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Appraisal of Beneficial Effects of Oral Supplementation with Folic Acid during Curative Chemo-Radiation for Head and Neck Cancer: An Observational Study

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Abstract

Background: In people undergoing curative radiation treatment to the head and neck region the local effects like mucositis, dysphasia, dermatitis, salivary dysfunction and systemic effects like anaemia and leucopoenia are major issues. Folic acid is always provided when a patient has anaemia and is also regularly used in the care of cancer patients. However, literature study indicates that the quantum of beneficial effects of folic acid supplementing to patients undergoing curative radiotherapy are lacking. In lieu of these observations the present study was conducted to ascertain the beneficial effect of folic acid supplementation to head and neck cancer (HNC) patients undergoing curative radiotherapy.

Methods: This was an observational study and was carried out in HNC patients planned for curative radiotherapy. The folic acid levels were estimated at the start of the study. Patients who had folic acid less than 20 ng/ml were prescribed folic acid (5 mg TID) for the first two weeks. The incidence of mucositis, dysphasia, dermatitis, salivary dysfunction, anaemia and leucopoenia were analysed at the end of the study. For analysis we studied what is the effect in people who had folic acid less than and, above 5 ng/ml and analysed the results using the X^2 analysis.

Results: The results indicated that there was a significant difference (p = 0.03) was seen in the incidence of leukopenia in the volunteers who had less than 5 ng/ml of folic acid. A significant difference in the incidence of severe dermatitis (P = 0.04) and in weight loss (P = 0.02) was also observed.

Conclusions: The study findings suggest that when compared to the patients who had folic acid less than 5 ng/ml, administering folic acid was beneficial in mitigating dermatitis, weight loss and leucopenia in people with folic acid above 5 ng/ml. More studies are required to ascertain the benefit of folic acid.

Keywords: ***Head and Neck Cancer; Radiation; Chemo-radiation; Folic acid; Weight loss; Leucopoenia; Mucositis; Dysphasia; Dermatitis; Salivary dysfunction***

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Introduction

Globally with an incidence of about 600,000 new cases, head and neck cancer (HNC) is annually the sixth most common cancer and leads to about 200,000 deaths [1]. On a geographical basis the incidence is very high in the Southeast Asia where tobacco abuse and alcohol consumption are the main risk factors [2]. With nearly 30% of all global cases, India is a major contributor to the global number [2,3]. It is the leading cancer in Indian men and the fifth most prevalent in females [2].

The most disturbing fact with regard to HNC is that that nearly two-thirds of all patients present in advanced stages of cancer when complete cure is difficult [2]. The other important observations are that most of the people afflicted with HNC are from the lower or lower-middle socio-economic class and many of these individuals may lack basic education and knowledge on diet [4].

Clinically, depending on the general health and the stage of the cancer, surgery, chemotherapy or radiotherapy may be used individually or in combination for curative or palliative purpose [5]. Of these external beam radiotherapy is an important treatment modality especially when the patient is debilitated and surgery difficult and to eliminate any residual cells following surgery [6]. When the treatment intent is curative, a dose of 60 to 70 Gy is used in fraction of 2 Gy every day for five consecutive days and 6 to 7 weeks with or without low doses of cisplatin or carboplatin [7].

On the downside, use of radiation (especially chemoradiation) is associated with adverse effects and when severe can cause treatment break and delay in completing the regimen [8]. In this regard the development of localised effects like mucositis, salivary dysfunction, dermatitis, dysphagia, weight loss and haematological changes like anaemia and leukopenia are important [9,10]. Of these, leukopenia is a feared adverse effect as it can increase the chances of infection and can consequentially increase morbidity, healthcare costs and can also cause death [11,12].

In adults, the process of lymphopoiesis occurs in the bone marrow and myriad growth factors and cytokines are involved in the intricate process [13, 14]. In addition to the various growth factors and cytokines, folic acid (generically also known as folate or folacin) also plays an important role [15,16]. Folic acid is water soluble, heat labile B-complex vitamin of dietary origin with important function in the body.

Folates are essential cofactors in metabolic pathways and their reduced forms are vital for facilitating methylation reactions in the synthesis of amino acids, purines, and DNA, and also in the formation and transfer of “one-carbon units” to purines and pyrimidines in the biosynthesis of nucleic acids [15,16]. Additionally, studies have also shown that a derailed folate metabolism can lead to hypomethylation, hyperhomocysteinemia, DNA damage, impaired cell proliferation and malignancy [15]. With respect to the dietary recommendations, the prescription dose of folic acid is in the range of 1-3 mg daily [15,17].

