CHAPTER IV

Results

4.1 Characteristics of Patients and Baseline Data

Eighty patients were enrolled in the study which 40 patients were randomly allocated into pilocarpine dissolved in carboxymethylcellulose (PCMC) group and the other 40 patients into carboxymethylcellulose alone (CMC) group. The patients' demographic data were showed in Table 3. There were no statistically significant differences between two groups in all variables. Of the 80 studied patients, 70% were men and 30 % were woman. The mean age (±SD) was 53 ± 13.9 years. The tumor sites were at nasopharynx 57.7%, oral cavity 20.5%, oropharynx 9%, larynx 3.8%, nose/paranasal sinus 2.6%, salivary gland 2.6%, unknown primary site 2.6% and hypopharynx 1.3%. Thirty five point nine percent of the patients were in stage 4, 26.9% were in stage 2, 20.5% were in stage 1 and 16.7% were in stage 3. An average total radiation dose was 6496 ± 798 cGy. Twenty seven percents of patients had xerostomia symptoms during radiotherapy while 73% after completed radiation. Among subjects having xerostomia symptoms after the completion of radiation, the mean onset of the symptoms was 1.98 months (ranging from 1 to 17 months) after radiation therapy.

Most of the patients (75.7% in PCMC group and 63.9% in CMC group respectively) had radiation field at bilateral parotids and submaxillary gland . The PCMC group had chemotherapy 64.1% compared to 64.9% in CMC group. There were no statistically differences in these variables.

Table 3: Baseline patient demographic data by treatment group

	Number (%) or Mean ± SD			P-value
	Total	PCMC (n=40)	CMC (n=40)	
Age (yrs)	53 ± 13.9	52 ± 15.3	53 ± 12.4	0.581#
Gender				
Male	56 (70.0)	27 (67.5)	29 (72.5)	0.808*
Female	24 (30.0)	13 (32.5)	11 (27.5)	
Total radiation dose (cGy)	6496 ± 798	6511 ± 772	6482 ± 834	0.720@
Tumor site				
Oropharynx	7 (9)	4 (10.3)	3 (7.7)	0.990*
Hypopharynx	1 (1.3)	1 (2.6)	0	
Oral cavity/tongue	16 (20.5)	8 (20.5)	8 (20.5)	
larynx	3 (3.8)	2 (5.1)	1 (2.6)	
Nose/PNS	2 (2.6)	1 (2.6)	1 (2.6)	
Salivary gland	2 (2.6)	1 2.6)	1 (2.6)	
Nasopharynx	45 (57.7)	21(53.8)	24 (61.5)	
Unknown	2(2.6)	1(2.6)	1 (2.6)	
Radiation route				
Bilat parotid & submax gland	51 (69.9)	28 (75.7)	23 (63.9)	0.715*
Bilat submax gland	3 (4.1)	2 (5.4)	1 (2.8)	
Bilat parotid gland	10 (6.3)	4 (10.8)	6 (16.7)	
Parotid gland Rt	4 (2.5)	1 (2.7)	3 (8.3)	
Parotid gland Lt	4 (2.5)	2 (5.4)	2 (5.6)	
Submax gland Lt	1 (0.6)	0	1 (2.8)	
Onset of xerostomia				
During irradiation	21 (26.6)	8 (20.5)	13 (32.5)	0.310*
Post irradiation	58 (73.4)	31 (79.5)	27 (67.5)	
Duration of xerostomia (months)	13.1 ± 14.4	13.8 ± 16.7	12.4 ± 13.4	0.984@
Chemotherapy	49 (64.5)	25 (64.1)	24 (64.9)	1.000*

Unpaired t-test, * Fisher's exact test , @ Mann-Whitney U test (Exact p-value)

4.2 Analysis of the primary outcomes

4.2.1 Xerostomia visual analog scales

At baseline, there was no statistically significant difference in the visual analog scales of all 6 items between two groups (Table4). In terms of total score, the PCMC group had the median (range) of 22.20(3.10-48.40) compared to 24.15(0-42.80) in CMC group (Table 5).

