CHAPTER 3
RESULTS

3.1 PATIENT CHARACTERISTICS

In total, 197 patients were screened and 140 patients with valid for inclusion criteria were randomized into two treatment groups; 70 patients in each group received 2 sprays of either MF (200 µg) or FF (110 µg) per nostril once daily for 4 weeks. All participants in the trial had symptoms of moderate to severe PER. At the end of the study, there were 126 patients (90%) completed the study, 14 patients were withdrawn form the study due to lost to follow up (n = 3), combined with antihistamine (n = 1), hospital admission due to dengue fever (n = 1), and upper respiratory infections (n = 9) (Figure 7). Since there were few patients withdrawn from the trial, the results were, therefore, not substantially affected, whether the analysis was performed by an intention to treat (ITT) analysis or an analysis on available completers. Thus, the following data showed the findings in ITT analysis. Data of last observation were carried forward for withdrawals. The demographic and baseline characteristics, e.g., sex, age, duration of AR for the ITT population, and baseline data for efficacy assessment (TNSSs, the individual nasal symptom scores and NAR) were similar between the two treatment groups (Table 2). At baseline data for TOSSs assessment, 87 in 140 patients (62.14%) had ocular symptoms, but only 28 patients (20%) (13 in MF group and 15 in FF group) had symptoms severity that met the inclusion criteria. Moreover, baseline eosinophils, neutrophils and basophils were presented for 106 (74%), 97 (68%) and 89 (64%) patients, respectively, of the total 140 patients enrolled in this study. Lymphocytes and macrophages were found in only 2 patients, therefore, their data were not shown. The baseline data of TOSSs, individual ocular symptom scores and mean percentage of the inflammatory cell types were not significantly different as shown in Table 3.

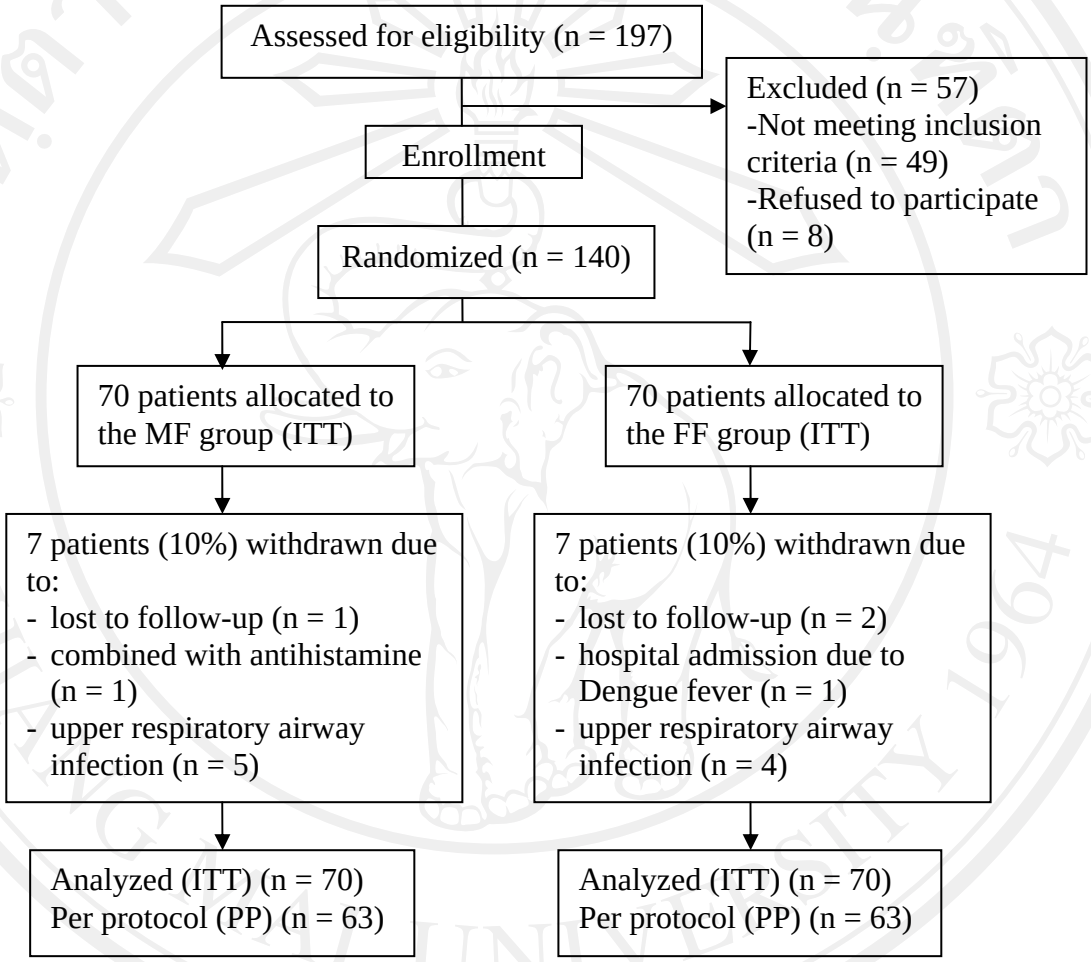

Figure 7 Flow chart of patient randomization and withdrawn.

Table 2 Patient characteristics and baseline data

Characteristic	MF group	FF group	*p* value
Number of patients	70	70	1.000
Mean age in years (Range)	33.96 ± 11.98 (18-57)	33.81 ± 11.73 (18-57)	0.932
Sex (n)			
• Male	26	27	0.862
• Female	44	43	0.862
Mean disease duration in years (Range)	8.03 ± 6.17 (0.5-30)	7.26 ± 6.28 (1-30)	0.469
TNSSs	7.60 ± 0.20	8.00 ± 0.20	0.168
• Rhinorrhea scores	1.86 ± 0.09	2.06 ± 0.09	0.128
• Itching scores	1.89 ± 0.08	1.94 ± 0.08	0.535
• Sneezing scores	1.84 ± 0.10	1.93 ± 0.10	0.467
• Congestion scores	2.07 ± 0.09	2.23 ± 0.09	0.144
Left nostril NAR			
• At 75 Pa	0.65 ± 0.08	0.64 ± 0.08	0.938
• At 150 Pa	0.91 ± 0.11	0.87 ± 0.12	0.792
Right nostril NAR			
• At 75 Pa	0.67 ± 0.08	0.60 ± 0.08	0.514
• At 150 Pa	0.95 ± 0.12	0.82 ± 0.12	0.429
Total NAR			
• At 75 Pa	0.26 ± 0.02	0.26 ± 0.02	0.864
• At 150 Pa	0.37 ± 0.03	0.35 ± 0.03	0.554