In the curative treatment for cancer of the head and neck, high doses of radiation is delivered to the cervical lymph nodes, located near to the carotid arteries and jugular vein through which substantial amounts of blood will be circulating through [12]. Lymphocytes are one of the highly radiosensitive cells and depending of the radiation dose delivered may undergo apoptosis or necrosis [18]. This will consequentially lead to leukopenia and aggravate the condition.

Literature studies and observations at our hospital have indicated that leukopenia is common in many cancer patients (at baseline) when treatment is yet to be initiated and also that administering cytotoxic treatment aggravates their health condition

[19, 20]. Folic acid is important in the synthesis of lymphoid cells and considering this we proposed to carry out a pilot study to ascertain whether oral supplementation of folic acid (5 mg TID for two weeks) would be useful in reducing the chances of radiation-induced leukopenia and treatment break.

Materials and Methods

Lymphopenia is a major issue and a feared side effect in the curative treatment of HNC with chemo-irradiation. This was a prospective observational study and was carried out to observe whether supplementation with folic acid is beneficial in mitigating lymphopenia. The inclusion criteria included people who were histopathologically confirmed to be affected by HNC and eligible to receive chemo-radiotherapy. Patients who had radical surgery for their HNC were also eligible provided the surgery was conducted atleast six weeks before the start of radiation treatment.

The exclusion criteria included patients less than 18 years of age; women with positive pregnancy test and lactating; patients with significant co morbidity such as (poorly controlled diabetes mellitus, hypertension, schizophrenia, bipolar disorders severe depression; tuberculosis, affected by haematological issues or any acute illness like malaria, dengue, leptospirosis, brucellosis, scrub typhus) and had received chemotherapy. Patients who have had oral surgery in less than 6 weeks, who have had chemotherapy within the last 6 weeks and previously treated with radiotherapy for cancers of their H&N regions, were excluded from the study.

Sample Size Calculation

$$N \geq \frac{Z^2_{1-\alpha/2} \times P(1-P)}{d^2}$$

The sample size was selected using the following formula: Where a = 0.05; estimated proportion (p) = 0.12 and estimated error (d) = 0.1 to give a sample size of 41. As attrition rate of 5% we considered to include a total 43 patients in the study.

Methodology

The study was carried out from March 1st to June 30th 2016 at Mangalore Institute of Oncology, Mangalore, India and in accordance to the guidelines stipulated by Helsinki Declaration and ICMR 2008 guidelines for research with humans after obtaining the approval from the hospital ethics committee. The volunteers included people diagnosed with HNC requiring curative radiotherapy, having blood folic acid levels < 5 ng/ml and willing to be part of the study. One of the authors explained the nature and purpose of the study to eligible patients satisfying the inclusion criteria, in either English or their mother tongue (Kannada, Tulu or Malayalam). The subjects were informed that they had the right to withdraw from the study at any time during the course of the study and that their non willingness to be a part of the study will not deprive them of the follow up investigations and medical care. The willing patients were then included in the study and a written informed consent was obtained.

Collection of Blood and Analysis

Five ml of peripheral blood was collected in vacutainer by a trained phlebotomist from willing volunteers using standard peripheral blood collection technique. The blood collected was analyzed for the standard haematological [red blood cells (RBC), haemoglobin (Hb), white blood cells (WBC), platelets (PLT)] and biochemical [AST,ALT] parameters for clinical

assessment before start of the radiation treatment. The blood remaining after the clinical examination was used to quantify the levels of folic acid.

Treatment with Folic Acid

All patients were prescribed to take 5 mg of folic acid thrice a day (morning, afternoon and evening) under the supervision of an oncology nurse. Aspects on drug-drug and drug food interaction were considered before the folic acid intake.

Radiation Treatment and Weekly Check up

All patients who participated in this study received external beam irradiation from a linear accelerator (Varian) of an energy level of 6 MV. The patients were treated every day with no more than one fraction of 2 Gy per day, five times a week without any intended gaps for a planned target dose of 60-70 Gy (six to seven consecutive weeks. Whenever chemo-irradiation was planned, cisplatin infusion (40 mg/m^2 IV) was administered on a weekly basis one hour before exposure to the first weekly radiation.

Clinical and Laboratory Examination during the Course of the Treatment

The clinical care of all patients were carried out by senior physicians and oncology nurses in accordance to the standard medical care. The radiation-induced adverse effects, haematological and biochemical changes were entered in the patient file on a regular basis in accordance to the standard guidelines [21,22].

Statistical Analysis

The accrued data were entered in to Microsoft excel and categorized as demographic details, clinical and investigative data. The data were then transferred to SPSS (IBM version 22) and calculated. The demographic and clinical details were subjected to the X^2 analysis. A statistical value of $p < 0.05$ was considered to be significant.

