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ROLE OF LOW LEVEL LASER THERAPY IN ORAL MUCOSITIS IN PATIENTS UNDERGOING CONCURRENT CHEMORADIATION

Oncology

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ABSTRACT

Background: Radiotherapy (RT) has been the traditional treatment approach for head and neck carcinoma (HNC) and has resulted in both excellent control rates and function preservation. Oral mucositis (OM) is a frequent, severe toxicity in patients treated with RT and may lead to hospitalization and the treatment interruptions, which influences quality of life. The aim of our study is to assess effect of low level laser therapy (LLLT) in the treatment of OM.

Materials And Methods: A prospective single arm study was conducted on 23 patients of locally advanced HNC undergoing chemoradiation.Grade 2 mucositis onwards (RTOG grading) were exposed to low LLLT in a scanning motion 3-5 times weekly for 4 weeks Patients were assessed with intra oral photographs and Visual Analogue Score (VAS) questionnaire was used before and after LLLT to assess pain.

Results: Eleven patients (47%) received 7 to 10 sessions of LLLT. Fifteen (65%) patients had grade three and seven (30%) had grade 2 before LLLT. Eleven and eight patients had grade 2 and 1 respectively after LLLT (p=0.007). Mean VAS score before and after LLLT was 6.32 and 3.32 respectively ($p < 0.01$)

Conclusion: LLLT is an effective intervention in patients with Grade 2 and 3 OM, both in terms of subjective and objective improvement.

KEYWORDS

Head and Neck cancer, Chemoradiation, Oral mucositis, Laser therapy.

INTRODUCTION

Head-and-neck cancer (HNC) is the most common malignancy according to GLOBOCAN 2018 report, worldwide HNC statistics indicate that there are 834,860 cases of HNC per year, resulting in approximately 431,131 deaths per year. High incidence rates have been reported from developing countries including India, Pakistan, Bangladesh, Taiwan, and Sri Lanka [1]. HNCs account for approximately 30–40% of all cancer sites, in India [2].

OM is by far the most common toxicity of chemo-radiation in HNCs. Not only does it cause severe pain and dysfunction but also it causes severe swallowing difficulties, which lead to frequent treatment interruptions and delay. This, finally adversely affects the outcome of the disease. OM includes symptoms like dryness, halitosis, pain, inflammation and oral mucosal ulceration, usually start after second week of radiotherapy and first cycle after chemotherapy [3]. Adequate prophylaxis and treatment may limit the severity of radiation mucositis and improve compliance to radiation which may translate in better disease control and survival [4]. Some of the treatments tried for prevention and treatment of OM are normal saline and alkali (soda bicarbonate) mouth washes, low level laser therapy, and benzydamine (non-steroidal analgesic and anti-inflammatory) have effectiveness in the prevention and treatment of radiation induced OM. Treatment of co-existing infection is also important and both topical (povidone iodine) and systemic anti fungals should be used judiciously. Although several agents have been tried, there is no standard guideline or recommendation for the treatment of chemoradiation-induced OM in HNC.

One of the most recent and promising modality of treatment proposed and used in the chemoradiation induced OM is LLLT which is a form of light therapy that utilizes non-ionizing light sources like Lasers in the visible (400 – 700 nm) and near-infrared (700 – 1100 nm) of electromagnetic spectrum[5].

Photobiomodulation is a process involving endogenous chromophores eliciting photophysical and photochemical events at various biological scales. Low level lasers - red non-surgical wavelengths of 635 nm and 655 nm for photo-bio modulation and output powers vary from from 50 to 500 mW with either pulse or continuous mode [6].

The aim of this prospective study is to evaluate the effectiveness of LLLT treatment for Chemo-radiation induced OM, in HNCs.

MATERIALS AND METHODS

A prospective single arm study was conducted on 23 patients who were locally advanced HNC with histologically proven squamous cell carcinoma of Oral cavity and oropharyngeal carcinomas undergoing radiotherapy with or without concurrent chemotherapy between December 2019 and December 2020. Based on a study done by Rezk-Allah et al., accepting 80% power, 95% confidence level and with effect size of 0.61, a Sample size of 23 was decided[7].

Patients who underwent neo-adjuvant chemotherapy; who have history of previous malignancy over the last 5 years severe allergy to platinum salts; pregnancy or breast feeding were excluded from the study. History of any coagulative disorders were also excluded from our study.

