Potassium:	4.5-5.5 mEq/L
Phosphate	2.5- 4.5 mg/dL
Magnesium	1.5-2.5 mEq/L
Sodium	134-145 mEq/L

Table No 1:Normal adult values

Magnesium

Magnesium, or *Mg*, is another element that has a strong effect on muscle contractions**.** The normal plasma range for magnesium is 1.5-2.5 mEq/L. Platinum-induced hypomagnesemia, which has been reported to persist for up to 6 years after cessation of treatment, is primarily attributed to renal magnesium wasting and/or reduced intestinal absorption. Clinical signs include confusion, irritability, delirium, muscle tremors and tachyarrhythmias.

Sodium

Sodium, or *Na*, is one of the most important electrolytes in the body and is responsible for a number of important functions, mostly related to fluid and water regulation. **T**he normal accepted range for sodium is 134 to 145 mEq/L. Hyponatraemia is considered to be a serum sodium below 134 mEq/L. Common symptoms of hyponatraemia include confusion, agitation, nausea and vomiting, muscle weakness, spasms or cramps,irritability, drowsiness, irritability, lethargy and confusion.

Potassium

Potassium, is responsible for the functioning of excitable tissues such as skeletal and cardiac muscle and nerves**.** The normal range for potassium is 3.5 to 5.0mmol/L.***Hypokalaemia*** is defined as a serum potassium less than 3.5 mmol/L. A low serum potassium may be caused by decreased oral intake, increased renal or gastrointestinal loss of potassium, or a shift of potassium within the body's fluid compartments.Common clinical features of hypokalaemia range from muscle weakness and ileus (lack of peristalsis), to serious cardiac arrhythmias such as ventricular tachycardias.

Calcium

Calcium, or *Ca*, is an important element in the body as it helps to control nerve impulses, muscle contractions and has a role in clotting. The serum calcium range should be between 4.5-5.5 mEq/L when normal. Symptoms of hypocalcemia include tetany, mental changesand cardiac morbidity.

Phosphate

Normal phosphate concentrations are between 2.5 and 4.5 mg/dL.Potential mechanisms of hypophosphatemia (<2.5 mg/dL) in platinum-treated patients are low magnesium, increased renal excretion due to tubular dysfunction, decreased intestinal absorption from diarrhea, tumor growth (presumably due to consumption of phosphate by the tumor cells), nutrient deprivation from cachexia, hyperparathyroidism ,hypercalcemia of malignancy, alcoholism due to generalized proximal tubule dysfunction.

Cisplatin and Radiotherapy in the Treatment of Locally Advanced Head and Neck Cancer.

Definitive concurrent chemoradiotherapy is considered standard of care for inoperable locoregionally advanced head and neck squamous cell carcinomas. Cisplatin is the most common chemotherapeutic agent used in combination with radiotherapy. The underlying mechanism of cisplatin induced radiosensitization include inhibition of the repair of potentially lethal damage and sublethal damage, its ability to form DNA adducts and cell cycle arrest in G2 phase. The optimal regimen of concurrent cisplatin chemotherapy remains undefined, although the most robust evidence is the use of 100mg/m^2 cisplatin on a 3-weekly basis.However, this high dose cisplatin is associated with significant acute and late toxicities and the completion rate of the regime remains a challenge[15-19]. Due to significant toxicities and poor compliance, there has been a trend toward the use of low dose weekly cisplatin concurrently with radiotherapy.

We use cisplatinat a dose of 100mg/m2 as part of our departmental protocol in concurrent chemoradiation treatment of locally advanced head and neck malignancy.This study intends to find out the electrolyte imbalance associated with the above protocol.

II. AIMS

The aim of this study was to find out the electrolyte abnormalitiesoccuring in radical chemoradiation with cisplatin in head and neck malignancies treated at Malabar cancer Centre.

III. OBJECTIVES

The primary objective was to find out the electrolyte abnormalities occuring with high dose cisplatin.The secondary objective was to find out the percentage of each electrolyte abnormality and grading of each electrolyte abnormality.

Time of appearance of Grade 3 and Grade 4 toxicity**.**

IV. MATERIALS AND METHODS

This was a retrospective study of patients who underwent radical chemoradiation treatment with cisplatin for locally advanced carcinoma oropharynx, Larynx, Nasopharynx and hypopharynx. 27 patients underwent radical chemoradiation with cisplatin during the study period.The study was carried out in the department of radiation oncology Malabar Cancer Centre.

