CHAPTER V

RESULTS

5.1 Demographic Characteristics of Patients

This study was conducted at 5 hospitals in Bangkok from April 2000 to June 2001. Seventy-one patients were enrolled in this study, 36 patients in the study group (latanoprost) and 35 patients in the control group (pilocarpine plus timolol) (Table 5.1.1). The mean age, the sex, the type of glaucoma, the number of patients from each hospital, the baseline IOP and the number of patients whose baseline IOP $\leq$ 25 mmHg and IOP > 25 mmHg in both groups, were comparable.

Of the 71 patients included, 68 patients completed the study. Two patients were withdrawn from the latanoprost group, and one patient from pilocarpine plus timolol group. The reason for withdrawal are presented in Table 5.1.2.

Table 5.1.1 : Demographic characteristics of patients

Characteristics	Latanoprost (n = 36)	Pilocarpine + Timolol (n = 35)	Total (n = 71)
Sex : number (%)			
Male	17 (47.2)	26 (74.3)	43 (60.6)
Female	19 (52.8)	9 (25.7)	28 (39.4)
Type of glaucoma : number (%)			
Primary open-angle	33 (91.7)	29 (82.8)	62 (87.3)
Pseudoexfoliation	0	5 (14.3)	5 (7.0)
Ocular Hypertension	3 (8.3)	1 (2.9)	4 (5.6)
Age (years)			
Mean (SD)	60.22 (14.37)	62.29 (11.41)	
Range	28 – 88	37 – 85	
Baseline IOP (mmHg)			
Mean (SD)	24.35 (1.84)	24.17 (1.94)	
Range	22.0 – 29.0	22.0 – 29.3	
Baseline IOP : number (%)			
$\leq$ 25 mmHg	25 (69.4)	25 (71.4)	50 (70.4)
> 25 mmHg	11 (30.6)	10 (28.6)	21 (29.6)
Hospital			
Bhumipol Adulyadej	9	8	17
Ramathibodi	10	11	21
Rajavithi	7	5	12
Somdej Pra Pinklao	2	3	5
Pramongkutklao	8	8	16

Table 5.1.2 : Reasons for patient withdrawal from the study

Reasons	Latanoprost (n = 36)	Pilocarpine + Timolol (n = 35)
- Low compliance	0	1
- Had cataract surgery at 2 months of the study	1	0
- Severe insomnia	1	0
Total number of patients withdrawn	**2**	**1**

5.2 Primary Outcome Analysis

5.2.1 Diurnal IOP Reduction from baseline at the third month

The mean diurnal IOP reduction from baseline was greater in the 36 latanoprost group than that in the 35 pilocarpine plus timolol group (7.34 $\pm$ 2.02 (SD) vs. 5.29 $\pm$ 2.91 mmHg, the mean difference between the two groups was 2.1 mmHg with 95% CI 0.632 to 3.553, p=0.005, 3 way ANOVA). Latanoprost lowered the mean diurnal IOP from 24.4 to 17 mmHg, a reduction of 30.1%. The corresponding figure for pilocarpine plus timolol group was a reduction from 24.2 to 18.9 mmHg (-21.9%). (Table 5.2.1.1, Table 5.2.1.2 and Fig. 5.2.1.1)

This *effectiveness analysis* was based on an intention to treat analysis, all 71 patients were analyzed according to their randomized

treatment, 3 withdrawal patients were analyzed with last observation carry forward approach.

We also did an *efficacy analysis* which was based on a per-protocol data set that included 68 completed adhere to protocol patients. The result was the same, IOP reduction from baseline was greater in the latanoprost group than in the control group ($p = 0.002$, 3 way ANOVA).