After 3 weeks of treatment, the median of all 6 items of xerostomia VAS were increased significantly in both groups compared to baseline ($p<0.01$) (Table 4 and Figure 1). These showed that the patients had improved xerostomia symptoms in both regimens. However, comparison of change from baseline at 3 weeks in xerostomia VAS between two treatment groups showed no statistically significant difference ($p=0.988$, (Table 5, Figure 2).

Table 4: Comparison of 6 xerostomia VAS scores at baseline and 3 weeks between two regimens

Xerostomia VAS	Treatment scores (median : range)		Exact
	PCMC(n=40)	CMC(n=40)	p-value*
General sensation			
Baseline	2.00 (0.0 - 7.3)	3.00 (0.0 - 9.4)	0.577
3 wks	5.10(0.0 – 9.5)	4.95(0.0 – 9.6)	0.975
Exact p-value#	< 0.001	< 0.001	
Daytime sensation			
Baseline	2.70 (0.0 - 9.3)	3.45 (0.0 - 9.4)	0.718
3 wks	5.30 (0.2 – 10.0)	5.65 (0.9 – 9.6)	0.427
Exact p-value#	< 0.001	< 0.001	
Nighttime sensation			
Baseline	4.25 (0.0 - 10.0)	4.65 (0.0 - 9.7)	0.675
3 wks	6.70 (2.0 – 10.0)	5.80 (0.8 – 10.0)	0.466
Exact p-value#	< 0.001	0.004	
Speaking difficulty			
Baseline	2.70 (0.0 - 10.0)	4.00 (0.0 - 9.7)	0.076
3 wks	6.00 (0.0 - 10.0)	6.25 (0.1 – 10.0)	0.556
Exact p-value#	< 0.001	< 0.001	
Swallowing difficulty			
Baseline	2.50 (0.0 - 10.0)	2.25 (0.0 - 6.3)	0.914
3 wks	5.50 (0.2 – 10.0)	5.45 (0.3 – 10.0)	0.731
Exact p-value#	< 0.001	< 0.001	
Burning sensation			
Baseline	4.90 (4.0 - 10.0)	4.75 (0.0 - 10.0)	0.647
3 wks	8.7 (0.5 – 10.0)	6.60 (0.9 – 10.0)	0.599
Exact p-value#	< 0.001	0.011	

Comparison between baseline and 3 weeks in each treatment group: Wilcoxon's signed-rank test

* Comparison of each variable at 3 weeks between 2 treatment groups: Mann-Whitney U test