Case records and radiation charts were reviewed and necessary data was collected. Electrolyte abnormalities was graded according to Common Terminology Criteria for adverse events CTCAE version4.0[20].

The study was approved by the Institutional Review Board (Ethics committee approval waived of as this was a retrospective study).

V. GRADING OF ELECTROLYTE ABNORMALITY:

The grading of electolyte abnormality is in accordance with common terminology criteria for toxicity assessment version4.0(CTCAE).This is shown in Table No 2.

TABLE NO 2

ELECTROLYTE ABNORMALITY	GRADE1	GRADE 2	GRADE 3	GRADE 4	GRADE 5
HYPONATREMIA	>130mmol/L	-	120-130	<120	Death
HYPOKALEMIA	<3mmol/L	<3mmol/L Symptomatic,intervention indicated	<3mmol-2.5 Hospitalization indicated	<2.5 Life threatening	Death
HYPOMAGNESEMIA	<1.2mg/dL	<1.2-0.9mg/dL	<0.9-O.7mg/dL	<0.7mg/Dl Life threatening	Death
HYPOCALCEMIA	Corrected calcium level less than 8 mg/dL	Corrected calcium level 7-8mg/dl	Corrected calcium level 6-<7mg/dL	Corrected calcium level <6mg/dL	Death

Table 2. Grading of electrolyte abnormality

VI. RESULTS AND DISCUSSION

A total of 27 patients underwent radical chemoradiation with high dose cisplatin during the study period.

AGE DISTRIBUTION

Mean age of the study group was 57 years.The age distribution of study population is depicted in Figure No 2.

FIGURE NO:2

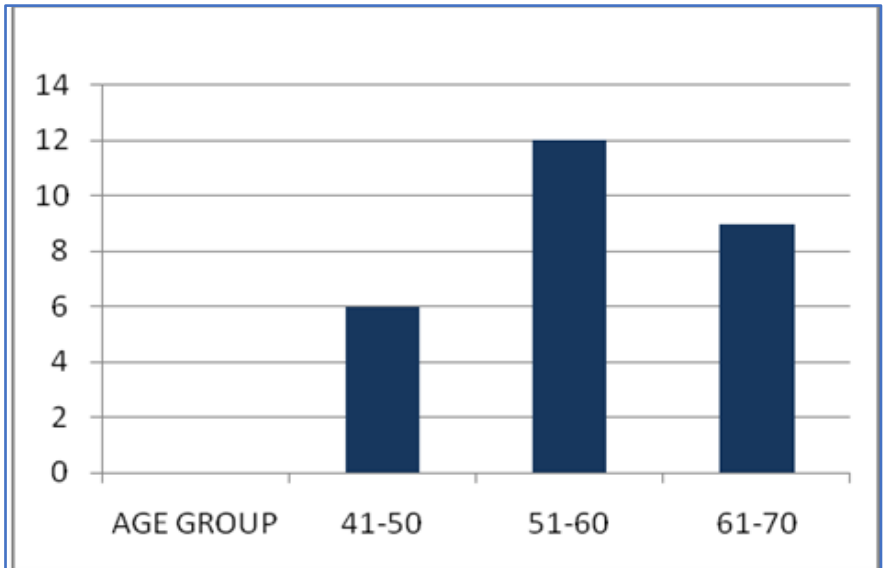

Figure No 2: Age distribution of study population

SEX DISTRIBUTION

Out of the total 27 patients , 24 were males and 4 were females.This is shown in Figure No 3.

FIGURE NO :3

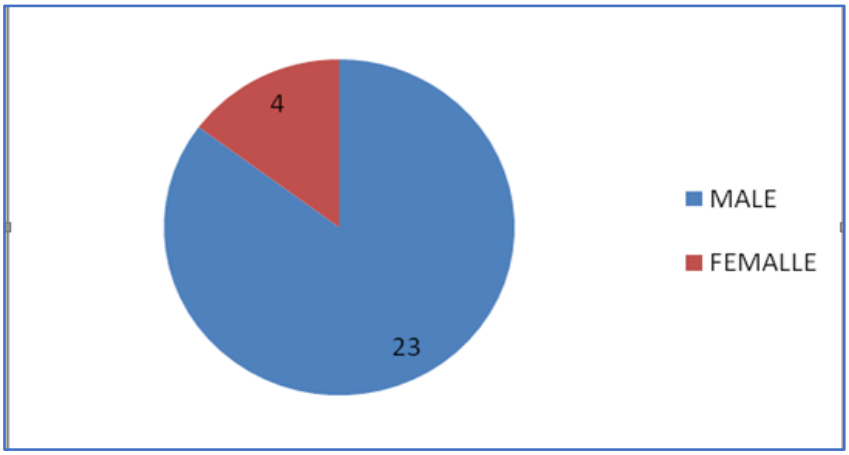

Figure No 3:Sex distribution of the population

PERFORMANCE STATUS

All had Eastern CoperativeOncology Group (ECOG) performance status one score.