Values are expressed as mean ± SD

Table 3 Baseline data presented with TOSSs and mean percentage of cell types

Characteristic	MF group	FF group	*p* value
TOSSs	4.78 ± 0.27 (n = 13)	5.27 ± 0.25 (n = 15)	0.421
• Itching scores	1.38 ± 0.18	1.87 ± 0.09	0.157
• Tearing scores	2.23 ± 0.17	2.40 ± 0.08	0.467
• Redness scores	1.38 ± 0.24	1.20 ± 0.26	0.582
Mean percentage of the cell type per total cell			
• Eosinophils	3.96 ± 0.86 (n = 54)	4.00 ± 0.92 (n = 52)	0.971
• Neutrophils	3.33 ± 1.02 (n = 49)	5.11 ± 1.02 (n = 48)	0.221
• Basophils	1.59 ± 0.23 (n = 48)	1.36 ± 0.25 (n = 41)	0.498

Values are expressed as mean ± SD

3.2 SKIN PRICK TEST

One hundred forty patients had positive SPT to at least 1 allergen. However, 125 (89.29%) patients had positive SPT to more than 1 allergens (77.86% to house dust, 83.57% to *D. farinae*, 77.86% to *D. pteronyssinus* and 50.71% to American cockroach).

3.3 SUBJECTIVE ASSESSMENT

3.3.1 TNSSs

The TNSSs and the individual symptom scores (rhinorrhea, sneezing, itching, and congestion) at the end of week 2 and 4 of both treatments were decreased significantly when compared with baseline values. Moreover, the TNSSs and the individual symptom scores (MF in rhinorrhea, sneezing and congestion scores; FF in itching and congestion scores) of both groups after week 4 were also significantly decreased when compared with week 2. However, there were no significant differences in the percentage of improvement after week 4 between the two treatment groups (Table 4). The mean change from baseline after week 2 (Figure 8) and week 4 (Figure 9) of TNSSs and the individual symptom scores did not differ significantly between both groups. Improvement in TNSSs of both treatment groups reached statistical significance within 24 h. The proportion of remaining responders after 4 weeks of treatment was similar in both treatment groups as shown in Figure 10. No patient reported worsening of symptoms in both treatment groups.

Table 4 Effects of MF and FF on TNSSs and the individual symptom scores before and after 2 and 4 weeks of treatment

Scores/ Treatment group	Treatment period			% Improvement†	*p* value‡
	Baseline	Week 2	Week 4		
TNSSs					
• MF	7.60 ± 0.20	2.31 ± 0.22*	1.33 ± 0.19*,**	82.42	0.557
• FF	8.00 ± 0.20	2.14 ± 0.22*	1.53 ± 0.19*,**	80.33	
Rhinorrhea					
• MF	1.86 ± 0.09	0.63 ± 0.08*	0.34 ± 0.07*,**	81.59	0.816
• FF	2.06 ± 0.09	0.59 ± 0.08*	0.41 ± 0.07*	80.43	
Sneezing					
• MF	1.89 ± 0.08	0.54 ± 0.08*	0.34 ± 0.06*,**	81.88	0.447
• FF	1.94 ± 0.08	0.44 ± 0.08*	0.31 ± 0.06*	85.48	
Itching					
• MF	1.84 ± 0.10	0.39 ± 0.08*	0.23 ± 0.05*	87.37	0.662
• FF	1.93 ± 0.10	0.41 ± 0.07*	0.20 ± 0.05*,**	89.03	
Congestion					
• MF	2.07 ± 0.09	0.79 ± 0.09*	0.43 ± 0.07*,**	77.05	0.979
• FF	2.23 ± 0.09	0.66 ± 0.09*	0.47 ± 0.07*,**	77.21	

Values are expressed as mean ± SEM

* Significantly different from base line at $p < 0.0001$

** Significantly different between week 2 and week 4 at $p < 0.05$

† Calculated by $(mean_{week0}\text{-}mean_{week4}) \times 100/mean_{week0}$

‡ Unpaired *t*-test comparing mean percent improvement between groups after week 4

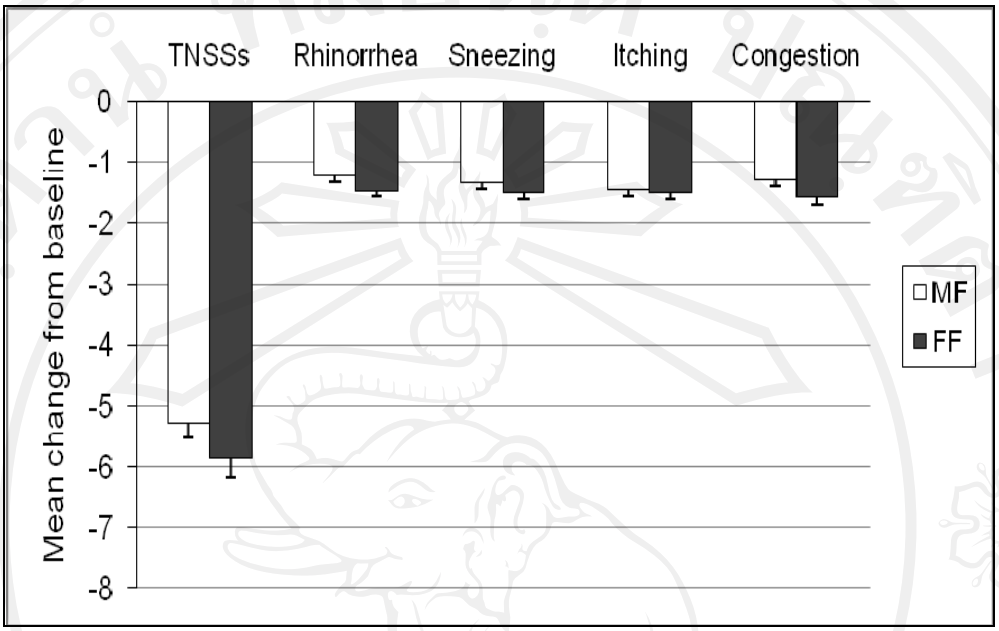

Figure 8 Mean change from baseline of TNSSs and the individual symptom scores after 2 weeks of treatment. Values are expressed as mean ± SEM.