RT was used either in radical or adjuvant setting, with or without concurrent chemotherapy between December 2019 and December 2020, after institutional ethical committee clearance and an informed consent. The radiation dose to HRCTV was 60-66 Gy and LRCTV/IRCTV was 50-54Gy in 1.8-2.2 Gy/ fraction using SIB IMRT technique delivered 5 fractions in a week. Concurrent chemotherapy was weekly cisplatin (40mg/m^2 of BSA) or Carboplatin (AUC5).

Tumor (site, TNM stage) and patients (age, sex, comorbidities, predisposing risk factors for OM i.e ill-fitting dentures, tobacco or smoking habits, previous history of irradiation) characteristics were noted.

All patients were monitored once a week and graded for OM using RTOG grading system and VAS for rating pain were documented pre- and post-laser therapy.

Patients who developed Grade 2 to Grade 3 OM (RTOG grading) during the course of treatment were irradiated with low level laser in a scanning motion 2-5 times weekly for 4 weeks using wavelength - 660nm, power-50mW, spot energy-4J, irradiation time-80 sec. Patients were also assessed pre, during and post laser therapy using intra oral photographs.

Treatment tolerance in terms of not completing planned treatment, need for feeding procedure, and unplanned treatment breaks were assessed. The reasons for treatment breaks were noted. The first follow up was at 2 weeks after completion of treatment. Thereafter patients were followed up at 3 months interval for 1 year. Any recurrence or death during follow up was noted.

All the quantitative variables were summarized using a descriptive statistics such as mean and standard deviation and analyzed using SPSS software version 24. Categorical data was compared using fisher exact test while continuous data was compared with the help of paired t test. A p value < 0.05 was considered to be statistically significant.

RESULTS

The patient, tumor and treatment characteristics are shown in table 1. As given in table 2, 15 (65%) patients had grade 3 mucositis, seven (30%) had grade 2 mucositis and one (5%) patient had grade 4 mucositis before laser therapy. One patient with grade 4 mucositis received only 1 session; 4 patients with grade 3 mucositis received 2 sessions and showed complete regression in mucositis after 2 sittings of LLLT. Three patients with grade 2 mucositis needed additional 2 sittings for complete regression of OM; eight patients with grade 3 mucositis received 3 sessions.

Post laser therapy; one patient with grade 4 mucositis before laser therapy remained grade 4, three (13.04%) remained grade 3 mucositis; eleven (47.8 %) patients showed grade 2 mucositis. Using fisher exact test, it was analysed, all patients with Grade 3 and 2 mucositis, showed significant reduction in mucositis (p=0.007). It was seen that there was improvement in mucositis even after the 2nd sitting of LLLT.

Using t test, visual analogue score (VAS) was compared between pre and post laser therapy. Average VAS was 6.32 ± 1.39 SD, 4.81 ± 2.17, 3.32 ± 2.03 pre laser therapy, post 2 sessions and more than 2 sessions of laser therapy respectively. Statistical significance observed were p=0.07 (pre vs post 2 sessions) and p=0.01(pre vs post more than 2 session) (table 3).

Two patients had treatment breaks, out of which, one patient with grade 3 mucositis had treatment interruption of 6 days after which, radiotherapy was restarted after reduction in OM, one patient with grade 4 mucositis had received only one session and discontinued for personal reasons and later patient died due to aspiration pneumonia. Treatment was not suspended in rest of the patients.

Table-1: Patient, Tumor And Treatment Characteristics

Patient characteristics	Frequency (n) (%)
Age	
< 40	1(4.3%)
40-50	3(13%)
51-60	10(43 %)
61-70	7(30%)
>70	2(16%)
Sex	
Male	5 (52%)
Female	11(48%)
ECOG	
0	4 (17.3%)
1	12 (52.1%)
2	6 (26%)
3	1 (4.3%)

Tumor characteristics	Frequency (n) (%)
T stage	
1	1 (4.3%)
2	5 (21%)
3	11 (47%)
4	5 (21%)
N stage	
0	12(52.17%)
1	3 (13%)
2	6 (26%)
3	2(8.6%)
Overall stage	
I	1 (4.3%)
II	1 (4.3%)
III	16(69%)
IV	5 (21%)
Treatment site	
Tongue	3 (17.3%)
Buccal mucosa	16 (69.5%)
Hard Palate	1 (4.3%)
FOM	1 (17%)
Maxilla	1(4.3%)
Parotid	1(4.3%)

Treatment characteristics	Frequency (n) (%)
Treatment given	
Sx+RT	14 (60.8%)
Sx+RT+CT	2 (8.6%)
RT+CT	6 (26%)
RT alone	1 (4.3%)
No of chemo cycles	
Nil	15 (65%)
</=3	5 (21%)
>/= 4	3 (13%)
Radiation dose	
60 Gy	18(78%)
66Gy	5(21%)
Feeding procedure	
Ryles tube	3 (13.04%)
Peg tube	0
Nil	20 (86.9%)
Completed Rx	
Yes	21(91.3%)
No	2(8.6%)
Use of Analgesics	
Non-Opioids	11(47.8%)
Opioids	2(8.6%)