COMORBIDITIES

Associated co morbidities were found for 7 patients out of total 27 patients.3 had diabetes mellitus,3 had hypertension and one had coronary artery disease as comorbidity.This is shown in Figure No 4.

FIGURE NO:4

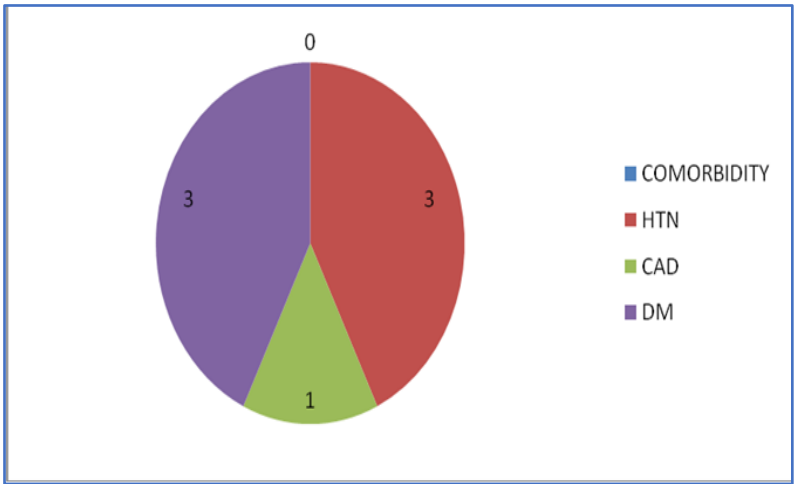

Figure No 4:Comorbidity

STAGE OF THE DISEASE

Majority were stage 1V A disease followed by stage 111 disease. One patient had stage 1V B disease.This is shown in Figure No 5.

FIGURE NO:5

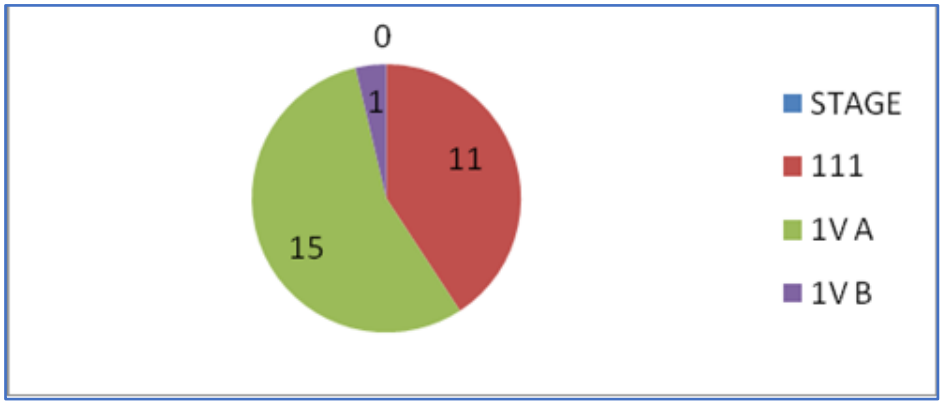

Figure No 5: Stage of the disease

SITE OF THE DISEASE

Among the head and neck subsites Carcinoma of Oropharynx constituted the majority followed by Carcinoma Hypopharynx.Other subsites include larynx and Nasopharynx.

TREATMENT

RADIATION

All patients were treated with Volumetric Arc Radiotherapy technique with the high risk volume receiving 69.3Gy,intermediate risk receiving 59.4 Gy and low risk receiving 54 Gy all in 33 fractions for 5 fractions per week.

All patients completed planned course of radiation treatment without any breaks.

NO OF CYCLES OF CHEMOTHERAPY RECEIVED

74% of patients received 2 cycles of cisplatin chemotherapy .All 3 cycles could be delivered only in 14%of patients.Reasons mainly being delay in starting first dose and issues with patient compliance.3 patients received only one cycle of chemo.Second dose could not be delivered in one patient since he had persistently low creatinine clearance and altered renal function which improved on conservative measures.Another patient developed active chest infection and pneumonia.So further chemo was not considered.However they completed the planned course of radiation treatment.One patient received only one cycle of chemo after which he was not willing for further chemotherapy.He also completed the radiation treatment.The total number of cycles of chemotherapy taken is shown in Figure No 5.