5.2.2 **Stratified patients effect**

Apart from a significant difference between the two treatment groups from drug effect ($p=0.005$), GMEANB1 (stratified patients into 2 groups, baseline IOP ≤ 25 and > 25 mmHg) also showed statistically significant difference effect ($p = 0.017$). (Table 5.2.1.1)

Table 5.2.1.1 : Univariate Analysis of Variance

Tests of Between-Subjects Effects

Dependent Variable: mean IOP at final visit

Source	Type III Sum of Squares	Df	Mean Square	F	Sig.
Corrected Model	165.881[a]	6	27.647	3.627	.004
Intercept	17647.741	1	17647.741	2315.127	.000
DRUG	63.926	1	63.926	8.386	**.005**
CENTER	44.904	4	11.226	1.473	.221
GMEANB1	46.132	1	46.132	6.052	**.017**
Error	487.859	64	7.623		
Total	23473.251	71			
Corrected Total	653.740	70			

a. R Squared = .254 (Adjusted R Squared = .184)

GMEANB1 = stratified patients into 2 groups as : 1.00 = IOP $\leq$ 25 mmHg

2.00 = IOP > 25 mmHg

Table 5.2.1.2 Diurnal IOP of the two treatment groups at each scheduled visit

Treatment	Baseline Mean (SD)	Week 2 Mean (SD)	Week 6 Mean (SD)	Month 3 Mean (SD)	IOP reduction from baseline Mean (SD) (% reduction)	P - Value
Latanoprost	24.35 (1.84)	17.78 (3.17)	17.69 (2.70)	17.01 (2.17)	7.34 (2.02) (30.14)	0.000 *
Pilocarpine plus Timolol	24.17 (1.94)	19.67 (2.79)	19.62 (3.28)	18.87 (3.55)	5.29 (2.91) (21.88)	0.000 *
						0.005 **

