CHAPTER V

DISCUSSION AND CONCLUSIONS

A detailed description of what we infer from the results analysis along with supporting evidence pertaining to Low-level laser therapy for prevention and treatment of oral mucositis are explained in this chapter. This is to give a clear picture about the existing evidence regarding our study.
5.1 DISCUSSION

Oral mucositis (OM) is the most burdensome acute side-effect in patients undergoing concurrent chemoradiation for Head and Neck Cancer. Various pharmacological and non-pharmacological modalities were used to prevent and treat OM caused by various cancer therapies, but none proved to be completely effective till date. FDA has approved only Palifermin for prevention of OM in Hematopoietic Stem Cell Transplant settings. Recent evidence is accumulating on the beneficial effects of low-level laser therapy as a physical modality for OM. Application of laser requires skilled professional to deliver the desired dosage to get appropriate therapeutic response. Therefore, we did this study to know and quantify the beneficial effects of LLLT when used prophylactically for the prevention and treatment of CCRT induced OM and its associated morbidities. To our knowledge, our study seems to be the largest study to date which investigated the effects of LLLT on CCRT induced oral mucositis and its associated morbidities in head and neck cancer patients. Also, our study seems to be the only randomized controlled trial which evaluated the effects of LLLT on patient’s subjective experience of OM and QOL in the largest number of HNC patients receiving CCRT. All the patients tolerated LLLT with ease and no adverse events were reported by any of the participant.

In this trial, we observed that though laser was not able to completely prevent the oral mucositis, but it significantly reduced the incidence of severe grades OM. Patients experienced less severe oral mucositis associated oral pain and swallowing difficulty in laser than control group. Need for supplement analgesics and total parenteral nutrition was also less in laser than control group patients. Loss of weight was also lesser in laser than control group patients. Patients in both the groups experienced significant weight loss from the baseline, but it was not
significant while comparing between the groups. In addition, LLLT was effective in improving the patient’s subjective experience of OM as well as QOL in HNC patients receiving CCRT.

5.2 LASER EFFECTS ON ORAL MUCOSITIS

Though almost every patient developed mucositis during the course of CCRT, but progression of oral mucositis towards higher grades was significantly slower in laser than control group patients. (Table 3, Figure 6) Also, patients in laser group experienced severe grades of OM for lesser duration than control group.

Professor **Endre Mester**, first introduced the Low-level laser in medicine in late 1960s. Since then, it is being used widely in several medical conditions like wound healing, pain relief and various dental conditions. Laser therapy is already established as a therapeutic modality for wound healing, various acute and chronic pain conditions. LLLT for cancer therapies induced OM is being used since 1990s. In early 1990s few studies reported improvement in chemotherapy induced OM.

The mechanisms proposed for therapeutic effects of LLLT against OM are its influence on various inflammatory markers and reduction of oxidative stress (reactive oxygen species) at local level. Its photo-bio-stimulatory effects at tissue and molecular level help in modulating various biochemical and metabolic processes. Laser can act on cellular enzymes, hence enhances oxidative chain mechanism in mitochondria (powerhouse of the cell). That results in increased Adenosine Triphosphates (ATPs) production. This provides more energy available to repair of cells. LLLT can enhance DNA synthesis in fibroblasts of human oral mucosa. This helps in protection of mucosa against early damage. Though laser is being already proved as therapeutic modality for wound healing and various dental conditions. Yet, more clinical and laboratory studies needed to prove the exact mechanisms of LLLT against OM.
From the results analysis of our study, it is clear that LLLT prevented the progression of OM towards higher grades. Because, most of the patients were at grade 2 mucositis in laser than control group until the end of CCRT. At the end of our study incidence of grade 3 and 4 mucositis was significantly lower in laser than control group patients. *(Table 3-4)* Similar trends were reported by Maiya et al\(^ {28}\) and Arora et al\(^ {29}\) in previous small sample studies on patients receiving radiotherapy for HNC at the same center. Maiya et al\(^ {28}\) reported significantly lower OM grades \((p<0.001)\) in laser \((1.72 \pm 0.67)\) than control \((3.32 \pm 0.69)\) group. At the end of their study in control group among 25 patients 14 and 11 had grade 3 and 4 mucositis respectively and no one in laser group had grades >2. Similarly, Arora et al.\(^ {29}\) reported that among 11 patients in laser group five had grade 3 and none had grade 4 mucositis. In control group among 13 patients, seven and four developed grade 3 and 4 mucositis respectively. In our study at the end of CCRT, among 111 patients in laser group 24 and 2 patients developed grade 3 and 4 mucositis respectively, while among 110 patients in control group, 49 and 28 patients developed grade 3 and 4 mucositis respectively. *(Table 3)* In laser group, two patients with grade 4 mucositis had extensive viscid secretions, despite extensive oral hygiene protocol prescribed to them so delivery of laser to viable mucosa was difficult.

