การศึกษาเปรียบเทียบคุณสมบัติการขยายรูม่านตาระหว่าง 1% tropicamide/2.5% phenylephrine hydrochloride และ 1% tropicamide/10% phenylephrine hydrochloride ในผู้ป่วยที่มีม่านตาสีคล้ำ: การทดลองแบบสุ่มตัวอย่าง มีตัวควบคุมและปิดสองทาง

กิตติศักดิ์ กุลวิชิต พ.บ.

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
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CLINICAL EQUIVALENCE BETWEEN A COMBINATION OF 1%TROPICAMIDE/2.5% PHENYLEPHRINE HYDROCHLORIDE AND 1%TROPICAMIDE/10%PHENYLEPHRINE IN PUPILLARY DILATATION EFFICACY IN DARK IRIDES: A DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL

KITTISAK KULVICHIT, M.D.

A Thesis Submitted in Partial Fulfillment of the Requirements
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Health Development Programme
Graduate School
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Thesis Title	Clinical equivalence between a combination of 1% tropicamide/2.5% phenylephrine hydrochloride and 1% tropicamide/10% phenylephrine in pupillary dilatation efficacy in dark irides: A double blind randomized controlled trial
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บทคัดย่อวิทยานิพนธ์

กิตติศักดิ์ กุลวิชิต : การศึกษาเปรียบเทียบคุณสมบัติการขยายรูม่านตาระหว่าง 1% tropicamide/2.5% phenylephrine hydrochloride และ 1% tropicamide/10% phenylephrine hydrochloride ในผู้ป่วยที่มีม่านตาสีคล้ำ: การทดลองแบบสุ่มตัวอย่าง มีตัวควบคุมและปิดสองทาง. (Clinical equivalence between a combination of 1%tropicamide/2.5% phenylephrine hydrochloride and 1%tropicamide/10%phenylephrine in pupillary dilatation efficacy in dark irides: a double blind randomized controlled trial) อ. ที่ปรึกษา : รศ.พญ.อรนุช เกี่ยวข้อง, 31หน้า. ISBN 974-03-0992-5.

วัตถุประสงค์ : เพื่อเปรียบเทียบประสิทธิภาพในการขยายม่านตาในผู้ป่วยที่มีม่านตาสีเข้มระหว่าง 2.5% เฟนนิลเอฟรีนไฮโดรคลอไรด์ร่วมกับ 1% ทรอปิคามายด์ กับ 10% เฟนนิลเอฟรีนไฮโดรคลอไรด์ร่วมกับ 1% ทรอปิคามายด์

รูปแบบการทดลอง : การทดลองทางคลีนิคแบบสุ่มทดลองโดยมีกลุ่มเปรียบเทียบ

สถานที่ทำการวิจัย : โรงพยาบาลจุฬาลงกรณ์ กรุงเทพมหานคร

ประชากรที่ทำการศึกษา : ผู้ป่วยที่มารับการตรวจที่แผนกผู้ป่วยนอก ภาควิชาจักษุวิทยา ที่แพทย์ผู้ทำการรักษาต้องการขยายม่านตาและเข้าได้กับเกณฑ์การศึกษาจำนวน 196 คน

ระเบียบวิธีวิจัย : ผู้ป่วยที่มารับการตรวจที่แผนกผู้ป่วยนอกภาควิชาจักษุวิทยาที่แพทย์ผู้ทำการรักษาต้องการขยายม่านตาและเข้าได้กับเกณฑ์การศึกษาจะได้รับการสุ่มเป็น 2 กลุ่ม กลุ่มแรกได้รับ 2.5% เฟนนิลเอฟรีนไฮโดรคลอไรด์ร่วมกับ 1% ทรอปิคามายด์ ส่วนกลุ่มที่สองได้รับ 10% เฟนนิลเอฟรีนไฮโดรคลอไรด์ร่วมกับ 1% ทรอปิคามายด์ ซึ่งผู้ป่วยทั้งสองกลุ่มจะได้รับการหยอดยาดังกล่าวทุก 10 นาทีรวม 3 ครั้ง การวัดผลทำโดยเปรียบเทียบขนาดม่านตาในแนวนอนที่เวลา 30 นาที ความดันโลหิต อัตราการเต้นของหัวใจและความดันลูกตา

ผลการวิจัย : ขนาดเฉลี่ยของม่านตาที่ 30 นาทีในกลุ่มที่ 1 เป็น 7.35 มิลลิเมตร (SD = 0.9) โดยมี 95% CI เท่ากับ 7.17-7.53 มม. ขนาดเฉลี่ยของม่านตาที่ 30 นาทีในกลุ่มที่ 2 เป็น 7.58 มม. (SD = 0.77) ความแตกต่างเฉลี่ยของม่านตาระหว่างสองกลุ่มมีค่าเท่ากับ 0.22 มม. และมี 95% CI เท่ากับ –0.46 ถึง 0.007 มม. ไม่พบความแตกต่างของความดันโลหิต อัตราการเต้นของหัวใจ และความดันลูกตาภายหลังการหยอดยาระหว่างสองกลุ่ม