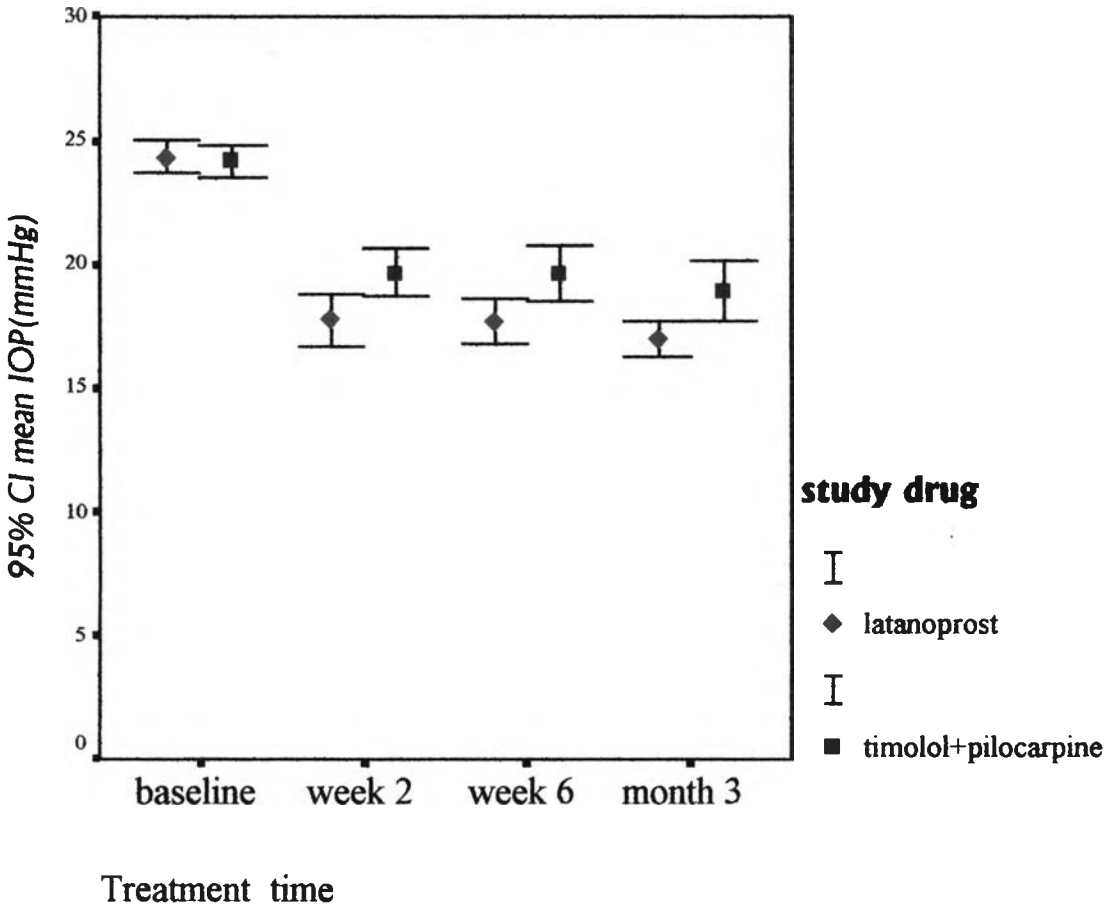
* By Paired t test

Difference in diurnal IOP at baseline and at month 3, in each treatment group.

** By 3 way ANOVA

Difference in diurnal IOP reduction from baseline at month 3, in two treatment groups.

Fig 5.2.1.1 : Diurnal IOP at each scheduled visit, in patients receiving latanoprost monotherapy (◆, n = 36), versus pilocarpine plus timolol (■ , n = 35).



5.3 Secondary Outcome Analysis

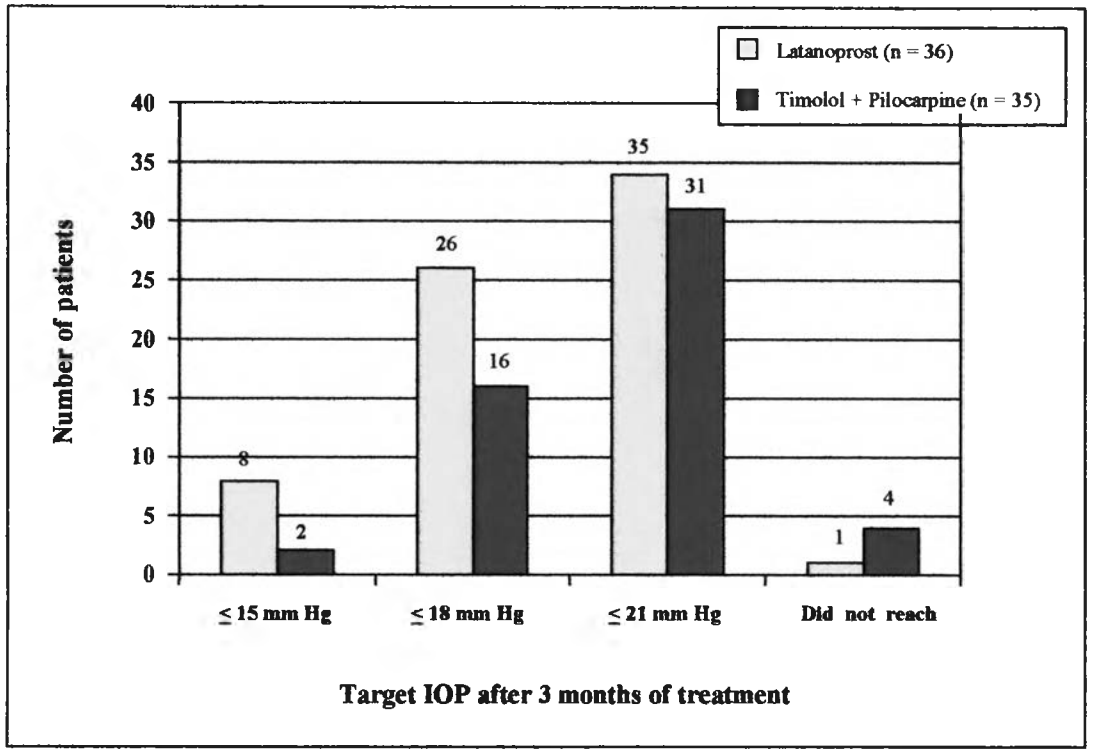
5.3.1 Success Rate of Treatment (number of patients who reached target IOP ≤ 15, ≤ 18, and ≤ 21 mmHg) in each treatment group. This study showed that more patients in the latanoprost group reached a target IOP ≤ 18 mmHg than in the control group. (Table 5.3.1 and Fig. 5.3.1)