Most of the previous studies\(^ {28-30,343-363}\) including two recent meta-analyses\(^ {364,365}\) reported reduction in severity of oral mucositis with the use of LLLT, despite variation in study population, LLLT Dosages delivered and outcomes used for assessing the mucositis. Previous studies involving HSCT patients, reported clinical as well as statistical significant reduction in the progression of OM grades after LLLT.\(^ {31,32,352,354,355}\) The energy density delivered in these studies varied from 1.0 to 4J/cm\(^ 2\). Barasch et al\(^ {31}\) used contra-lateral side as control so to avoid the confounding effects, they reported decrease in OM severity compared to non-treated side
with LLLT. Jaguar et al\textsuperscript{355}, used the retrospective controls to compare the results. The trends similar to our study were reported by Kuhn et al\textsuperscript{343-345} and Wong et al\textsuperscript{339}, in chemotherapy induced OM. The energy density delivered in these studies varied from 0.7 to 5J/cm\textsuperscript{2} (5-60J). A study by Wong et al\textsuperscript{339}, 15 patients who had grade 3-4 OM after first fraction of 5Fluoro Uracil chemotherapy were treated once in a week with LLLT (energy density of 0.7 – 0.8J/cm\textsuperscript{2}, total dosage of 50-60J). Bensadoun et al\textsuperscript{30}, Maiya et al\textsuperscript{28}, and Arora et al\textsuperscript{29}, also reported decrease in incidence and progression of radiation induced OM in HNC patients. Most of the studies used WHO criteria for assessing the grades of OM. Barasch et al\textsuperscript{31} used OMI-A and B along with ECOG oral toxicity scale, Cowen et al\textsuperscript{352} used Daily Mucositis Index and Cumulative Oral Mucositis Scores, and Wong et al\textsuperscript{339} used OM Grading scale for assessing the OM. In our study we used the EORTC/RTOG Scale for assessing the OM.

Our study involved the patients, who were receiving CCRT for locally advanced unresectable HNC. Our study results were compared with the studies by Bensadoun et al\textsuperscript{30}, Maiya et al\textsuperscript{28}, Arora et al\textsuperscript{29}, and Lima et al\textsuperscript{350} where patients had similar characteristics, dosages of radiation and dosages of LLLT used with almost equivalent dosages as in our study. Bensadoun et al\textsuperscript{30}, reported that mean grades of OM were significantly lower (p=0.001) in laser (1.7 ±0.26) than control (2.1 ±0.26) group. Also, number of weeks in which patients had grade 3 OM was also significantly less (p=0.001) in laser than control group. In Bensadoun et al\textsuperscript{30}, Maiya et al\textsuperscript{28}, studies patients were assessed weekly whereas in our study assessment was done daily. A recently published trial by Lima et al\textsuperscript{350} involving HNC patients receiving CCRT, reported lesser incidence of severe OM grades in laser group by fourth week. But at the end of CCRT, the incidence becomes almost equal in both the groups. In our trial incidence of severe
grades OM was consistently lower throughout the course of CCRT. *(Figure 6)* This may be due to higher energy density delivered to the mucosa in our study.