FIGURE NO:6

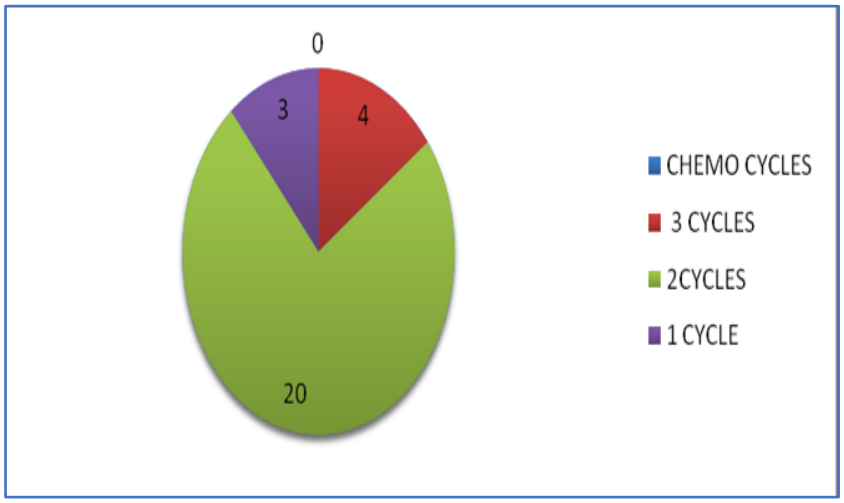

Figure No 6:No of cycles of chemotherapy taken

INCIDENCE OF ELECTROLYTE ABNORMALITY

The commonest electrolyte abnormality that we encountered was hyponatremia in 74% of patients followed by hypomagnesemia in 14% of patients.Incidence of electrolyte abnormality is shown in Figure No 7.

FIGURE NO:7

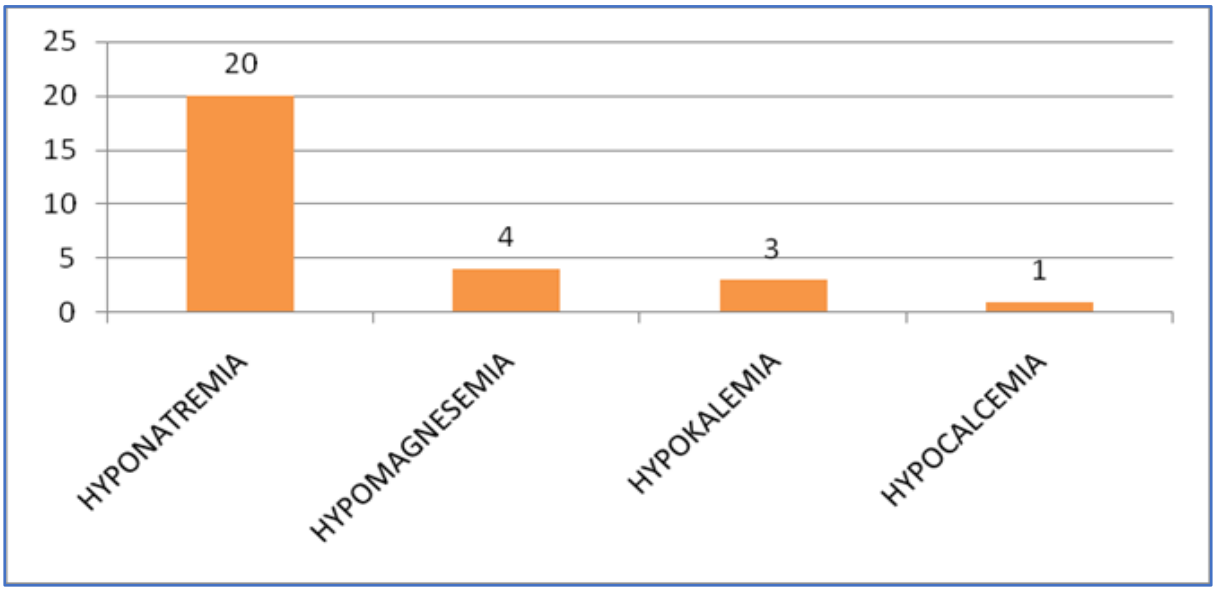

Figure No 7:Incidence of electrolyte abnormality

HYPONATREMIA

Hyponatremia was the commonest electrolyte abnormality detected in the study group.20 out of 27 patients developed some grade of hyponatremia during the entire treatment period.Out of the 20 patients grade 1 hyponatremia was found in 10 patients and grade 3 hyponatremia occurred in 9 patients.One patient had grade 4 hyponatremia which improved with medical measures.No grade 5 toxicity was encounterd.Grading of hyponatremia is shown in Figure No 8.