Table 5.3.1 : Number of patients who reached a target IOP after 3 months of treatment

Target intraocular pressure (mm Hg)	Latanoprost (n = 36) number (%)	Pilocarpine + Timolol (n = 35) number (%)	P-value*
≤ 15	8 (22.2)	2 (5.7)	0.084
≤ 18	26 (72.2)	16 (45.7)	**0.042**
≤ 21	35 (97.2)	31 (88.6)	0.198
Did not reach	1 (2.78)	4 (11.4)	0.198

* By Fisher's exact test

Fig 5.3.1 : Number of patients who reached a target IOP after 3 months of treatment



5.3.2 Response Rate of Treatment (number of patients whose IOP reduction from baseline ≥ 10%, ≥ 20%, ≥ 30% and ≥40%)

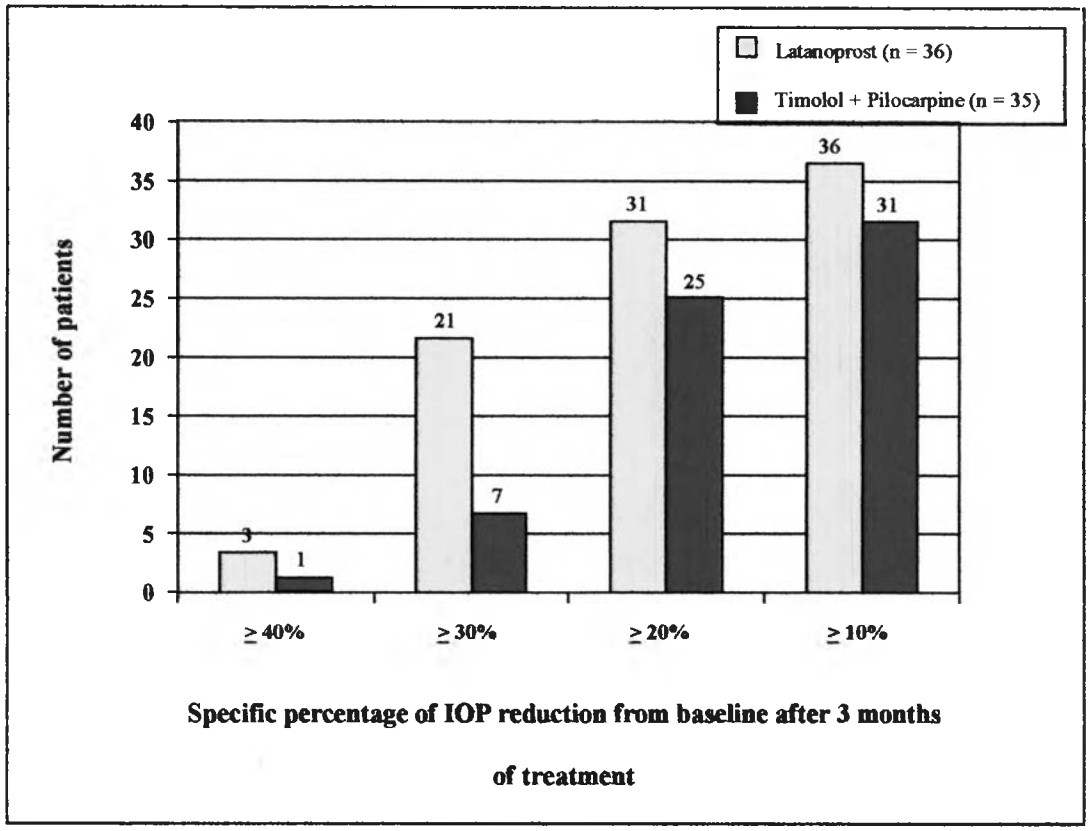
This study showed that more patients in the latanoprost group reached a reduction in diurnal IOP from baseline ≥ 30% than the control group. (Table 5.3.2 and Fig 5.3.2)

