



A PROSPECTIVE RANDOMIZED STUDY ON IMPACT OF POST-OPERATIVE ENTERAL NUTRITION ON CLINICAL OUTCOMES IN HEAD AND NECK CANCER PATIENTS

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ABSTRACT

Introduction:- Head and neck cancer patients have a high rate of complications and lead to significant malnutrition postoperatively. Arginine, L-Glutamine, Pro-biotics, Multivitamins with Enteral formula enriched diet (Immuno-nutrition) have shown promising results in decreasing complications and improving clinical outcomes in cancer patients. The aim of our study is to investigate whether postoperative nutrition of Head and Neck cancer patients, using home based feeding formula mixed with arginine (predominantly), glutamine, pro-biotics, multivitamins, etc. could improve nutritional variables as well as clinical outcomes, when compared with an iso-nitrogenous and iso-caloric control enteral diet without immune-nutrition. **Patients and Methods:** An accrual study was conducted in patients who had undergone head and neck cancer surgery and were administered enteral nutrition with immune-nutrition via naso-gastric tube postoperatively. A population of 60 patients with Head and Neck Cancers were enrolled for study. At surgery patients were randomly allocated to two groups and immune-nutrition was given to one group and nutritional and anthropometric assessment was done between the two groups. **Results:** The mean fall in values of Hemoglobin, Serum Albumin, Weight, Mid Arm Circumference (MAC), Mid Thigh Circumference (MTC), and Mid Calf Circumference (MCC). was significantly less in Supplement Group (Group 1). There was significant prevention of Post-operative complications like Fistula Formation, Wound Dehiscence, and Respiratory Tract Infections. Diarrhea, UTI and Length of Hospital Stay Post-operatively had no significant difference between the two groups. **Conclusions:** It can be concluded that patients supplemented with nutritional formula had lesser post-operative complications, better blood picture, lesser duration of hospital stay, less weight loss and less decrease in muscle mass in terms of Mid Arm Circumference (MAC), Mid Thigh Circumference (MTC), and Mid Calf Circumference (MCC). Overall better post-operative results were observed and hence better quality of life.

KEYWORDS : Head and Neck Cancers, Arginine , Immuno -nutrition, malnutrition.

INTRODUCTION

Cancer is a group of diseases characterized by the abnormal and rapid division of cells and has been the one of the leading cause of death in the India. ⁽¹⁾ Head and neck cancers are a grouping of oncologic diagnoses that can have significant repercussions with nutrition status due to the location of the disease.

Head and Neck cancer patients are hyper-metabolic and have elevated needs for calories and protein in the diet. According to European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines, calorie needs are often elevated to 25-30 calories per kilogram of body weight and protein needs are often estimated at 1.2-1.5 grams per kilogram of body weight⁽²⁾. It has been estimated that 3-52% of squamous cell carcinoma Head and Neck cancer patients are considered malnourished upon diagnosis. Malnutrition in these patients is associated with weight loss, reduced immune competence, increased risk of infections, increased treatment toxicities, and higher mortality risk. Between 20–50% of patients with high-risk for Head and Neck cancer will present with post-surgical complications such as Wound Infections/Dehiscence, Fistulas, Respiratory Tract Infections (RTI), Urinary Tract Infections (UTI), Diarrhea etc.

Most previous studies have used commercially available nutritional formulas which impose economic burden for poor population suffering from head and neck cancers. Hence we have used a homemade feeding formula combining seasonally available grains, fruits and vegetables supplemented with immuno-nutrition like arginine, glutamine, pro-biotics and multivitamins which are to be administered via naso-gastric tube in post-surgical head and

neck cancer patients.

The aim of our study is to investigate whether postoperative nutrition of head and neck cancer patients, using home based immune-nutrition formula comprising of arginine (predominantly), glutamine, pro-biotics, multivitamins, etc. could improve nutritional variables as well as clinical outcomes, when compared with an iso-nitrogenous and iso-caloric based control enteral diet.

Patients And Methods

A total of 60 patients were included on accrual in this study.

Inclusion Criteria

All patients with head and neck cancers coming to various units in Department of surgery. (Buccal Mucosa Cancers, Tongue Cancers, Lip Cancers, Hard and Soft Palate Cancers, Pharynx and Larynx Cancers.)