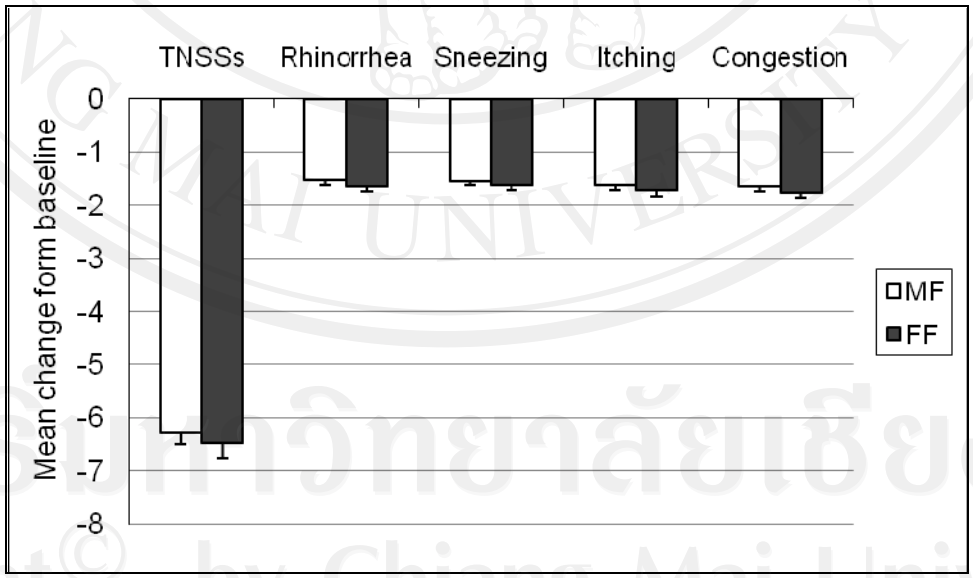

Figure 9 Mean change from baseline of TNSSs and the individual symptom scores after 4 weeks of treatment. Values are expressed as mean ± SEM.

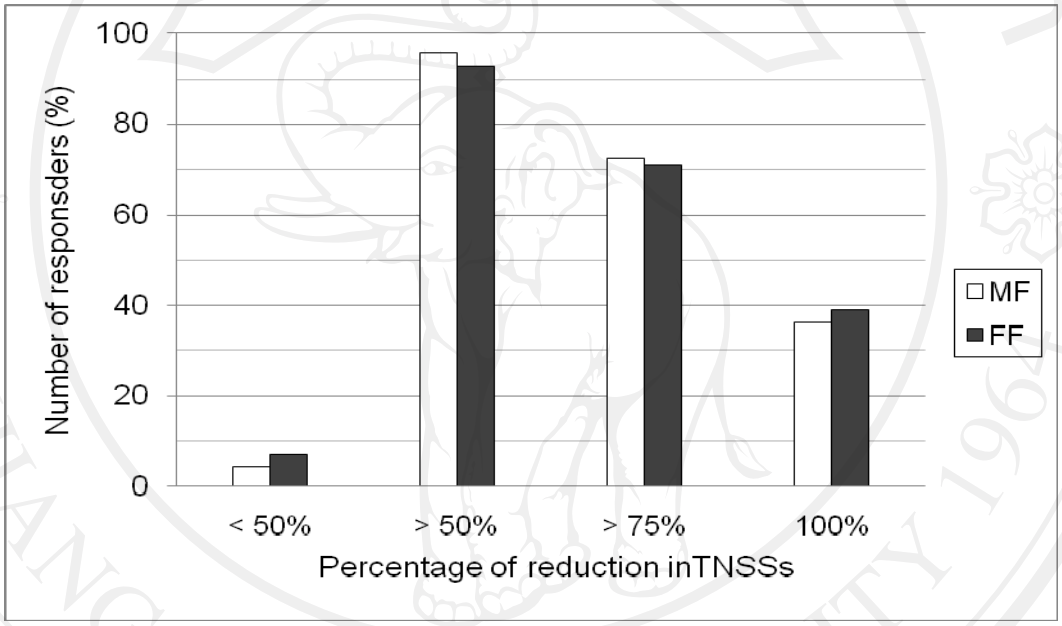

Figure 10 The number of responders in MF (n=69) and FF (n=69) treatment groups, 2 patients who were lost to follow-up after baseline were not included in the analysis.

3.3.2 TOSSs

The TOSSs and the individual symptom scores (ocular itching, tearing, and redness) of both MF and FF groups were significantly improved after week 2 and remained significantly improved at week 4 of treatment. After week 4, TOSSs of FF treatment group was also significantly decreased in TOSSs when compared with week 2 (Table 5). However, there were no significant differences in mean change of TOSSs and the individual symptom scores of both treatment groups after week 2 (Figure 11) and week 4 from baseline (Figure 12).