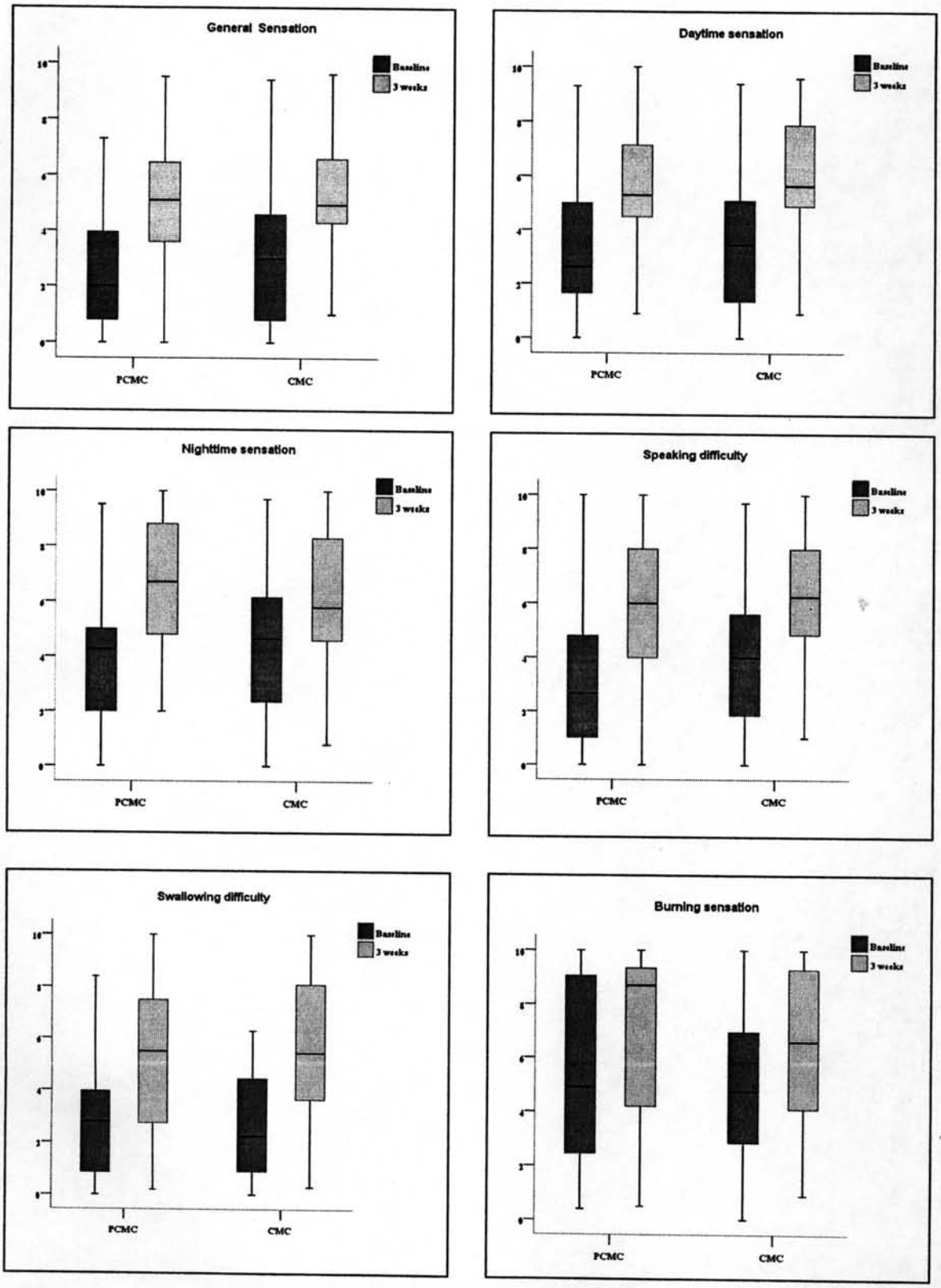

Figure 1. Box plot of 6 xerostomia variables at baseline and 3 weeks in PCMC and CMC group. Pre and post treatment VAS were statistically significant difference in each group ($P<0.01$).

Table5: Comparison of total VAS scores at baseline ,3 weeks and different of baseline and 3 weeks score between two regimens

Total xerostomia VAS	Treatment scores (median : range)		Exact
	PCMC	CMC	p-value*
Baseline	22.20(3.10-48.40)	24.15(0-42.80)	0.359
3 Weeks	36.80(6.0-51.0)	34.40(10.0-56.0)	0.779
3 Weeks - Baseline	13.70(-10.80-40.40)	13.30(-24.30-40.90)	0.988
p-value#	< 0.001	< 0.001	

Test of change from baseline in each treatment group: Wilcoxon's signed-rank test