Exclusion Criteria

1. Severely impaired hepatic function (Total Bilirubin concentration >3.5mg/dl)
2. Nephropathy (serum creatinine >2.5mg/dl);
3. Ongoing infections;
4. Ongoing Steroid treatment for any other medical condition;
5. H/o Nutritional oral supplementation in the previous 6 months;

METHODS

A total of 60 patients were studied which were divided into 2 equal groups of 30 patients each post- surgery.

A. First the baseline (pre-operative) parameters i.e.

Hemoglobin(g/dl) , Total Leukocyte counts(per cubic mm), Serum Albumin(g/dl) ,Weight(kgs.), Mid- Arm circumference(cm.),Mid-Thigh circumference(cm.) , Mid-Calf circumference(cm.) were recorded for enrolled patients.

- B. Post- surgery patients were randomly allocated to two groups:
 - a) Group 1(supplement group) = 30 patients received an enteral diet supplemented with immune -nutrition { arginine , glutamine , pro-biotics, multivitamins };
 - b) Group 2(non-supplement group) =30 patients received an iso-caloric, iso-nitrogenous enteral formula (Non-supplement Group).
- All the patients were blinded to the treatment given.
- C. Enteral feeding was started from Post operative day-2 of surgery and 200ml of feeding formula was administered twice a day which was then increased to 5 times a day until daily nutritional goal (32 total kcal/kg; 1.7 g protein/kg) was achieved.

Feeding was done via an intra-operatively placed Naso-gastric Tube (16 Fr and larger).

All patients attained 100% of calculated requirements on postoperative day (POD-4).

- D. On post-operative day-6 Naso-gastric Tube was removed and enteral formula was continued per-orally till the patient was discharged.
- E. On Post operative day 7 / Day of discharge all above Lab values and anthropometric parameters were recorded to compare with baseline (pre-operative) values.
- F. All the above mentioned parameters were first compared within the group [post-op parameters vs. pre-operative parameters and the mean differences were compared between the two study groups.
- G. Data was then analyzed using student-t test and SPSS Software (Statistics v27 version)

- A. In all patients, antibiotic treatment was given for 7 days post-operatively (Amoxycillin + Clavulanic acid 1.2 g i.v. TDS and Ceftriaxone 1g i.v.BD).
- B. Other clinical modalities studied in two comparison groups were:-
 - Fistula Formation
 - Wound infection/ dehiscence
 - RTI
 - UTI
 - Diarrhea and
 - Post-operative Length of Hospital Stay.

Tube Feeding Formula

Prepared by blending and sieving of various ingredients mixed with water and milk to make it thin.

Daily calorie requirement for a adult male (60kg) is 2320 kcal/day.

Table 1:- Example Of Formula Feed To Be Administered Via NG Tube In Our Study

SR. NO.	INGREDIENTS.	K. CALORIES.
1.	White rice (1 Katori)	110
2.	Banana 1(Medium Sized)	100
3.	Mashed potato (100 grams.)	100
4.	Paneer (100 grams.)	265
5.	Dal water (1 Katori)	170
6.	Egg (Quantity 1)	70
7.	Vegetable oil (1 Table Spoon)	120
8.	Milk (1 Katori)	170
9.	Daliya (1 Cup)	220

10.	L-Arginine + L-Glutamine + Probiotics (1 sachet)	15 grams sachet
	Total calories (per-feed)	1325 k.cal per feed.

RESULTS

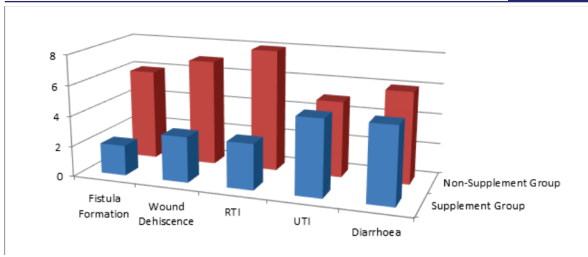
- The study involved total no. of 60 patients blindly randomized into 2 groups in an alternating manner. Patients were evaluated on multiple parameters.
- The majority of cases in Supplement Group were seen in age group of 50-59 yrs and in Non-Supplement Group were seen in age group of 50-59yrs.
- The mean age of patients in Supplement Group was 53.20 yrs and in Non-Supplement Group was 52.36 yrs.
- Among total subjects in supplement group 20 (66.7%) were males and 10 (33.3%) were females.
- Among total subjects in non-supplement group 19(63.3%) were male and 11(36.7%) were females.
- Mean Hemoglobin fall was significantly less in supplement group (0.4gm/dl) decrease and more in non-supplement group (1.1gm/dl) decrease t value =-2.790 and p = 0.009.
- Mean Serum Albumin fall was significantly less in supplement group (0.2mg/dl) decrease and more in non-supplement group (0.6mg/dl) decrease t value =-2.790 and p = 0.031.
- Mean Weight loss was significantly less in supplement group (0.8kg) decrease and more in non-supplement group (1.1kg) decrease With t value=-6.387&p=0.000.
- Mean Mid-Arm Circumference fall was significantly less in supplement group (0.5 cm.) decrease and more in non-supplement group (1.9cm.) decrease with t value = -6.387 &p value =0.000.
- Mean Mid- Thigh Circumference fall was significantly less in supplement group (0.2cm) decrease and more in non-supplement group (2.7cm.) decrease with t value =-6.387&p value =0.000.
- Mean Mid-Calf Circumference fall was significantly less in supplement group (0.8cm.) decrease and more in non-supplement group (2.3cm.) decrease with t value=-6.387&p value =0.000.