Table 5 Effects of MF and FF on TOSSs and the individual symptom scores before and after 2 and 4 weeks of treatment

Scores/ Treatment group	Treatment period			% Improvement†	*p* value‡
	Baseline	Week 2	Week 4		
TOSSs					
• MF	4.78 ± 0.27	1.85 ± 0.55*	1.31 ± 0.41*	72.69	0.456
• FF	5.27 ± 0.25	2.13 ± 0.52*	1.00 ± 0.38*,**	83.22	
Tearing					
• MF	1.38 ± 0.18	0.62 ± 0.27*	0.38 ± 0.24*	70.83	0.975
• FF	1.87 ± 0.09	0.60 ± 0.08*	0.33 ± 0.07*	74.44	
Itching eyes					
• MF	2.23 ± 0.17	1.00 ± 0.23*	0.69 ± 0.24*	73.33	0.787
• FF	2.40 ± 0.08	1.07 ± 0.25*	0.67 ± 0.19*	72.08	
Redness					
• MF	1.38 ± 0.24	0.38 ± 0.18*	0.23 ± 0.12*	85.00	0.778
• FF	1.20 ± 0.26	0.47 ± 0.17*	0.20 ± 0.11*	75.00	

Values are expressed as mean ± SEM

* Significantly different from base line at $p < 0.05$

** Significantly different between week 2 and week 4 at $p = 0.017$

† Calculated by $(mean_{week0}\text{-}mean_{week4}) \times 100/mean_{week0}$

‡ Unpaired *t*-test comparing mean percent improvement between groups after week 4

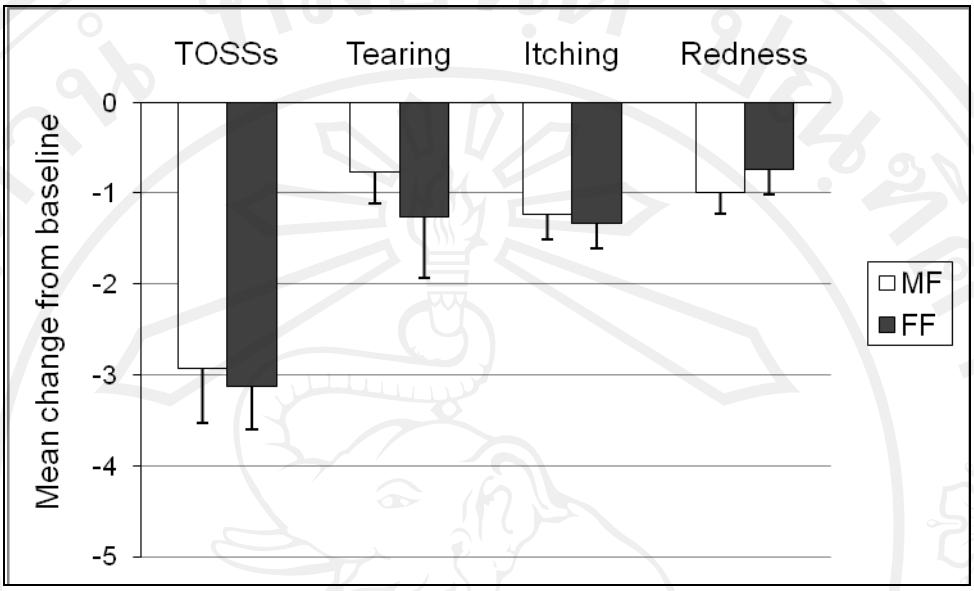

Figure 11 Mean change from baseline of TOSSs and the individual symptom scores after 2 weeks of treatment. Values are expressed as mean ± SEM.

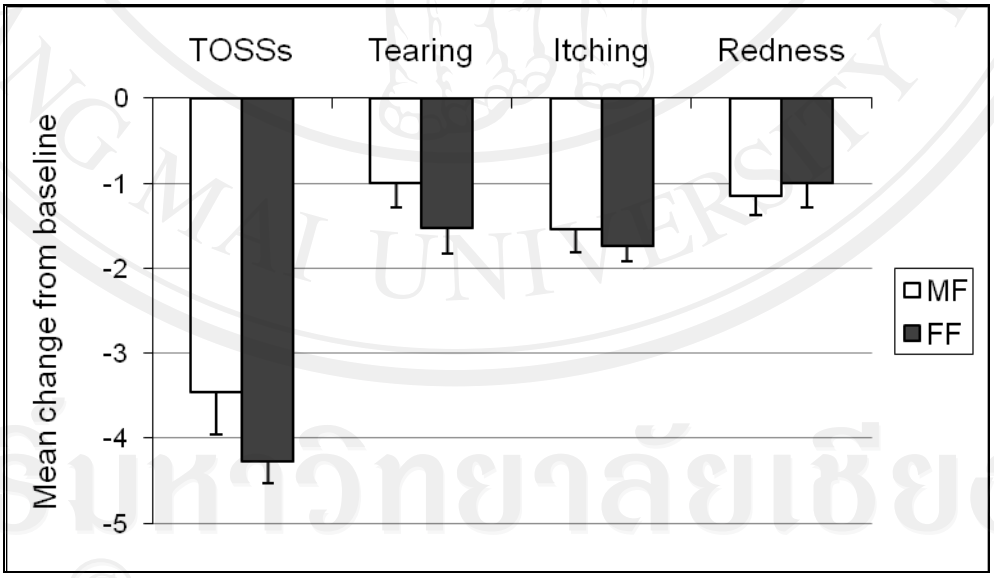

Figure 12 Mean change from baseline of TOSSs and the individual symptom scores after 4 weeks of treatment. Values are expressed as mean ± SEM.

3.4 OBJECTIVE ASSESSMENT

3.4.1 NAR

After week 4, only FF but not MF significantly reduced the left nostril NAR at 75 and 150 Pa (Table 6). Mean change from baseline after week 2 and week 4 in unilateral at 75 and 150 Pa was not significantly different between the two drug treatments (Figure 13). Both MF and FF produced statistically significant improvement in the total NAR at 75 and 150 Pa from baseline at the second and the fourth weeks of treatment (Table 6). FF improved total NAR more than MF but with no statistically significant difference between both drug treatments (Figure 13).