* Comparison of each variable between 2 treatment groups: Mann-Whitney U test

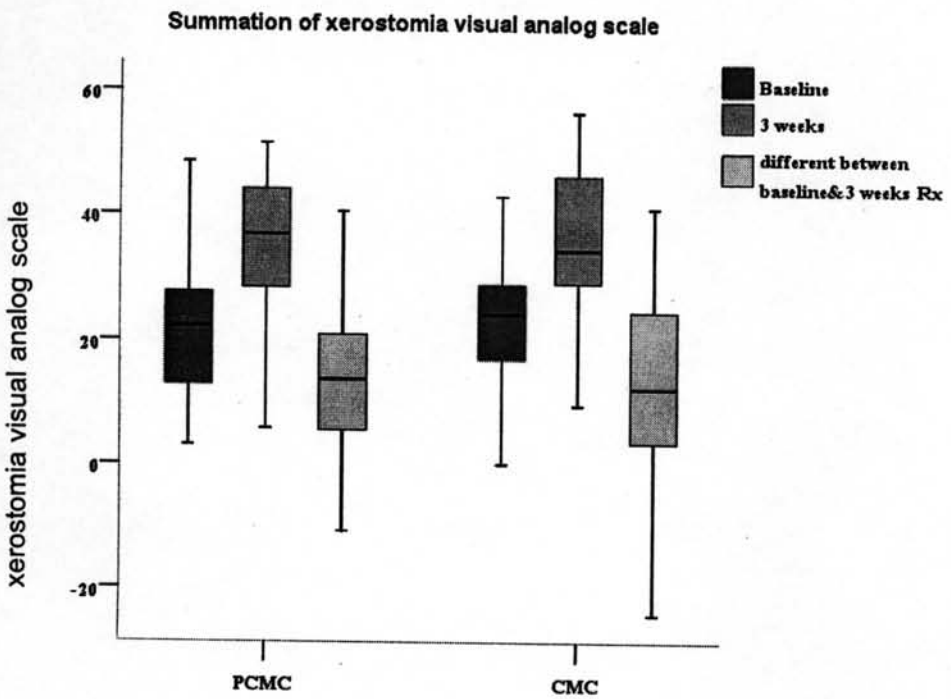

Figure2. Box plot of *summation* of xerostomia visual analog scale at baseline and 3 weeks in each treatment group. No difference in change of baseline scores was found between these two regimens (p=0.988).

4.3 Analysis of the secondary outcomes

4.3.1 Frequency of fluid intake

Distribution of frequency of fluid intake at baseline and 3 weeks in PCMC group and CMC group was showed in figure 3. There was no difference in frequency of fluid intake (times/day) between both groups at baseline (p=0.228, Table 6). At the end of the treatment, the frequency of fluid intake in each group was decreased significantly between pre and post treatment (p=0.003 and 0.004 respectively, Table 7). However, no difference in change from baseline at 3 weeks of fluid intake score between PCMC and CMC group was found (p= 0.897, Table 8).

At baseline, there was one missing data in PCMC group. At 3 weeks, there were 3 missing data in PCMC group and 1 missing data in CMC group from recording error.

Figure 3: Distribution of frequency of fluid intake (times per day) at baseline and 3 weeks in PCMC group and CMC group.