Table 2 : Comparison Of The Complications In Both Supplement And Non-supplement Groups.

Complications	Supplement Group (n=30)	Non-Supplement Group (n=30)
Fistula Formation	2	6
Wound Dehiscence	3	7
RTI	3	8
UTI	5	5
Diarrhoea	5	6

Complications

- There was a significant difference in prevention of Fistula Formation in supplement group 2(6.7%) when compared with non-supplement group 6(20%) with t-value =1.523&p value =0.002.
- There was a significant difference in prevention of wound dehiscence in supplement group 3 (10%) when compared with non-supplement group 7(23.3%) with t-value =1.385&p value =0.005.
- There was a significant difference in prevention of RTI in supplement group3 (10%) when compared with non-supplement group8 (26.7%) conditions, with t value =1.680&p value =0.002.
- There was No significant difference in prevention of UTI in supplement group 5(16.7%) when compared with non-supplement group 5(16.7%) conditions, t-value =1.523&p value =1.000.
- There was No significant difference in prevention of Diarrhea in supplement group 5 (16.7%) when compared with non-supplement group6(20%) conditions, with t value =0.328, p value =0.513.



Graph 1: Comparison Of The Complications In Both Supplement And Non-Supplement Groups.

The graph clearly shows that there is more rate of complications in non-supplement group when compared with supplemented groups.

- The mean length of hospital stay in supplement group was 12.30 days and in non-supplement group was 13.16 days. The maximum and minimum days of hospital stay in supplement group were 10 days and 15 days respectively.
- The maximum and minimum days of hospital stay in non-supplement group were 10 days and 16 days respectively.
- Length of hospital stay is less in supplemented group (mean stay = 12.30 days) when compared to non-supplemented group (mean stay = 13.16 days)

There was no significant difference in length of hospital stay in supplement group when compared with non-supplement group.

DISCUSSION

Head and neck cancer patients are at high nutritional risk due to locations of tumor burden and treatment impact. Enteral nutrition is often implemented for these same reasons, especially with surgical intervention. The optimal regimen and timing of enteral nutrition in this population is still under investigation. (4)The greatest variation between studies is the timing of the immuno-nutrition intervention. Mueller et al. (2019) focused on preoperative intervention. (5) Buijs et al. (2010) and Falawee et al. (2013) focused on peri-operative intervention. Lastly, Azman et al. (2015), Barajas-Galindo et al. (2019), and De Luis et al. (2013) focused on postoperative supplement with immune-nutrition. The review by Vidal-Casariago et al. (2014) included many studies, all of which were either perioperative or postoperative interventions. The findings of each article varied due to different outcomes of interest, but overall a correlation was found between immune-nutrition in the peri-operative or postoperative phase and improvement in post-surgical outcomes and length of stay. Article design also varied greatly, with most articles being prospective randomized non supplement trials or retrospective with historical cohorts.

These positive correlations were noted across immunonutrients, although most research being reviewed included arginine. Barajas-Galindo et al. (2019), Buijs et al. (2010), Falawee et al. (2013) and Vidal-Casariago et al. (2014) studies included arginine alone. Azman et al. (2015) investigated glutamine alone and De Luis et al. (2013) investigated w3 fatty acids alone. Mueller et al. (2019) studied a combination of arginine and w3 fatty acids together. All studies were conducted on adult patients and occurred in the past 20 years. In our study, Head and Neck Cancer patients admitted recruited for study were in patients who underwent surgery were administered immune-nutrition post-operatively and effects were compared between supplement and non-supplement groups. This study analysis is aimed to investigate the impact of immune-nutrition implementation in the postoperative phase may have on the outcomes of patients in post-operative period.