สรุป : ในกลุ่มผู้ป่วยที่มีม่านตาสีเข้มพบว่า 2.5% เฟนนิลเอฟรีนไฮโดรคลอไรด์ร่วมกับ 1% ทรอปิคามายด์มีประสิทธิภาพในการขยายม่านตาเทียบเท่า 10% เฟนนิลเอฟรีนไฮโดรคลอไรด์ร่วมกับ 1% ทรอปิคามายด์

ภาควิชา	การพัฒนาสุขภาพ	ลายมือชื่อ
สาขาวิชา	การพัฒนาสุขภาพ	ลายมือชื่ออาจารย์ที่ปรึกษา
ปีการศึกษา	2544	

ABSTRACT

4275377330 : MAJOR HEALTH DEVELOPMENT

KEY WORD: EQUIVALENCE / PUPILLARY DILATATION / DARK IRIDES / RANDOMIZED / PHENYLEPHRINE HYDROCHLORIDE

KITTISAK KULVICHIT : CLINICAL EQUIVALENCE BETWEEN A COMBINATION OF 1%TROPICAMIDE/2.5% PHENYLEPHRINE HYDROCHLORIDE AND 1%TROPICAMIDE/10%PHENYLEPHRINE IN PUPILLARY DILATATION EFFICACY IN DARK IRIDES: A DOUBLE BLIND RANDOMIZED CONTROLLED TRIAL. THESIS ADVISOR : ASSOC.PROF.ORANUCH KYOKONG, M.D., M.Sc., 31 pp. ISBN 974-03-0992-5.

Objectives : To compare the efficacy of pupillary dilatation between 1%tropicamide with 2.5%phenylephrine hydrochloride and 1%tropicamide with 10%phenylephrine hydrochloride in dark irides.

Design : A double blind randomized controlled trial

Setting : Chulalongkorn Hospital, Bangkok

Participants : One hundred and ninty six out-patient department patients who required pupillary dilatation

Methodology : The pateints were randomized into two groups. The experimental group received 2.5% Phenylephrine Hydrochloride with 1% Tropicamide and the conventional group received 10% Phenylephrine Hydrochloride with 1% Tropicamide. The combination of drops were instilled every 10 minutes for three times. The horizontal diameter of the pupil was measured at 30 minutes.

Results : The mean pupil size at 30 minutes in the experimental group (2.5% Phenylephrine) was 7.35 mm (SD = 0.9) and the 95% CI was 7.17-7.53 mm. The mean pupil size of the conventional group (10% Phenylephrine) was 7.58 mm (SD = 0.77). The mean difference in pupil size between these groups was 0.22 mm and the 95% CI was –0.46mm to 0.007 mm. There was no difference found in terms of adverse effects.

Conclusion : When combined with 1% Tropicamide, 2.5% Phenylephrine hydrochloride was clinically equivalent to 10% Phenylephrine hydrochloride in terms of pupillary dilatation in dark irides.

Department	Health Development	Student's signature
Field of study	Health Development	Advisor's signature
Academic year	2001	

ACKNOWLEDGEMENTS

Objectives: To describe the process and the background of this thesis.

Design: Descriptive, non-comparative acknowledgements.

Methodology: The data in my fond memory was reviewed from day 1 since I took on this clinical epidemiology endeavour. All the possible biases were subjectively (also known as biasly) removed.

Results: As I traveled down the memory lane, I remembered that I started this master degree course with a lot of uncertainties and scepticisms. As time went by and I gathered more and more data, I was a lot more confident that I had taken the right course. Jane and Ben have been the greatest inspiration for me to strive forward. I would have never been at this point without them.

At the end of the course, I felt that I was another person. A person that looks at things from all the angles. A person that is so critical. A person that is enthusiastic to find unfound truth. And a person who knows the best things are still ahead of him. Being as ungrateful as one could be, I intentionally omitted a traditional list of persons to be thanked. If you think you deserve your name being mentioned here, please consider you are sincerely thanked and appreciated. This way, I won't miss anybody. Conversely, if you think you are not deserved a thank you, you may secretly be admired deep inside of my heart.

Conclusion: As the author, I must take full responsibilities myself. As to the thesis, it must speak for itself. As a reader, you must judge the value of this work for yourself

CONTENTS

CHAPTER I
RATIONALE & BACKGROUND

The complete eye examination requires dilatation of the pupil, which is usually achieved by instillation of parasympatholytic and sympathomimetic eye drops. The parasympatholytic drug will block the parasympathetic innervations to the iris sphincter, while the sympathomimetic drug will stimulate the dilator muscle of the iris. These two kinds of eye drops work synergistically.