Table 2: Grade Of Mucositis Before And After Laser Therapy

Grade of Mucositis	Pre Laser Therapy		Post Laser Therapy		Fisher Exact Test	p value
	N	%	N	%		
Grade 1	0	0	8	34.78	1.79	0.007*
Grade 2	7	30.4	11	47.83		
Grade 3	15	65	3	13.04		
Grade 4	1	4.34	1	4.34		

*: statistically significant

Table 3: Comparison Of VAS Score Before And After Laser Therapy

Interval	Mean	SD	Pre vs Post laser (Only 2 Sessions)		Pre vs Post Laser (After >2 Sessions)	
			t test	p value	T test	P value
Pre-Laser	6.32	1.39	2.81	0.007*		
Post-Laser					5.85	<0.01*
Only 2 Sessions	4.81	2.17				
>2 Sessions	3.32	2.03				

*: statistically significant

DISCUSSION

This is a prospective single arm study done on HNC patients receiving definitive or adjuvant radiotherapy with or without chemotherapy, to assess the effect of LLLT in radiation induced OM. Similarly Y zadik et al conducted systematic review and meta-analysis on 7 studies and showed that application of LLLT in patients on radiotherapy is nearly 9 times more effective to prevent OM of grade >3 than in patients who did not receive laser therapy[5]. M. Schubert in his study concluded that 650 nm wavelength reduced the severity of OM and pain scores. LLLT was well-tolerated and no adverse events were noted [8]. In our present study we used 660 nm / 50 mW showed no adverse events on 1 year follow however long follow up is required to comment on long term side effects.

Objective evaluation of severity of OM and correlation with various markers were done in a study by Oton-Leite et al [9]. There was a trend for reduced levels of IL-1β, TNF-α, IL-10, TGF-β, MMP2/TIMP2, MMP9/TIMP2 in the laser group compared to the control but was not statistically significant. In our study, severity of OM was assessed clinically by RTOG grading scales and VAS based pain score and we did not correlate with any biomarkers because of the financial issues.

Study by F.Arbabi-Kalati et al measured the intensity of pain with visual analogue score and he concluded that low-power laser decreases the intensity of mucositis [10]. Study Gouvea De LimaIt observed better outcomes in the laser group when compared with the control in the follow-up sessions, indicating lower degrees of OM, pain and higher salivary flow (p <.05)[11]. These findings support the use of laser therapy as an adjuvant treatment for the control of oral complications. We measured intensity of pain with VAS and found that mean VAS reduced significantly from 6.3 to 3.3(p 0.002).

A. Gautam et al, in his study also concluded that Low Level He-Ne Laser significantly decreased the incidence of chemoradiation induced severe OM and its associated pain, opioid analgesic use (p.039) and use of total parenteral nutrition was significantly less in laser group [12]. We observed that out of eleven patients only 2 required opioids and seven patients switched over to lower analgesics after LLLT.

Unplanned treatment interruptions resulting in prolongation of the overall treatment time gives a negative impact on the tumor control [13, 14].In our study, grade of mucositis improved with LLLT, almost all patients completed treatment on time.

Similar results were observed by a phase III RCT by Gouvea De LimaIt et al that although LLLT didn't reduce the incidence of severe OM, it reduced the treatment interruptions due to OM and better long term outcomes can be expected [15].

LLLT has been used to prevent OM. Arora. H et al [16] tried low level He-Ne Laser in prevention of OM and concluded that patients who received LLLT had lesser incidence of OM (p .019 at 6th week). Simões A et al [17], analysed the role of two different powers of lasers and three different schedules (3 vs 1 sitting/week). They observed that the pain relief was better in 3 sittings per week (p 0.011). Oberoi V et al [18] have done a systematic review and meta analysis on 18 studies on the effect of LLLT on OM and concluded that prophylactic LLLT reduces the incidence of severe OM compared to no LLLT (p .001).

The strengths of our study are that it is a prospective study and we assessed objective as well as subjective relief in resolution of OM. The limitations are the lesser sample size and shorter follow up.

CONCLUSION

Low Level Laser Therapy was found to be an effective treatment of OM in terms of subjective as well as objective improvement. It is also cost effective and an outpatient treatment and hence can be easily incorporated as a protocol for patients undergoing chemoradiation for HNC.

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