Table 6 Effect of MF and FF on unilateral and total NAR ($Pa/cm^3/s$) before and after 2 and 4 weeks of treatment

NAR/ Treatment group	Treatment period		
	Baseline	Week 2	Week 4
Left nostril			
At 75 Pa			
• MF	0.65 ± 0.08	0.50 ± 0.04	0.52 ± 0.06
• FF	0.64 ± 0.08	0.45 ± 0.05	0.43 ± 0.06*
At 150 Pa			
• MF	0.91 ± 0.11	0.66 ± 0.05	0.71 ± 0.08
• FF	0.87 ± 0.12	0.59 ± 0.05*	0.58 ± 0.08*
Right nostril			
At 75 Pa			
• MF	0.67 ± 0.08	0.53 ± 0.05	0.46 ± 0.03*
• FF	0.60 ± 0.08	0.45 ± 0.05	0.39 ± 0.03*
At 150 Pa			
• MF	0.95 ± 0.12	0.70 ± 0.07	0.60 ± 0.04*
• FF	0.82 ± 0.12	0.63 ± 0.07	0.51 ± 0.04*
Total			
At 75 Pa			
• MF	0.26 ± 0.02	0.21 ± 0.01*	0.21 ± 0.01*
• FF	0.26 ± 0.02	0.19 ± 0.01*	0.17 ± 0.01*
At 150 Pa			
• MF	0.37 ± 0.03	0.29 ± 0.02*	0.28 ± 0.02*
• FF	0.35 ± 0.03	0.26 ± 0.02*	0.23 ± 0.02*

Values are expressed as mean ± SEM

* Significantly different from base line at $p < 0.05$

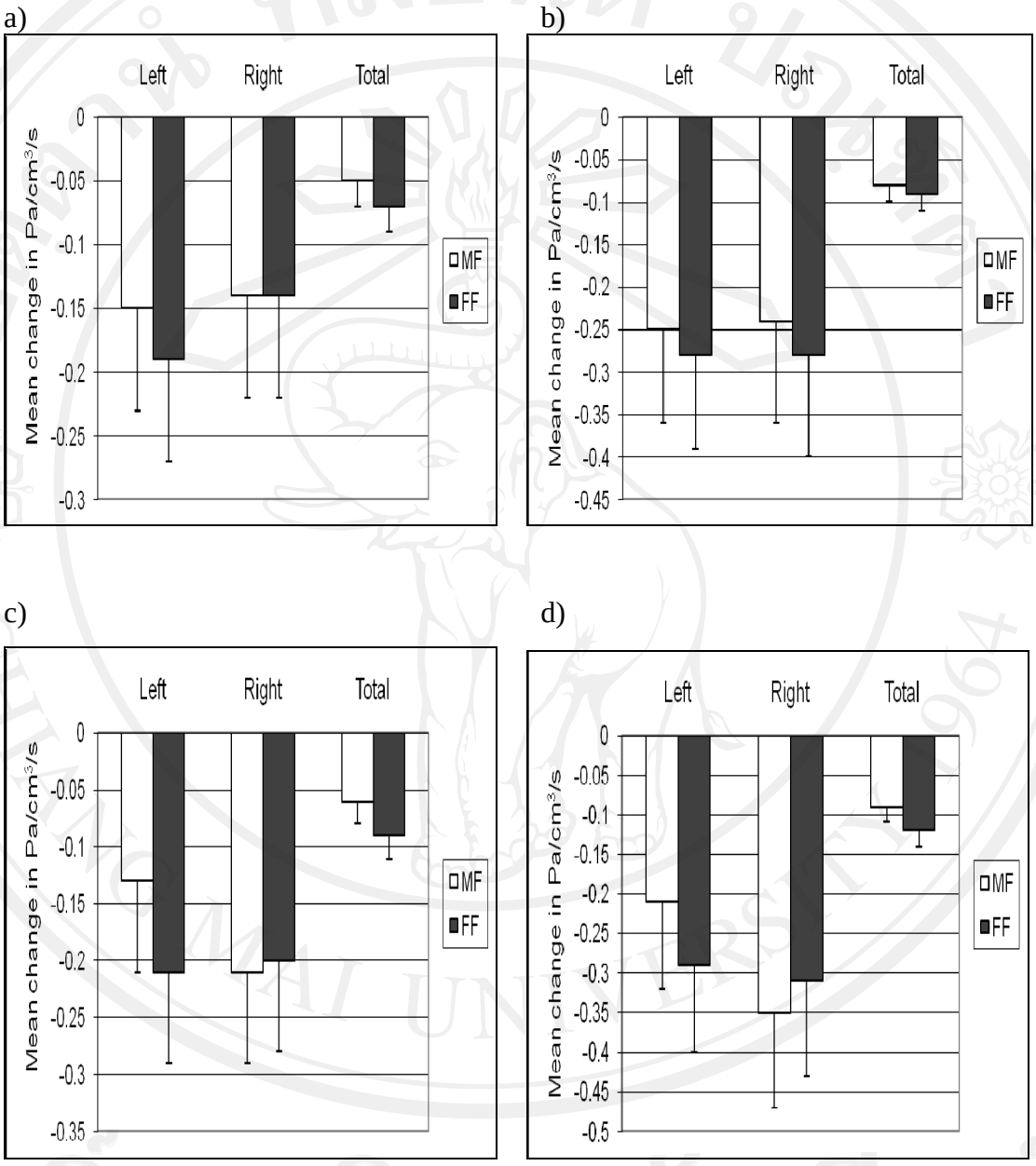

Figure 13 Mean change from baseline in unilateral and total NAR (Pa/cm^3/s) after 2 weeks of treatment at 75 (a) and 150 Pa (b); and after 4 weeks of treatment at 75 (c) and 150 Pa (d). Values are expressed as mean ± SEM.

3.4.2 Nasal cytology

After week 2 and week 4, MF and FF significantly reduced the mean percentage of eosinophils and basophils but without effects on the mean percentage of neutrophil from baseline (Table 7). Mean change of inflammatory cells from baseline after week 2 and week 4 was not significantly different between the two drug treatments (Figures 14 and 15). The percentage of patients with increased and decreased number of each inflammatory cell type after week 4 of MF and FF treatment from baseline was summarized in Figure 16.