FIGURE NO:8

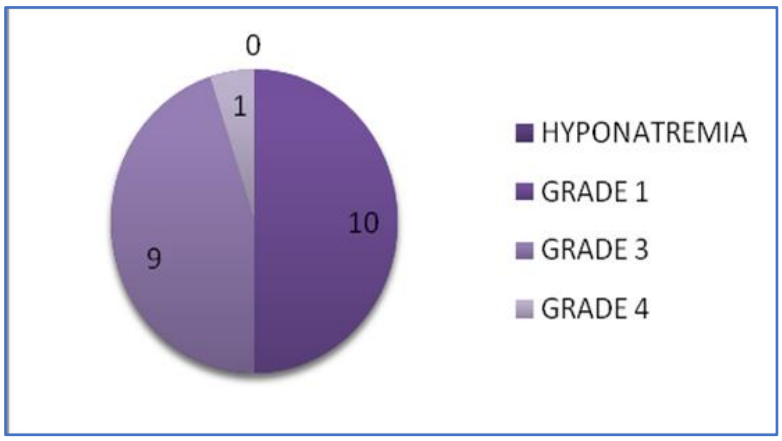

Figure No 8:Grades of hyponatremia

HYPOMAGNESEMIA

4 out of 27 patients had hypomagnesemia.3 were grade 1 and one was grade 2.No grade 3 or 4 toxicity occurred.

HYPOKALEMIA

Patients had hypokalemia of which two had grade 2 and one had grade 1 hypokalemia.
No grade 3 or 4 toxicity was noted.

HYPOCALCEMIA

Only one patient had grade 1 hypocalemia .No other grades occurred.

TIME OF OCCURRENCE

All toxicities occurred at second and third week post chemotherapy.

VII. DISCUSSION

27 patients underwent radical chemoradiation with cispaltin at a dose of 100mg/m2 during the study period.23 were males and 4 were females.All had Squamous cell carcinoma histology. Moderately differentiated squamous cell carcinoma was the most common histological grade .Among the head and neck subsites carcinoma of oropharynx constituted the majority followed by carcinoma Hypopharynx.59% had stage 111 disease and 33%had stage 1V disease at diagnosis. All 27 patients completed the planned course of radiation treatment without any significant breaks.Only 11% of patients were able to complete all three planned course of cisplatin. Reasons were mainly due to delay in starting first cycle of chemo,incidence of neutropenia,aspiration pneumonia and renal issues.70% of patients were able to complete 2 courses of cisplatin.25% of patients could take only one cycle of cisplatin. All tolerated chemotherapy well.Hyponatremia followed by hypomagnesemia was the most common electrolyte abnormality encounterd in our practice.Grade 4 hyponatremia occurred in one patient which was medically managed and subsequent cycles could not be given.No treatment related mortality occurred. In a study conducted in India by Anand et al the most common individual electrolyte abnormality seen was hypomagnesaemia, which was seen in 91.8% of patients, followed by hyponatremiain 88.2% hypocalcaemia in 70.6% and hypokalemia in 27.1%of patients.[21]

Ours is a tertiary cancer centre catering to the needs of a large population. Administering weekly chemotherapy in a resource constrained setting is of a little concern. Moreover three weekly cisplatin has demonstrated its superiority in various trials. Only issue is with the toxicity and tolerance profile. This study has shown that three weekly cisplatin was well tolerated. Atleast two cycles could be completed in 70% of patients accounting for a cumulative dose of 200mg/m2.This regime is feasible even in a resource constrained setting. Electrolyte abnormality was the cause of noncompliance to further chemotherapy in only one patient (who had grade 4 hyponatremia). The drawbacks of this study is that study population was not large enough to draw any conclusion regarding superiority of three weekly cispaltin. Large studies needs to be carried out before drawing conclusions regarding the same protocol.

VIII. CONCLUSION

Cisplatin at a dose of 100 mg/m2 appears preferable for definitive radiochemotherapy of locally advanced squamous cell carcinoma head and neck. However, this regimen given every 3 weeks is associated with considerable acute toxicity including electrolyte abnormalities. Patients receiving this regimen need close monitoring and timely supportive care.

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