Table 5.3.2 : Number of patients who reached a specific IOP reduction from baseline after 3 months of treatment

Percentage of IOP Reduction from Baseline	Latanoprost (n = 36) number (%)	Pilocarpine + Timolol (n = 35) number (%)	P-value*
≥ 40%	3 (8.3)	1 (2.9)	0.614
≥ 30%	21 (58.3)	7 (20)	**0.002**
≥ 20%	31 (86.1)	25 (71.4)	0.221
≥ 10%	36(100)	31 (88.6)	0.054
< 10 %	0	4 (11.4)	0.054

* By Fisher's exact test

Fig 5.3.2 : Number of patients who reached a specific IOP reduction from baseline after 3 months of treatment



5.3.3 Ocular and systemic side effects in each treatment group. Serious ocular side effects did not occur in any patient in both the latanoprost and pilocarpine plus timolol groups. However, 25 ocular side effects occurred in each group.(Table 5.3.3.1) Eye discomfort and conjunctival hyperemia occurred more frequently in the latanoprost group, whereas decreased vision was more common in the pilocarpine plus timolol group. Apparent worsening of the visual field was reported in one patient in the pilocarpine plus timolol group.

No serious systemic side effect occurred in both groups.(Table 5.3.3.2) Severe insomnia was reported in one patient in latanoprost group that made the patient withdrawn from the study. Headache and browache were reported in two patients in pilocarpine plus timolol group.

For heart rate, systolic and diastolic blood pressure, no statistically difference detected between the two groups. (Table 5.3.3.3)

Table 5.3.3.1 : Number of patients with ocular side effects

Side Effects	Latanoprost (n = 36)	Pilocarpine + Timolol (n = 35)	P-value*
Ocular Effect			
Conjunctival hyperemia	10	7	0.550
Eye discomfort	10	6	0.363
Decrease vision	2	8	0.377
Superficial punctate keratitis	1	3	0.609
Cell in anterior chamber	(mild) 1	0	1.0
Visual field change	0	1	1.0
Visual acuity change	1	0	1.0
Total ocular side effects	**25**	**25**	

* By Fisher's exact test

Table 5.3.3.2 : Number of patients with systemic side effects

Side Effects	Latanoprost (n = 36)	Pilocarpine + Timolol (n = 35)	P-value*
Systemic effect			
Headache, browache	0	2	
Severe insomnia	1	0	
Total systemic side effects	**1**	**2**	**1.0**
Total number of side effects (Ocular + Systemic)	**26**	**27**	

* By Fisher's exact test

Table 5.3.3.3 : Resting blood pressure and heart rate at baseline and final visit

	Latanoprost (n = 36)		Pilocarpine + Timolol (n = 35)		P value*
	IOP ≤ 25 Mean (SD)	IOP > 25 Mean (SD)	IOP ≤ 25 Mean (SD)	IOP > 25 Mean (SD)	
SBP at baseline	136.67 (17.61)	136.36 (29.42)	137.60 (14.22)	135.00 (23.69)	< 0.001
SBP at final visit	139.92 (20.00)	129.09 (19.73)	136.40 (14.11)	140.30 (26.09)	**0.188**
DBP at baseline	80.42 (9.55)	85.00 (12.85)	79.00 (8.66)	77.00 (12.52)	< 0.001
DBP at final visit	79.96 (10.21)	78.18 (6.03)	79.40 (8.46)	78.30 (14.83)	**0.174**
HR at baseline	73.92 (11.55)	68.36 (5.78)	72.28 (7.86)	74.60 (8.69)	< 0.001
HR at final visit	77.17 (15.87)	68.55 (8.44)	71.75 (10.42)	75.00 (8.60)	**0.908**

SBP = Systolic blood pressure

DBP = Diastolic blood pressure

HR = Heart rate

*By 3 way ANCOVA

5.3.4 Cost-effectiveness Analysis:

Only direct medical cost (drug cost) from patient perspective and effectiveness of the drugs were analyzed. The main outcome measurement in this analysis was number of patients who reached the target IOP ≤15, ≤18 and ≤21 mmHg.