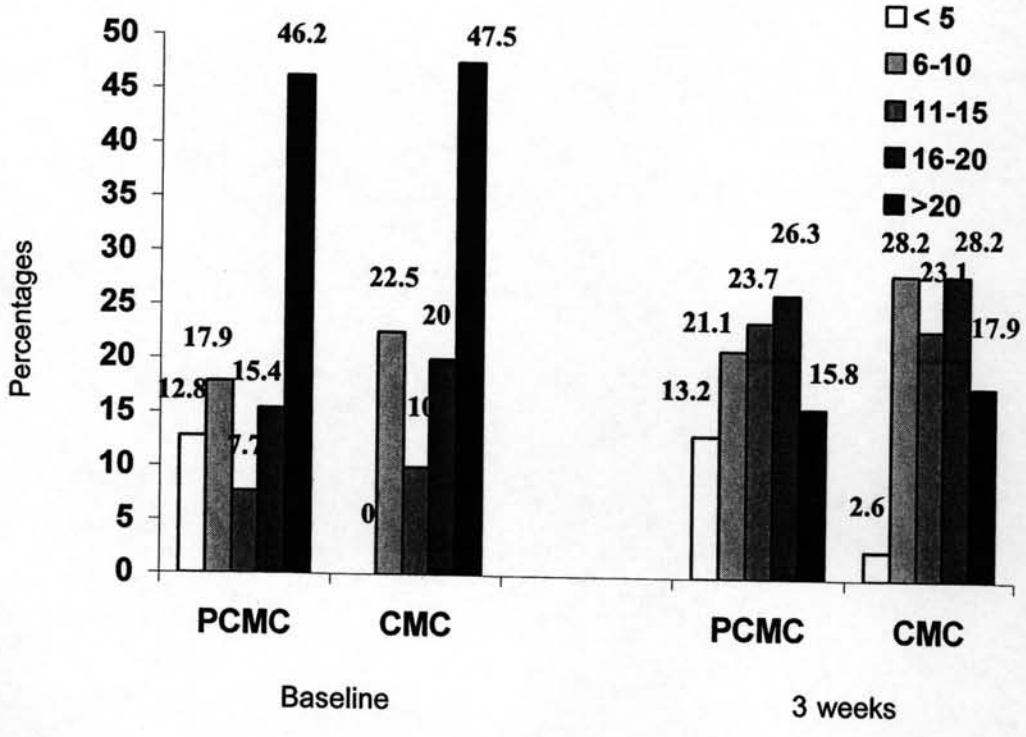

Table 6: Frequency of fluid intake at baseline in each treatment group

Frequency of fluid intake (times/day)	Baseline: Number (%)		Exact P-value*
	PCMC (n=39)	CMC (n=40)	
≤ 5	5 (12.8)	0	0.228
6-10	7 (17.9)	9 (22.5)	
11-15	3 (7.7)	4 (10.0)	
16-20	6 (15.4)	8 (20.0)	
>20	18 (46.2)	19 (47.5)	

Fisher's exact test

Table7: Baseline and 3 weeks frequency of fluid intake in PCMC and CMC regimens

		Frequency of fluid intake (times/day)						
		3 Weeks						Exact
Group	Baseline	≤5	6-10	11-15	16-20	>20	Total	p-value#
PCMC	≤5	3	2	-	-	-	5	0.003
	6-10	1	2	4	-	-	7	
	11-15	1	2	-	-	-	3	
	16-20	-	1	4	-	-	5	
	>20	-	1	1	9	6	17	
	Total	5	8	9	9	6	37	
CMC	≤5	-	-	-	-	-	0	0.004
	6-10	-	4	5	-	-	9	
	11-15	-	3	-	1	-	4	
	16-20	-	2	2	3	1	8	
	>20	1	2	2	7	6	18	
	Total	1	11	9	11	7	39	

Wilcoxon's signed rank test

Table8: C hange of frequency of fluid intake at baseline and 3 weeks between two regimens

Change of fluid intake (Baseline - 3 Weeks)*	Number (%)		Exact p-value#
	PCMC (n=37)	CMC (n=39)	
-1	6 (16.2)	7 (17.9)	0.897
0	11 (29.7)	13 (33.3)	
1	16 (43.2)	12 (30.8)	
2	3 (8.1)	4 (10.3)	
3	1 (2.7)	2 (5.1)	
4	0	1 (2.6)	

* Positive values mean improvement of the score, # Fisher's exact test

4.3.2 LENT SOMA scale

Distribution of LENT SOMA score at baseline and 3 weeks in each treatment group was showed in Figure 4. The analysis of the LENT SOMA scale showed no statistically significant difference between two groups at baseline (P=0.694, Table 9). After 3 weeks of treatment, pre and post therapy scores of LENT SOMA in each regimen was statistically significantly improved (P=0.004 and 0.020 respectively, Table 10). However, no significant difference in change from baseline at 3 weeks of LENT SOMA score between PCMC and CMC groups was found (P=0.880, Table11).