Table 7 Effects of MF and FF on inflammatory cell before and after 2 and 4 weeks of treatment

Inflammatory cell types/ Treatment group	Treatment period		
	Baseline	Week 2	Week 4
Eosinophils (%)			
• MF	3.96 ± 0.86	0.50 ± 0.18*	0.40 ± 0.15*
• FF	4.00 ± 0.92	0.61 ± 0.19*	0.18 ± 0.16*
Neutrophils (%)			
• MF	3.33 ± 1.02	1.01 ± 0.88	2.28 ± 0.75
• FF	5.11 ± 1.02	3.39 ± 0.88	3.24 ± 0.75
Basophils (%)			
• MF	1.59 ± 0.23	0.73 ± 0.22*	0.61 ± 0.23*
• FF	1.36 ± 0.25	0.37 ± 0.21*	0.25 ± 0.21*

Values are expressed as mean ± SEM [mean percentage of the inflammatory cell types per total cells per 20 high-power fields (x1000)]

* Significantly different from base line at $p < 0.05$

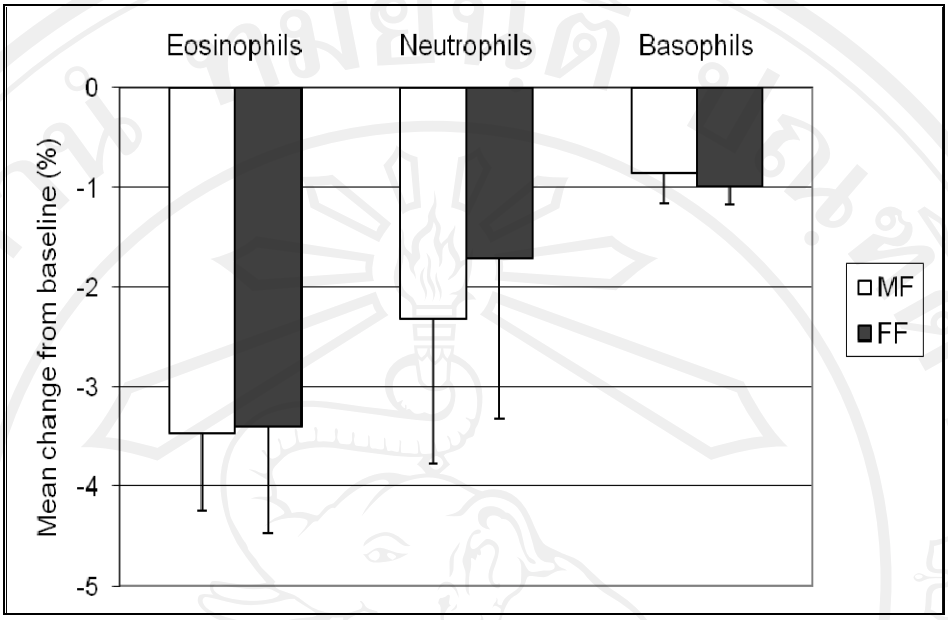

Figure 14 Mean percent change from baseline of inflammatory cells after 2 weeks of treatment**.** Values are expressed as mean ± SEM**.**

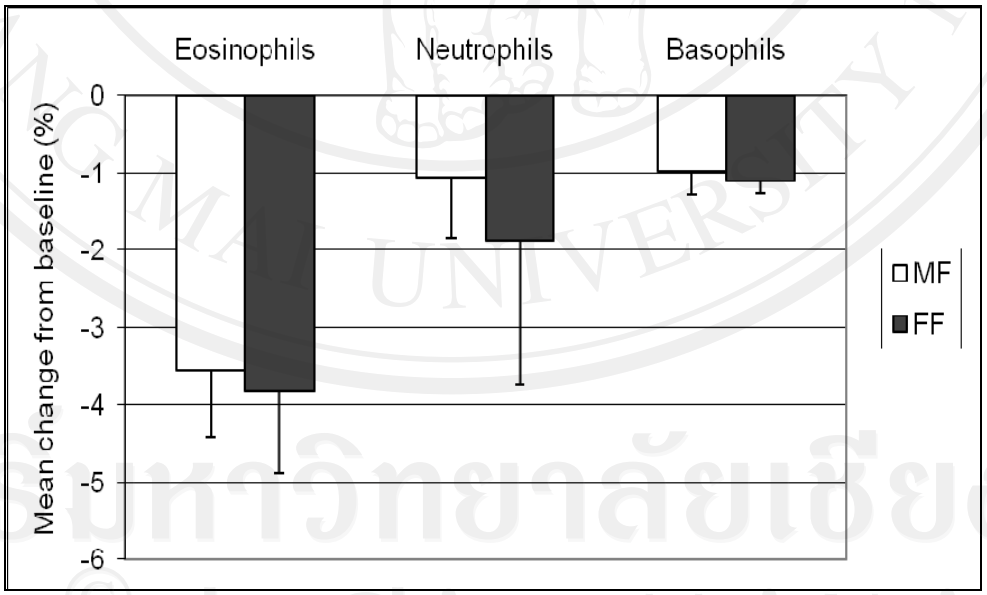

Figure 15 Mean percent change from baseline of inflammatory cells after 4 weeks of treatment**.** Values are expressed as mean ± SEM**.**