Cost-effectiveness ratio (Baht/one patient IOP control/year) for each group was analyzed by using:

$$\text{Cost-effectiveness ratio} = \frac{\text{cost/year/100 patients}}{\text{effectiveness/100 patients}}$$

Incremental analysis was performed by using:

$$\text{Incremental CE ratio} = \frac{\text{cost A - cost B}}{\text{effectiveness A - effectiveness B}}$$

Sensitivity analysis : varying cost of latanoprost and varying cost of timolol was done.

5.3.4.1 Cost-effectiveness ratio and incremental analysis

1. Drug cost :

   - Latanoprost (Xalatan^{R}Pharmacia) = 900 Baht/bottle/month-used

     So, it costs = 900*12 = 10,800 Baht/year/1 patient

     Then cost/year/100 patients = 10,800 x 100 = 1,080,000 Baht/year

   - Pilocarpine (IsoptoCarpine^{R}Alcon) = 78 Baht/bottle/month-used

- Timolol (Timoptol ^{R} MSD) = 150 Baht/bottle/month used

So, combination drug costs = (78+150)*12=2736 Baht/year/1 patient

Then cost/year/100 patients = 2,736 x 100 = 273,600 Baht/year

2. Effectiveness (see detail for using in calculation in Table 5.3.1)

2.1 ***When target IOP≤15 mmHg***

1. Latanoprost group: number of patients who reached *IOP ≤ 15 mmHg.* = 8 cases from n = 36,

then effectiveness/100 patients $= \frac{8}{36} \times 100 = 22.22$

2. Combination group: number of patients who reached *IOP≤ 15 mmHg.* = 2 cases from n = 35,

then effectiveness/100 patients $= \frac{2}{35} \times 100 = 5.71$

3. Cost-effectiveness ratio (Baht/one patient IOP control /year)

$$= \frac{\text{cost / year / 100 patients}}{\text{effectiveness / 100 patients}}$$

CE of latanoprost/year $= \frac{1{,}080{,}000}{22.22} = 48{,}600$

CE of pilocarpine + timolol/year $= \frac{273{,}600}{5.71} = 47{,}880$

4. Incremental analysis (in 100 patients) : latanoprost versus pilocarpine+timolol

$$= \frac{\text{cost A} - \text{cost B}}{\text{effectiveness A} - \text{effectiveness B}}$$

$$= \frac{1{,}080{,}000 - 273{,}600}{22.22 - 5.71}$$

$$= \frac{806{,}400}{16.51}$$

$$= 48{,}872.7 \quad \text{Bath/patient}$$

This incremental CE ratio shows that, in every 100 patients, if we want to cure (IOP control) one more patient by changing from the combination drug to latanoprost, we have to spend 48,872 Baht more for target IOP $\leq$ 15 mmHg.

2.2 ***When target IOP≤18 mmHg***

1. Latanoprost group: number of patients who reached *IOP≤18 mmHg* = 26 cases from n = 36,

then effectiveness/100 patients $= \frac{26}{36} \times 100 = 72.22$

2. Combination group: number of patients who reached *IOP≤ 18 mmHg* = 16 cases from n = 35,

then effectiveness/100 patients $= \frac{16}{35} \times 100 = 45.71$

3. Cost-effectiveness ratio (Baht/one patient IOP control/year)

$$= \frac{\text{cost / year / 100 patients}}{\text{effectiveness / 100 patients}}$$