### 5.3 LASER EFFECTS ON OM ASSOCIATED PAIN

Oral mucositis cause severe pain which compromises patient’s daily oral functions. In our study patients in laser group experienced less severe OM associated pain than control group. Patients in laser group experienced moderate pain, whereas in control progressed towards the severe pain both in VAS and Verbal Scale during the last four weeks of CCRT. *(Figure 7-8, Table 6)* Pain scores were directly correlated with mucositis grades higher was the grade greater was the intensity of pain.

Use of Laser therapy has already been established as analgesic modality in treating various acute and chronic pain conditions including sports injuries, post-operative, post traumatic, chronic low back pain, osteoarthritis, rheumatoid arthritis, tendinitis, gingivitis, etc.\(^{25,41,370}\) Evidence suggests that laser selectively targets the slow conducting fibers, mainly afferent axons from nociceptors. Possible mechanism of analgesic effect is its action on pain gate mechanism; it selectively inhibits the nociceptive signal arising from the peripheral nerves, hence blocking the pain gate.\(^{22}\)

Most of the studies using low power laser for the treatment of OM associated pain documented lower pain scores in their study subjects. Uniformity in outcomes used for the assessment of pain, i.e. Visual Analog Scale helped us to generalize the results easily. Barasch et al\(^ {31}\) found significant reduction (P=0.027) in pain scores on the Laser treated side than control side within same subjects, mean pain scores in laser and control side were 11.8739 and 14.2342 respectively. Cowen et al\(^ {352}\) found significant decrease (P=0.05) in cumulative daily pain scores in laser than control group. Bensadoun et al\(^ {30}\), Maiya et al\(^ {28}\), Kuhn et al\(^ {343-345}\) and Arora et al\(^ {29}\),
observed significant reduction in mean pain scores in laser treated than control patients, first three studies patients were assessed weekly. Antunes et al.\textsuperscript{32} reported no significant difference (P=0.13) between Laser and Control group for pain scores. Among 19 patients in both group, 14 (73.7\%) in laser and 16 (84.2\%) in control group experienced VAS 7 and 8 scores respectively. They neither reported average pain scores experienced nor duration of severe pain. They also reported that patients started experiencing pain before the oral lesion appeared in oropharyngeal region. A study by Wong et al.\textsuperscript{339} 15 patients that already had chemo induced mucositis were divided into three groups (5 each) and were treated with two different types of laser. They found significant reduction in pain at 7\textsuperscript{th} (P=0.0072) and 15\textsuperscript{th} day (P=0.0009) compare to control group. Another study by Nes and Posso,\textsuperscript{372} specifically measured pain in chemotherapy induced mucositis found significant reduction (P =0.007) in pain score by 67\% before and immediately after laser therapy. In their study there was no control group. In our study patients were assessed by a blinded assessor.

\textbf{5.4 LASER EFFECTS ON SUPPLEMENT ANALGESICS NEED}

Pain associated with oral mucositis often requires analgesics use. Sometimes opioid analgesics and anesthetics may be required to decrease the oral pain. During our study we advised all the patients not to take analgesics until pain was not tolerable. At the baseline patients in laser and control groups were on 29\% and 27\% WHO step I (NSAID) analgesics either due to PEG tube or dental extraction pain. We have considered pain scores only when patients developed grade 1 oral mucositis. In our study 40\% and 11\% patients in laser and control respectively did not require any analgesics until the end of CCRT. About 9\% in laser and 26\% in control group patients required Step III analgesics at any point of time during the course of CCRT. Step II analgesics were required for 22\% and 31\%, while Step I analgesics were required for 29\% and
32% in laser and control group respectively. (*Figure 9*) Average number of days step III analgesia required was also significantly less (p<0.001) in laser (3.2 ±1.4 days) than control (6.7 ±2.6 days) group.