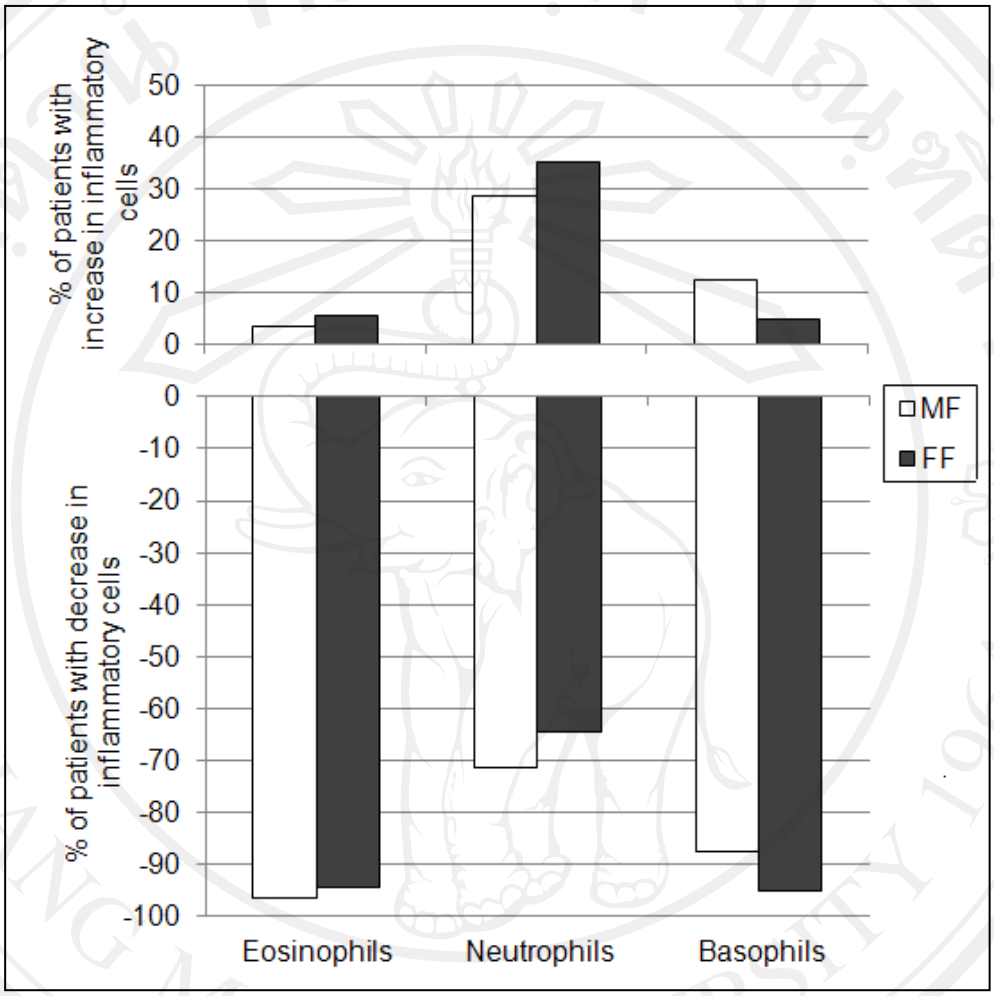

Figure 16 Percent of patients with increase or decrease in eosinophils, neutrophils and basophils at the end of week 4 treatment compared with pretreatment.

3.5 ASSESSMENT OF PATIENT PREFERENCE

Preference of MF and FF attributes after week 2 and 4 of treatment were similar (Table 8). After week 4, mean of preference rating scores of MF and FF were not significantly different, however, preference of ease of use of FF was less than MF (Figure 17). 15% of FF and 4% of MF groups rated “very dissatisfied”, “dissatisfied” and “neither satisfied nor dissatisfied” to ease of use. Moreover, 6 patients of FF group were troublesome to use the device of drug such as unable to press the side-actuated trigger. Percent of patients reported that they were very satisfied and satisfied with MF and FF treatment was not significantly different as shown in Figure 18.

Table 8 Effects of MF and FF attributes on patient preference after 2 and 4 weeks of treatment

Attribute/ Treatment group	Patient preference		*p* value†
	Week 2	Week 4	
Odor satisfaction			
• MF	4.26 ± 0.09	4.20 ± 0.09	0.646
• FF	4.33 ± 0.09	4.25 ± 0.09	0.530
Taste satisfaction			
• MF	3.96 ± 0.11	4.12 ± 0.11	0.300
• FF	3.97 ± 0.10	4.12 ± 0.09	0.286
Odor			
• MF	4.01±0.12	4.09±0.11	0.625
• FF	4.07±0.11	4.25±0.10	0.241
Taste			
• MF	3.88 ± 0.12	4.01 ± 0.10	0.412
• FF	3.90 ± 0.13	4.15 ± 0.11	0.152
Ease of use			
• MF	4.33 ± 0.08	4.49 ± 0.07	0.149
• FF	4.31 ± 0.09	4.28 ± 0.10	0.799
Not run out of nose			
• MF	4.38 ± 0.08	4.39 ± 0.78	0.897
• FF	4.30 ± 0.10	4.38 ± 0.09	0.521
Feeling of non-invasive			
• MF	4.90 ± 0.10	4.48 ± 0.09	0.165
• FF	4.40 ± 0.09	4.40 ± 0.08	0.962
Patient overall opinions on improvement			
• MF	4.33 ± 0.08	4.52 ± 0.67	0.066
• FF	4.28 ± 0.07	4.47 ± 0.07	0.080
Patient overall satisfaction			
• MF	4.42 ± 0.08	4.55 ± 0.06	0.208
• FF	4.40 ± 0.08	4.53 ± 0.07	0.238

Values are expressed as mean ± SEM.

† Unpaired *t*-test comparing mean of preference rating scores between drug treatment after week 2 and week 4.