Results

The study was prospective and included the patients who satisfied the inclusion criteria and were willing to be a part of the study. A total of consecutive 43 patients satisfying the inclusion criteria were enrolled. Of these, 1 patient withdrew from the treatment in the fourth week on personal grounds. At the end of the study we had data of 42 patients and included them in the analysis.

The study proposed to analyse the results based on the levels of folic acid and there for were stratified as below 5 ng/ml (folic acid deficient) and above 5 ng/ml (folic acid proficient) group and the clinical end points were ascertained. A total of 24volunteers had folic acid below 5 ng/ml while 18 had above it.

The sociodemographic and the tumor details are enlisted in Table 1 while the clinical details before and after treatment are enlisted in (Table 2 and Table 3). The study had more males than the females and majority were mixed dietary in habit. The mean age of participants with folic acid below 5 ng/ml was 58.83 ± 11.18, while that of above 5 ng/ml was 55.38 ± 9.17. With regard to the cancer details most of the volunteers had stage 3 cancer (Table 1).

With reference to the alterations in the haemoglobin, total leucocytes count, plates, random blood sugar, creatinine and urea difference was seen in both the groups but was not significant (Table 2). In connection with treatment-induced ill effects, there

was no difference in the incidence in mucositis, dysphasia and salivary dysfunction, and in treatment breaks in the two cohorts (Table 3).

A noteworthy variation (p = 0.03) was seen in the incidence of leukopenia and high proportion (41.66%) was observed in volunteers who had less than 5 ng/ml of folic acid. In the study it was also observed that the volunteers who had higher levels of folic acid had lesser percentage of weight loss (9.29 ± 2.69 *vs.* 6.59 ± 4.05) and was significant (P = 0.02) (Table 3). A significant difference in the incidence of severe dermatitis was also seen between the two cohorts (P = 0.04) (Table 3).

		Less than 5 (N = 24)		More than 5 (N = 18)	
		Frequency	**Percentage**	**Frequency**	**Percentage**
Se	**Male**	11	61.11	13	54.17
	Female	7	38.89	11	61.11
Diet	**Vegetarian**	1	5.56	1	4.17
	Mixed	12	66.67	11	45.83
	Non vegetarian	11	61.11	6	25
Cancer site	**Base of tongue**	0	0	2	8.33
	Buccal mucosa	4	22.22	3	12.5
	Floor of the Mouth	1	5.56	1	4.17
	GBS	1	5.56	1	4.17
	Larynx	1	5.56	1	4.17
	Maxilla	1	5.56	0	0
	Oropharynx	1	5.56	0	0
	Post cricoid	1	5.56	1	4.17
	Parotid	1	5.56	1	4.17
	Pyriform sinus	1	5.56	1	4.17
	Tongue	2	11.11	2	8.33
	Vallecula	1	5.56	0	0
	Vocal cord	1	5.56	0	0
	Hypopharynx	3	16.67	3	12.5
	Naso pharynx	0	0	1	4.17
	Pharynx	5	27.78	1	4.17
Stage	**Stage 1**	1	5.55	0	0
	Stage 2	2	11.11	4	16.67
	Stage 3	12	66.66	9	37.5
	Stage 4	1	50	5	20.83

Table 1: The demographic and tumor details of the study volunteers.

	Below 5 Folic acid (N = 24)			More than 5 Folic acid (N = 18)		
	Before IR	**After IR**	**Percent Difference**	**Before IR**	**After IR**	**Percent Difference**
Hemoglobin	9.97 ± 2.51	10.09 ± 1.50	104.93 ± 24.24	10.22 ± 2.32	10.84 ± 1.38	110.49 ± 28.00
Total WBC count	7080.42 ± 2306.42	6447.62 ± 2793.98	100.17 ± 49.44	7606.67 ± 2073.13	7585.33 ± 1615.11	110.78 ± 37.71
Platelets	3.24 ± 1.58	2.66 ± 0.86	102.94 ± 67.18	3.40 ± 1.61	2.95 ± 0.85	101.25 ± 31.76
RBS	105.29 ± 22.24	109.95 ± 26.3	108.15 ± 30.41	128.05 ± 85.85	119.47 ± 46	111.3 ± 28.61
Creatinine	0.93 ± 0.23	1.04 ± 0.23	115.9 ± 32.96	1.01 ± 0.27	1.14 ± 0.28	116.06 ± 31.26
Urea	25.79 ± 6.8	27.29 ± 8.86	110.1 ± 39.69	29.11 ± 7.79	31.67 ± 11.26	113.96 ± 44.47
Weight change	48.92 ± 9.4	44.50 ± 9.39	4.42 ± 1.10	53.94 ± 12.3	50.61 ± 12.67	3.33 ± 1.81
% Weight decrease	100	90.70 ± 2.69	9.29 ± 2.69	100	93.40 ± 4.05	6.59 ± 4.05 **P = 0.02**

Table 2: Changes in the haematological parameters in the folic acid supplementation study.