Figure4: Distribution of LENT SOMA score at baseline and 3 weeks in treatment groups

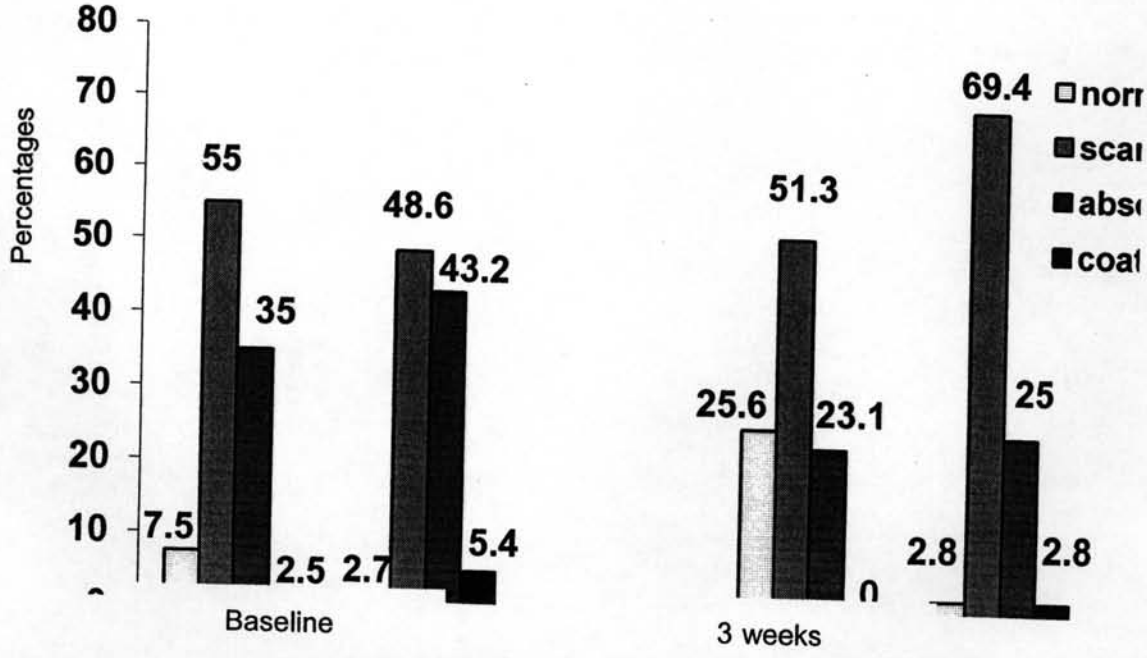

Table 9 : LENT SOMA scale at baseline in PCMC and CMC regimens

LENT SOMA scales	Pre treatment: Number (%)		Exact P-value*
	PCMC (n=40)	CMC (n=37)	
Gr.1 normal	3 (7.5)	1 (2.7)	0.694
Gr.2 scant saliva	22 (55.0)	18 (48.6)	
Gr.3 absent moisture	14 (35.0)	16 (43.2)	
Gr.4 coated mucosa	1 (2.5)	2 (5.4)	

* Fisher's exact test

Table10: Baseline and 3 weeks LENT SOMA scores in PCMC and CMC regimens

Group	Baseline	LENT soma scale: 3 Weeks				Total	Exact p-value#
		Normal	Scant saliva	Absent moisture	Coated mucosa		
PCMC	Normal	2	-	-	-	2	0.004
	Scant saliva	4	17	1	-	22	
	Absent moisture	3	3	8	-	14	
	Coated mucosa	1	-	-	-	1	
	Total	10	20	9	-	39	
CMC	Normal	-	1	-	-	1	0.020
	Scant saliva	-	17	-	-	17	
	Absent moisture	1	7	8	-	16	
	Coated mucosa	-	-	1	1	2	
	Total	1	25	9	1	36	

Wilcoxon's signed rank test

At baseline, there was 3 missing data in CMC group .At 3 weeks, there were 1 missing data in PCMC group and 4 missing data in CMC group from recording error.

Table11 : Change of LENT SOMA score at 3 weeks of each treatment group.