5.5 LASER EFFECTS ON OM ASSOCIATED SWALLOWING DIFFICULTY

Oral mucositis severely affect oral functions which sometime require total parenteral nutrition. In our study at the end of CCRT, oral alimentation was not possible for 45% in laser and 65.5% in control group patients. (*Figure 10*) Third week onwards significantly lesser number of patients needed total parenteral nutrition in laser than control group. This may be due to lower oral mucositis scores and hence lesser pain experienced by laser than control group patients as discussed above. Average duration of total parenteral nutrition required was significantly less in laser (12.76±12.84 days) than control (16.93±14.03 days) group patients. Similar trends were noticed by Bensadoun et al.\(^{30}\) in their study. Average duration of swallowing difficulty was significantly improved in laser (4.9± 1.33 weeks) than control (6 ±0.84 weeks) group. Cowen et al.\(^{352}\) also found significant improvement (P=0.01) in the ability to swallow scores in laser (12.8 ±3.1) than control (19.8 ±4.6) group. They did not observe significant difference between laser and control group for the duration of TPN required.

5.6 LASER EFFECTS ON OM ASSOCIATED WEIGHT LOSS

Generally loss of weight happens during the course of CCRT, because the patients will be in the catabolic state of metabolism. In addition, oral mucositis associated swallowing difficulty can hamper the nutritional status of the patients, hence their overall general health. Overall there was a progressive loss of weight during the seven weeks course of CCRT in all the patients, but loss was not statistically significant between the two groups. Average weight loss was 4.4Kg and 5.5Kg laser and control group respectively. (*Figure 11*) This may be because of patients in both
the group were using tube feeding hence getting equal nutrition, despite having more swallowing difficulty in control group.

5.7 LASER EFFECTS ON SUBJECTIVE EXPERIENCE OF OM

Chemoradiotherapy induced OM is a cause of concern for the patient as well as treating therapist because it may affect patient’s QOL and sometime therapy outcomes. Results of our study showed that LT was effective in improving the patient’s subjective experience of OM. Usually while assessing the efficacy of therapy outcome objective measures are always considered gold standard. There is always a difference in therapist observation and patient’s perception of symptoms, OM is an example of one such condition where clinician perception of OM markedly differs with patients experience with OM. In patients receiving radiation and/or chemotherapy for HNC, OM at its milder form is the most debilitating acute adverse event while for therapist severe grades of OM may be the cause of concern because of patient’s increased susceptibility to infections and other associated complications. Till date no therapeutic modality proved to be completely successful against OM, so standard of care of it is symptomatic management. If any difference exists about the perception of OM between the therapist and patient, it may lead to inadequate symptoms management. This may give inappropriate conclusions about the effectiveness of the treatment modality against OM. Therefore, to decide a therapy outcome against OM both objective and subjective tools should be used.

There are several assessment tools which can objectively measure the OM like WHO, RTOG, NCI-CTC and WCCNR scales. Most of these tools are based on the anatomical measurements that require skilled and experienced professionals to quantify exactly the OM severity and its associated symptoms. Also, various instruments like OM daily Questionnaire (OMDQ), Patient-Reported Oral Mucositis Symptom (PROMS) Scale, etc. were developed
Discussion

which can subjectively measure the patient’s experience with OM. In our study we used the OMWQ-HN\textsuperscript{259} which was developed specifically for assessing the impact of OM in HNC patients. To our knowledge through extensive literature search this is the only study which used patient’s reported measures of OM as well as head and neck specific assessment tool to find the effects of laser therapy on patient’s perception with OM and QOL in HNC patients receiving CCRT.

Patients in laser group reported lesser difficulty with OM throughout the course of CCRT. \textbf{(Table 9, Figure 12)} This may be due to lesser incidence of OM in laser than control group. LLLT proved to be effective in decreasing the severity of OM and its associated pain and swallowing difficulty in HNC patients receiving radiation/CRT in previous trials.\textsuperscript{29,30} We noticed similar trends in our study. Patients in laser group experienced less severe MTS hence their oral functions (e.g., swallowing, drinking, eating, talking and brushing) were better than control group. \textbf{(Table 10, Figure 13)} Sleep disturbance was also less in laser than control group, which may be due to less severe OM and lesser MTS.