Age Distribution

In a study by Syndermann et al (6) was mean age was 63yrs in

supplement group and 61yrs in non-supplement group respectively where as in our study the majority of cases in Supplement as well as non-supplement Group were seen in age range of 50-59 yrs with mean age of patients in Supplement Group being 53.20 yrs. and 52.36 yrs. in non-supplement group.

Mean Weight

Research studies by Syndermann et al were done on the mean weight of 71 kg in supplement group and 67 kg in non-supplement group respectively where as in our study the mean weight of patients in Supplement Group was 58.66kg. and 58.13kg. in non-supplement group. Similarly in the studies of Riso et al, De Luis et al, and Felekis et al, the mean weight of patients in supplement group and non supplement group is less than our study as shown in the table below :-

Fistula Formation

In our study Fistula Formation observed in patients of supplement group is less i.e. 2(6.7%) as compared to 6(20%) in non-supplement group with t value = 1.523 , p value = 0.002 (significant). Hence, there was a significant difference in prevention of fistula formation in supplement group as compared to non-supplement group. In study by Syndermann et al however it was reported that incidence of fistula formation in supplement group is 4.8% which is higher in comparison to the lower 2.1% in non supplement group. Although in other studies reported by Sorensen et al (8), Felekis et al (9), Falawee et al, incidence of fistula formation is lower in supplement group which is in agreement with findings of our study as shown the table below :

Table 3:- Percentage Of Patients With Fistula Formation In Supplement And Non-Supplement Groups.

Study	Supplement group	Non supplement group
This study	6.7%	20%
Snyderman et al	4.8%	2.1%
Sorensen et al	0 %	28.5%
Felekis et al	0%	10%
Falawee et al	8.6%	6.6%

Wound infection / dehiscence:- In our study Wound Dehiscence occurred in patients of supplement group is less i.e. 3(10%) as compared to 7(23.3%) in non-supplement group with t value = 1.385, p value = 0.005 (significant). Hence, there was a significant difference in prevention of wound dehiscence in supplement group when compared with non-supplement group conditions. This is in agreement with study of Falawee et al which also reported similar result.

Postoperative length of hospital stay:- In our study, mean length of hospital stay in supplement group is 12.30 days. The maximum and minimum days of hospital stay in supplement group were 15 days and 10 days respectively. Length of hospital stay is less in supplemented group (mean stay = 12.30 days)

The mean length of hospital stay in non-supplement group is 13.16 days.

The maximum and minimum days of hospital stay in non-supplement group were 16 days and 10 days respectively. Length of hospital stay is more in non-supplemented group (mean stay = 13.16 days) Using Levene's Test for Equality of Variances and t-test for Equality of Means, this is statistically insignificant as (t = -1.993) and (p = 0.754) (p > 0.05). This result is comparable with studies reported by Syndermann et al Falawee et al (10), Ghosh et al (11) and Turnock et al (12) as shown in the table.

Table 4:- Comparison Of Post-operative Length Of Hospital Stay In Supplement And Non-Supplement Groups.

Study	Supplement group Mean stay (in days)	Non-Supplement group Mean stay (in days)	P - value

This study	12.30	13.16	0.75
Syndermann et al	15.3	17.4	0.83
Falewee et al	23.6	22.3	1.13
Ghosh et al	31.1	35.3	0.89
Turnock et al	18	18.5	0.74

Limitation Of Current Literature

There are several limitations in the current literature. The primary limitation is the scarcity of studies available that investigate immune-nutrition in the adult head and neck cancer surgery population. Even though this population is at great nutritional risk, the research has not been prevalent in immuno-nutrition interventions. In addition to the number of studies available in current research, another limitation is that in most of the studies that have been conducted have limited subject sample size which could be attributed to high mortality in cancer care. Lastly, another limitation is that most studies included arginine as a component of the immunonutrition regimen. It is yet to be determined whether arginine is essential in showing benefits of immunonutrition, or if any immunonutrient will produce the same results. Each of these limitations in the current literature will need to be addressed by future research in order to appropriately apply findings to clinical practice.

CONCLUSION

After the analysis of data, it can be concluded that patients supplemented with nutritional formula had lesser post-operative complications, better blood picture, lesser duration of hospital stay, less weight loss and less decrease in muscle mass in terms of MAC, MTC, MCC. Overall better post-operative results were observed and hence better quality of life.

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