Change of LENT SOMA scales (Baseline - 3 Weeks)*	Treatment number (%)		Exact P-value#
	PCMC (n=39)	CMC (n=36)	
-1	1 (2.6)	1 (2.8)	0.880
0	27 (69.2)	26 (72.2)	
1	7 (17.9)	8 (22.2)	
2	3 (7.7)	1 (2.8)	
3	1 (2.6)	0	

* Positive values mean improvement of the scores, # Fisher's exact test

From table11, although pre and post treatment LENT SOMA scores were statistically improved, but most of the patients (69% in PCMC group and 72% in CMC group) still had got the same LENT SOMA scores (difference=0)

4.3.3 The correlation of the xerostomia VAS and LENT SOMA scale

The correlation between post therapy VAS, total VAS and LENT SOMA scale was determined by Spearman's rank correlation (Table 12), which was poor (correlation coefficients between -0.239 and 0.043). Although "general sensation" had some correlation with LENT SOMA scale (p=0.039), the correlation was rather poor (r=-0.239).

Table 12: The correlation between post therapy VAS and LENT SOMA scale

VAS	LENT SOMA scale (r)	P-value
General sensation	-0.239	0.039*
Daytime sensation	-0.070	0.548
Nighttime sensation	0.043	0.714
Speaking difficulty	-0.085	0.470
Swallowing difficulty	-0.075	0.522
Burning sensation	-0.075	0.521
Total	-0.109	0.371

4.3.4 Validity of the questionnaire

The content validity of the xerostomia VAS was evaluated by 5 senior experts in otolaryngology. Using Item Objective Congruence (IOC), the $\sum$R/N of 0.8-1 showed good congruence of the questionnaires in all 6 variables (Table 13).

Table 13: Item Objective Congruence (IOC) from original Thai language questionnaires

ประเด็นที่ต้องการวัด	ข้อคำถาม	ความสอดคล้อง			IOC= $\sum$R/N
		สอดคล้อง (1)	ไม่แน่ใจ (0)	ไม่สอดคล้อง (-1)	
อาการน้ำลายแห้งหลังการฉายแสง	1.ในช่วง 3 วันที่ผ่านมาโดยรวมแล้ว...	5	-	-	1
	2.โดยทั่วไปในช่วงเวลากลางวัน..	5	-	-	1
	3.ในช่วงเวลาลางคืนความแห้งของช่องปากและลิ้น...	5	-	-	1
	4.ถ้าท่านไม่ดื่มน้ำช่วยในการพูด..	4	1	-	0.8
	5.การเคี้ยวและการกลืนอาหารของท่าน.	4	1	-	0.8
	6.ท่านมีอาการเจ็บหรือแสบในเยื่อบุ..	5	-	-	1

R= Score x number of experts (N) in each congruence level

4.3.5 The internal consistency of the Thai xerostomia symptom questionnaires

The internal consistency of 6 variables of the xerostomia visual analog scales was assessed in 32 patients. The Cronbach's alpha of 0.793 indicated the good internal consistency of the questionnaires.

4.3.6 Measure of agreement between 2 observers

The inter-observer variation in LENT SOMA between 2 clinicians was analyzed using weighted kappa with quadratic weight. The weighted kappa of 0.88 (95% CI: 0.71, 1.00) revealed the good agreement between 2 observers.

4.3.7 Adverse effects and compliance

Adverse effects observed in the study were very mild and found in 3 cases. One patient who received pilocarpine experienced nausea and headache. Other two patients who received carboxymethylcellulose alone reported increase dryness of mouths. None of them withdrew from the study.

For the compliance of the treatments, two patients failed to complete the medication after the therapy. The reason of one patient who received pilocarpine regimen stopped the medication at 2^{nd} week of the therapy because he "feels better". The other patient broke the spay bottle at the end of 2^{nd} week and he did not call us to replace it. However, at the followed up period, both patients had completed the questionnaire including physical examinations and their data were also analyzed.