\textbf{5.8 LASER EFFECTS ON QUALITY OF LIFE}

Oral mucositis associated morbidities significantly reduce the patient’s QOL.\textsuperscript{13} In our study patients reported better physical, functional and emotional well-being in laser than control group. \textbf{(Table 11, Figure 14-16)} This may be because of reduced incidence of severe OM thus lesser experience of MTS and pain, hence better oral functions and nutrition in laser than control group. Also, head and neck specific experience was better in terms of oral function like swallowing, voice strength, mouth dryness and pain in laser than control group patients. \textbf{(Figure 17)} Social/family well-being scores remained constant throughout the study. \textbf{(Table 11)} This may be due to socio-cultural norms of Indian subcontinent. Similar improvement in QOL was
reported in a recent study by Oton-Leite et al.\textsuperscript{358} in HNC patients undergoing radiation/CRT, using University of Washington-QOL questionnaire. Assessment was done at the baseline, at middle and at the end of radiotherapy; they did not take follow-up measures in their study. Also, they did not report the incidence of OM in their study. In our study QOL was assessed at the baseline, at the end and after one month follow-up. At one month follow-up QOL scores improved in both the groups, but the performance was better in laser than control group. This may be due to mouth dryness as well as swallowing difficulty which was lesser in laser than control group at the end of CRT. A single case report by Campos et al\textsuperscript{359} showed the better QOL in a pediatric oncology patient with LT. Few other authors have reported better QOL of cancer patients with LT in terms reduction of OM severity and its related pain and dysphagia. But, they did not use any tools to measure the QOL.\textsuperscript{339}

5.9 LASER EFFECTS ON UNPLANNED RADIATION INTERRUPTION

Unplanned radiation interruption happened for three patients in laser and eight patients in control group due to severe OM. (Figure 18) Average duration of radiation interruption was 9 days in laser and 12 days in control group. The average number of radiation fractions after which unplanned radiation interruption happened in laser and control group patients was 23 and 19 respectively. Bensadoun et al.\textsuperscript{30} reported no significant difference between two groups in their study for unplanned radiation interruption. Lima et al.\textsuperscript{350} also reported lesser incidence of treatment break due to mucositis in laser treated patients.
5.10 LIMITATIONS AND FUTURE RECOMMENDATIONS

We did not deliver the LLLT to the lower oropharyngeal region because fiber-optic pharyngeal probes were not available with the laser instrument. We did not follow the patients for resolution of OM grades after the end of CCRT. Hence, studies involving long-term follow up of the patients should be carried out to know carry-over effects of LLLT. Also, Microscopic or histopathological studies to be carried out to find out exact mechanisms by which LLLT help in reducing CCRT induced OM. We did not compare the impact of various OM grades with patient’s subjective experience of OM and QOL between laser and control group, so future studies are recommended in this regard.
CONCLUSIONS

Prophylactic use of LLLT was

1. Able to prevent progression of oral mucositis towards higher grades significantly lesser number of patients who received laser therapy experienced severe grades of oral mucositis.

2. Able to decrease the oral mucositis associated pain, significantly lesser number of patients who received laser therapy experienced severe oral pain.

3. Able to decrease the supplement analgesics need for oral pain.

4. Able to decrease the oral mucositis associated total parenteral nutrition need.

5. Able to decrease the severe oral mucositis associated radiation break.

6. Able to decrease the oral mucositis associated mouth and throat soreness and hence improved various oral functions like phonation, deglutition, brushing, etc.

7. Able to improve the quality of life of head and neck cancer patients receiving Concurrent Chemoradiotherapy.

Hence, Low-level laser therapy can be considered a non-traumatic modality for the prevention and treatment of Oral Mucositis and its associated morbidities.
CLINICAL IMPLICATIONS AND RECOMMENDATIONS

Low level laser therapy should be used as a therapeutic modality to prevent and treat the cancer therapy induced oral mucositis. Those centers who can avail this facility should be used as a safe modality because no patient reported any side effects with LLLT. Initial dosages of 1.8J should be delivered as a preventive measure until grade one OM appears. For grade 1 OM dosages of 1.8-3J should be used as a preventive as well as a therapeutic modality. When OM grades will be 2-4 dosage of 3J should be used at the periphery of the mucositis lesions and 5J should be used over the lesion.

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“Walk in the path of truth, it will always keep your moral high.”