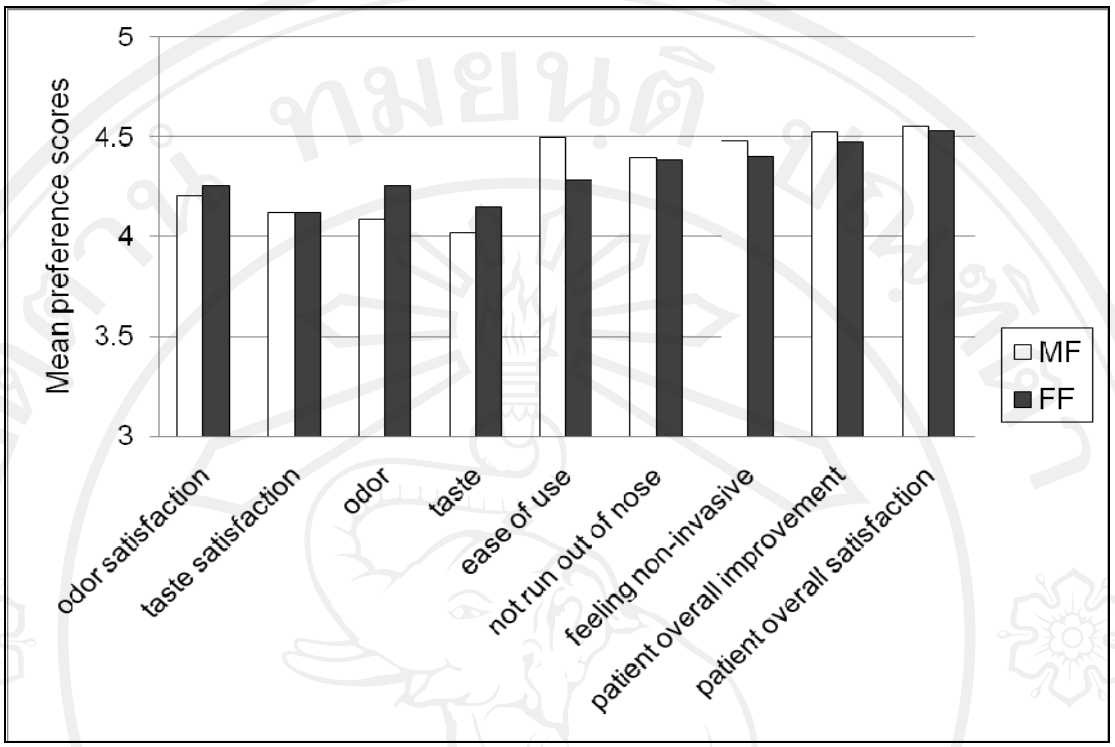

Figure 17 Effects of MF and FF attributes on patient preference after 4 weeks of treatment**.**

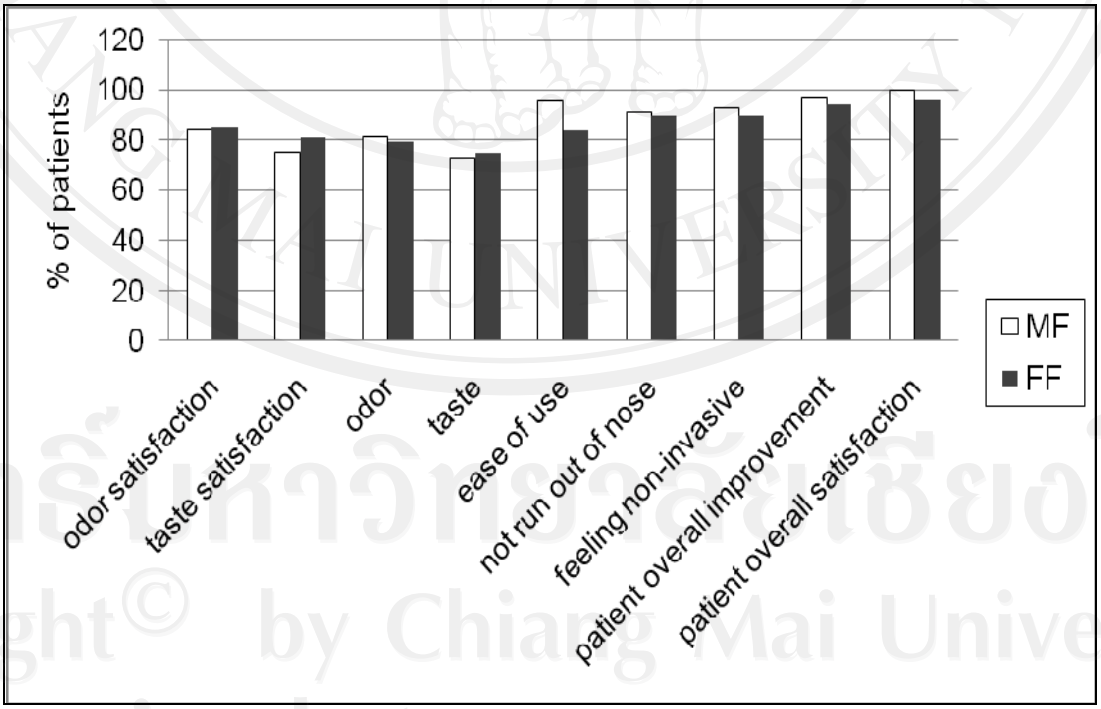

Figure 18 Percentage of patients very satisfied and satisfied with MF and FF treatment after 4 weeks of treatment**.**

3.6 ASSESSMENT OF AEs

Both drug treatments were well tolerated. AEs were reported by 50.71% of 140 patients. The overall incidence of AEs with both drugs was similar. Most AEs were mild or moderate in intensity and no severe AEs were reported. Burning or stinging in the nose, cough and dry/sore throat and upper respiratory infection were among the most common AEs reported by patients in both groups of treatment. More than one AEs might be reported by some patients. Burning or stinging in the nose was reported only in first week treatment, however, two patients in each group affected by this symptom throughout the study. The percentages of patients in both groups who experienced each AEs were not significantly different (Table 9).

Table 9 AEs in MF and FF treatment groups

Adverse event	% (n) of patients	
	MF (n = 70)	FF (n = 70)
Overall	57 (40)	44 (31)
Burning or stinging in the nose	14 (10)	13 (9)
Upper respiratory infection	10 (7)	7 (5)
Cough and dry/sore throat	10 (7)	7 (5)
Postnasal drip	6 (4)	1 (1)
Headache	9 (6)	4 (3)
Epistaxis	1 (1)	3 (2)
Nausea or vomiting	0	4 (3)
Rash	3 (2)	3 (2)
Anorexia	1 (1)	0
Insomnia	1 (1)	0
Myalgia	1 (1)	0

3.7 ASSESSMENT OF USE OF RESCUE THERAPY

There was statistically significant decrease in the requirement of rescue therapy at 4 weeks in MF and FF groups when compared to week 2. However, there was no statistically significant difference in requirement of rescue therapy between MF and FF treatment groups at 2 and 4 weeks (Table 10).

Table 10 Use of rescue therapy of MF and FF groups

Rescue therapy	Treatment period	Treatment group		*p* value †
		MF	FF	
NSS	Week 2			
	- times of use	63	49	0.146
	- number of subject	15	7	
	- range of use	1 - 14	1 - 9	
	Week4			
	- times of use	24*	9*	0.233
	- number of subject	7	4	
	- range of use	1 - 7	2 - 8	
Pseudoephedrine hydrochloride	Week2			
	- number of tablets	27	15	0.217
	- number of subject	7	3	
	- range of tablets	1 - 9	2 - 8	
	Week4			
	- number of tablets	9*	3*	0.623
	- number of subject	5	2	
	- range of tablets	1 - 4	1 - 2	

Values are expressed as mean ± SEM

* Significantly different from week 2 at $p < 0.05$

† Between group comparison