

CHAPTER V

Discussion and Conclusion

Discussion

In this randomized - controlled study, we investigated whether pilocarpine dissolved in carboxymethylcellulose (PCMC) solution, which act as both saliva stimulant and oral lubricant had more effectiveness compared to carboxymethylcellulose (CMC) alone. According to its pharmacologic properties which the time of pilocarpine to appear in the blood stream was 0.31 ± 0.32 hours [20], the follow up time for its obvious effects and for appropriated transportation from rural areas of the patients was decided to be 3 weeks in this study. Over all analysis showed no statistically significant difference between the PCMC group and the CMC group regarding to xerostomia visual analog scale and frequency of fluid intake. There was, also, a non significant difference in pre and post treatment LENT SOMA scores in the PCMC group compared with CMC group. From the p value of 0.988 and 0.880, comparison of change from baseline at 3 weeks in xerostomia VAS and LENT SOMA scale between two treatment groups had no tendency to have significant difference even though more sample size might be increased.

For additional analysis, taking into account of the patient-rated-xerostomia VAS scores in each regimen, there were significantly increased in post medication than pre medication- VAS scores in all 6 variables of both arms. Post therapy scores of LENT SOMA were significantly improved from pre therapy scores in both PCMC and CMC groups. So, these both regimens could improve xerostomia and its associated symptoms and signs in comparable results. However, as mention above, there were no statistical difference when VAS and LENT SOMA scales were compared between the groups. Although there were some reports on the positive effects of oral pilocarpine administered *during* radiotherapy using VAS and salivary flow as the measurements [27, 32], the study from Warde [28] and Gornitsky [29] found no significant improvement of both salivary flow and patient-perceived xerostomia when pilocarpine administered during radiotherapy group was compared with control group.

For the LENT SOMA score which had no statistically significant difference between PCMC and CMC group in this study, Burlarge [43] also reported the LENT SOMA scale at different time points after administered concomitant pilocarpine during radiotherapy compared with the placebo. He found no significant difference of LENT SOMA scale or VAS or parotid flow rate at any time points except in subgroup of the patients who received mean parotid radiation dose above 40cGy. which the improvement of parotid flow rate was found at 12 months after pilocarpine therapy. In contrast, Haddad [30] reported the significant improvement of both subjective xerostomia and LENT SOMA score after used concomitant pilocarpine with the radiation.

In the 4 randomized trials reported in the literature assessing the effect of systemic oral pilocarpine administered *after* radiotherapy, 1 double blind cross over trial [31] and 3 randomized double-blind placebo-controlled trials were identified. [21, 44, 45] All also showed statistically significant patient-perceived improvement in over all xerostomia sensation as measured by visual analog scales at first 4 week and every 4 weeks for 12 week- end points.

However, by the objective measurements using parotid flow rate assessed every 4 weeks, Greenspan [31] found no significant difference between pilocarpine and placebo group except at 3rd visit. Other 3 studies [21, 44, 45] had found significantly increased in salivary flow rate among pilocarpine than placebo group for some visits but not all, especially at visit 4. The positive effects of pilocarpine on salivary flow were not consistent through the 12 week-end points; these might be because the percent changes of salivary flow between 2 measurements were at times very small which made the measurement have been difficult.

The low salivary flow rate and methodology used to measure the small volumes contributed to the inability to distinguish a significant benefit of the medication. Reports of the symptom of the oral dryness by the patients do not always correlate with the degree of diminished salivary flow. [46] These lead to the abandon of salivary flow measurement in ours protocol and many studies.

For the topical pilocarpine study in this clinical trial, patient-rated-xerostomia and LENT SOMA scales were improved significantly in both PCMC and CMC group but no difference were found between the groups. Such no beneficial effects over control

group were also observed in others two randomized double-blind clinical trials of topical pilocarpine. [10, 34] One study explored the effect of pilocarpine pastilles versus placebo on 34 participants. [10] The other explored the effect of pilocarpine spray versus CMC solution on 23 subjects, using much lower concentration than this study (0.07mg/cc VS 1mg/cc). [34] Visual analog scales and salivary flow measurements did not reveal any difference between cases and controls. As in this study, a large placebo effect was noted. This might be due to the lubrication afforded by the carboxymethylcellulose itself and in case of pastilles, by mechanical stimulation [10]. Therefore, small increase in the amount of saliva or the appropriated lubricant might be sufficient for clinical improvement in both groups. In contrast, the recent cross over study, Taweekhaisupapong [47] reported the statistically significant improvement in subjective perceptions and increase salivary flow measurement at time interval of 180 minutes after taking pilocarpine lozenges. However, each of the 33 participants was studied in 4 cross over trials (salagen tablets, pilocarpine lozenges 3 or 5 mg. and placebo), so more population is required in further study.

Although LENT SOMA scale was correlated with patient-rated xerostomia in some studies [30, 48, 49] it was not found in this study. In table 11, nearly seventy percents of the patients in both groups had got the same LENT SOMA scale level after treatment while they had better subjective VAS. This might be due to some insensitivity of 4 levels- physical examination scales to discriminate the better scores perceived by the patients in this study. Grading of oral physical examination score should be reevaluated and constructed for more levels of grading in the future.

Anyway, the prerequisites for the effectiveness of pilocarpine on xerostomia are depended on the residual salivary gland function, the degree of surrounding tissue fibrosis which are time and field-dependent of the radiation therapy. Furthermore, although 15mg. per day of pilocarpine is the most commonly effective dose which also was used in this study, the topical solution should be titrated into several concentrations to find the best effective dose. Finally, the evaluation time of the result, although it is not clear for the optimum length of time, some study reported the significant effects of pilocarpine was only 180 minutes[47] but some study did not observe these effects until 1 year after therapy. [43] Longer assessment time with several interval follow up periods

may be needed in the further study to demonstrate the late effect of pilocarpine in improving survival of salivary gland tissue.

No significant side-effect was founded for PCMC or CMC group. One patient from PCMC regimen experienced some headache and vomiting which was mild and tolerable. Two patients from CMC group reported increased dryness of mouth which also had been reported from one previous study on carboxymethylcellulose solution. [34] These adverse events are thought to be possibly from the stress of the trials or from their diseases and poor health. Due to the very mild side effects from the topical formula, none of the patients lost to follow-up as compared to the pilocarpine systemic route which had higher number of the patients withdrew. [31, 43, 44]

Considering the comparable result of the PCMC group and CMC group in reducing xerostomia symptoms and amount of fluid intake, the cost of each regimen should be taking into account. The cost of pilocarpine dissolved in carboxymethylcellulose solution is 10 dollars while carboxymethylcellulose alone is 1.5 dollars which is far less expensive. This should be considered in treatment planning for each individual.

Conclusion

Topical pilocarpine dissolved in carboxymethylcellulose solution (PCMC) did not has a significant effect in reducing xerostomia signs and symptom scores in post irradiation head and neck cancer over carboxymethylcellulose (CMC) containing saliva substitute. No significant side-effect was observed in both groups. Xerostomia VAS had no correlation with LENT SOMA scale in this study. Further investigation with longer follow up time and different pilocarpine concentration are needed to investigate the tendency of patient-rated xerostomia scores and LENT SOMA scales.