	< 5 Folic acid (N = 24)		>5 Folic acid (N = 18)		
	Number	**%**	**Number**	**%**	
Treatment Break	10	41.66	5	27.77	P value = 0.35 X^2 value =0.86
Leucopoenia	10	41.66	2	11.11	P value = 0 .03 X^2 value = 4.70
Severe Mucositis	22	8.33	15	16.6	P value = 0.40 X^2 value = 0.68
Severe Salivary Dysfunction	23	95.83	16	88.89	P value = 0.38 X^2 value = 0.75
Severe Dysphagia	23	95.83	15	16.6	P value = 0.35 X^2 value = 0.85
Severe Dermatitis	22	91.67	11	61.11	P value = 0.04 X^2 value = 4.16

Table 3: Details on treatment breaks and the cause for it in the two folic acid supplementation stratification groups.

Discussion

Folic acid is an important vitamin for the human because we are unable to synthesize it and need to take it from dietary sources [15]. Folic acid deficiency is common and is common when its dietary intake is less, when the demands are high and supply less (like in pregnancy), when there is defects in utilization (in alcoholics) and in medical conditions like liver dysfunction, cancer or HIV [23].

Clinical studies have indicated that deficiency of folic acid increases chances of birth defects and low birth weight, cardiovascular disease, cancer and neuropsychiatric disorders [15,17]. With regard to cancer, folate deficiencies have been linked to genesis of cancers of colon [24], breast [25], pancreas [26], stomach [27], cervix [28], bronchus [29], and blood [30]. Folic acid is also shown to be useful in preventing contraceptive induced cervical dysplasia [31] and to protecting against ulcerative colitis-induced carcinogenesis [32].

In the treatment of Head and Neck cancer with radiation, leukopenia is arguably one of the most dangerous side effects because it increases the risk of infections and can in turn lead to death of the individual [33]. To further substantiate, reports indicate that leukopenia are independent biomarker for predicting survival in non-small cell lung cancer, gastric cancer, head and neck, breast cancer, Hodgkin's disease, and colorectal cancer and that severe leukopenia represents higher risk of death [11,12,33-39].

In the current study we attempted at understanding the beneficial effects of oral administration of 5 mg of folic acid thrice a day for two weeks in preventing the treatment breaks due to hemotoxic effects of radiation. The observations indicated that the folic acid intervention had beneficial effect in people who had a baseline value of >5 ng/ml of folic acid where 2 of the 18 volunteers (11.11%) did not have any treatment break due to hemotoxic effects. However in volunteers with folic acid less than 5 ng/ml, the beneficial effects was not prominent as 41.66% (10/24) had hemotoxic effects and was significant (P = 0.03).

The other important observation is that in the cohort where the baseline blood folic acid was greater than 5 ng/ml, the incidence of severe grade 3 and 4 dermatitis was less and was significant (Table 3). With regard to the role of folic acid in skin previous studies have shown that folic acid is important for skin homeostasis and that it serves to facilitate the cellular response following solar irradiation [40]. Studies have also shown that blood folic acid levels were less in people afflicted with atopic dermatitis [41] and basal cell carcinoma [42]. Additionally, folic acid supplementation is also shown to be beneficial in patients affected

by chronic inflammatory skin diseases, such as moderate to severe psoriasis [43] and to reduce the ill effects of methotrexate (without compromising the therapeutic effects)in psoriatic patients[44]. It lieu of all these observation it can be postulated that folic acid may trigger a similar underlying protective mechanism against the radiation damage and needs to be validated.

Conclusions

The observations from the pilot study are suggestive that oral administration of folic acid (5 mg TID for two weeks) was effective in reducing the incidence of treatment breaks due to leukopenia and radiation dermatitis in people who had blood folic acid above 5 ng/ml. The possible reason for this observation could be that in people with less than 5 ng/ml of folic acid, oral supplementation for two weeks was insufficient to elicit protective effects against radiation-induced leucopoenia. As far as the authors are aware of this is the first study in these lines and studies are underway to bridge the gaps in the lacunae. Efforts are underway to ascertain the most suitable dose and schedule of folic acid alone and in combination with vitamin B12 in preventing radiation-induced leucopoenia. In this regard the fact that folic acid is a FDA approved drug, in use in clinics and is relatively cheap is of added advantage in being of use in clinics in preventing and decreasing the incidence of treatment breaks and outcome.

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