CE of latanoprost/year $= \frac{1{,}080{,}000}{72.22} = 14{,}953.80$

CE of pilocarpine + timolol/year $= \frac{273{,}600}{45.71} = 5{,}985$

4. Incremental analysis (in 100 patients) : latanoprost versus pilocarpine+timolol

$$= \frac{\text{cost A} - \text{cost B}}{\text{effectiveness A} - \text{effectiveness B}}$$

$$= \frac{1{,}080{,}000 - 273{,}600}{72.22 - 45.71}$$

$$= \frac{806{,}400}{26.51}$$

$$= 30{,}418.7 \quad \text{Bath/patient}$$

This incremental CE ratio shows that, in every 100 patients, if we want to cure (IOP control) one more patient by changing from the combination drug to latanoprost, we have to spend 30,4183.7 Baht more for target IOP $\leq$ 18 mmHg.

2.3 ***When target IOP≤21 mmHg***

1. Latanoprost group: number of patients who reached target IOP = 35 cases from n = 36,

then effectiveness/100 patients $= \frac{35}{36} \times 100 = 97.22$

2. Combination group: number of patients who reached target IOP = 31 cases from n = 35,

then effectiveness/100 patients $= \frac{31}{35} \times 100 = 88.57$

3. Cost-effectiveness ratio (Baht/one patient IOP control /year)

$$= \frac{\text{cost / year / 100 patients}}{\text{effectiveness / 100 patients}}$$

CE of latanoprost/year $= \frac{1,080,000}{97.22} = 11,108.60$

CE of pilocarpine + timolol/year $= \frac{273,600}{88.57} = 3,089.00$

4. Incremental analysis (in 100 patients) : latanoprost versus pilocarpine+timolol

$$= \frac{\text{cost A} - \text{cost B}}{\text{effectiveness A} - \text{effectiveness B}}$$

$$= \frac{1{,}080{,}000 - 273{,}600}{97.22 - 88.57}$$

$$= \frac{806{,}400}{8.65}$$

$$= 93{,}225.4 \quad \text{Bath/patient}$$

This incremental CE ratio shows that, in every 100 patients, if we want to cure (IOP control) one more patient by changing from the combination drug to latanoprost, we have to spend 93,225.4 Baht more for target IOP $\leq$ 21 mmHg.

Table 5.3.4.1 : Cost-effectiveness ratio and incremental analysis for target IOP $\leq$15, $\leq$18 and $\leq$21 mmHg in both treatment groups.

	IOP$\leq$15	**IOP$\leq$18**	**IOP$\leq$21**
CE of latanoprost / year	48,600.00	14,953.80	11,108.60
CE of pilocarpine + timolol / year	47,880.00	5,985.00	3,089.00
Incremental analysis	48,872.70	30,418.70	93,225.40

5.3.4.2 Sensitivity analysis

We did sensitivity analysis only for target ***IOP≤18 mmHg.*** Because when target IOP≤15 mmHg, the CE ratio of the two groups were nearly equal and when target IOP ≤ 21 mmHg, it was clearly shown that the combination group had much more cost effectiveness than latanoprost group.

Sensitivity analysis with IOP ≤18 mmHg :

$$\text{CE/year} = \frac{\text{cost / year / 100 patients}}{\text{effectiveness / 100 patients}}$$

CE of pilocarpine + timolol/year = 5,985.00

5.3.4.2.1 Varying the cost of latanoprost

- If latanoprost cost/bottle = 360 Baht

$$\text{CE of latanoprost/year} = \frac{360 \times 12 \times 100}{72.22} = 5{,}983.40$$

- If latanoprost cost/bottle = 280 Baht

$$\text{CE of latanoprost/year} = \frac{280 \times 12 \times 100}{72.22} = 4{,}653.70$$

5.3.4.2.2 Varying the cost of timolol

- If timolol cost/bottle = 100 Baht (pilocarpine cost/bottle = 78 Baht)

$$\text{CE of pilocarpine+timolol/year} = \frac{(78+100) \times 12 \times 100}{45.71}$$

$$= 4{,}674$$

(See interpretation in discussion, pp. 63-64)