In most, if not all ophthalmic outpatient services in Thailand including the Department of Ophthalmology, Chulalongkorn University Hospital, 1% tropicamide drops are used as the parasympatholytic drug and 10% phenylephrine hydrochloride drops as the sympathomimetic drug. However, since 10% phenylephrine hydrochloride is a potent sympathomimetic drug, it can cause several serious ophthalmic and systemic side effects.(1-8) One drop of 10% phenylephrine hydrochloride contains three or four times the maximum safe dose for intravenous administration of the drug to a young and healthy adult.(1) There are various reports indicating that 2.5% phenylephrine hydrochloride, which is thought to have less adverse effects, is not as effective in terms of pupillary dilatation as 10% phenylephrine hydrochloride in dark irides.(9-11) Nonetheless there is no single well-controlled trial to support such a claim. On the other hand, it is well documented that, in Caucasians, 2.5% phenylephrine hydrochloride is as effective as 10% phenylephrine hydrochloride with fewer complications.

To address this issue, a double blind randomized controlled trial should be conducted in a population with dark irides to determine either superiority of one over the other or equivalency between 2.5% phenylephrine hydrochloride and 10% phenylephrine hydrochloride in terms of pupillary dilatation efficacy.

CHAPTER II
REVIEW OF LITERATURE

2.1 Adverse effects

In 1956, McReynolds reported a case of acute subarachnoid hemorrhage resulting from the use of phenylephrine.(12) Since then, there have been many reports on various adverse reactions associated with 10% phenylephrine, e.g. severe hypertension(1, 3, 4, 13) and ventricular arrhythmia.(14) Fraunfelder reported a series of 33 cases with adverse effects from the drug.(1) These cases included both systemic and local complications. The systemic cases exhibited severe increase of systemic blood pressure, tachycardia, reflex bradycardia and myocardial infarcts. Fifteen cases of myocardial infarcts were reported, 11 of which died. In the series, one local ocular reaction, a massive subconjunctival hemorrhage, occurred within five to ten minutes after application of topical ocular 10% phenylephrine in a preoperative cataract case. In conclusion, morbidity and mortality caused by local ophthalmic administration of 10% phenylephrine hydrochloride are well documented.

2.2 Iris Colour and Mydriatic Effect of Phenylephrine

In 1927, Howard and Lee first reported the difference between Caucasians with light coloured irides and Chinese with dark irides. They stated that light coloured irides responded to smaller doses and gave a larger mydriasis, which developed more rapidly to equal doses.(15) Later on, Chen and Poth observed that ephedrine was considerably less active in dilating the pupils in Americans of African and Chinese descent than in white Americans.(16) There are many postulates to explain this phenomenon. One postulate is that phenylephrine has to be absorbed through the cornea into the aqueous humour whereupon it will be absorbed by the iris surface. In darker irides, the anterior border layer of the iris is thicker with denser iris chromatophores and has fewer crypts. The absorption of a mydriatic from the aqueous fluid would be much slower than in an iris with more numerous and larger crypts and pores.(11) It is also possible that some enzymes play a role. Angenent and Koelle (9) suggested that the difference might be due to increased destruction of the sympathetic transmitter in pigmented irides and they found that adrenaline was oxidized more rapidly by homogenates of

pigmented irides than of albino irides from rabbits, owing to the presence of a more active catechol-oxidase system.

2.3 Previous articles that compared 2.5% and 10% phenylephrine hydrochloride

Duffin(17) et al compared 2.5% aqueous phenylephrine hydrochloride with 10% viscous phenylephrine hydrochloride in maintaining pupillary dilatation during cataract surgery. The study was based on the idea that viscous solution might be systematically absorbed more slowly than the aqueous solution hence causing fewer complications. The authors found that iris colour was a significant variable in the maintenance of intraoperative mydriasis. Blood pressure increases were no more significant with 10% phenylephrine hydrochloride in viscous form than with 2.5% concentration in aqueous. However, they found no significant effect of the iris colour on the initial preoperative pupil dilatation.

Neuhaus and Hepler(18) reported no statistical difference between 2.5% phenylephrine hydrochloride and 10% phenylephrine hydrochloride in 11 randomly selected patients. The sample was rather small and both 2.5% and 10% solutions were given to the same patient, one in each eye. This can cause a bias from systemic absorption. Moreover, they had only blue and brown irides in the sample groups and the proportions of iris colour within the groups were not clearly stated.

In conclusion, none of the previous studies has fulfilled the following criteria:

- Comparison between 1%tropicamide with 2.5%phenylephrine and 1%tropicamide with 10%phenylephrine.
- Double blind randomized controlled trial in dark irides.
- Big enough sample size in order to establish equivalency or superiority.

CHAPTER III
RESEARCH DESIGN AND METHODOLOGY

3.1 Research Questions

Primary: Allowing for 1mm differences in pupil size, was 1%tropicamide with 2.5%phenylephrine as effective as 1%tropicamide with 10%phenylephrine for pupillary dilatation in dark irides?

Secondary: Were there any differences in adverse effects between the two groups? Adverse effects of interest were those such as:

- Increase in blood pressure
- Increase in heart rate
- Increase in intraocular pressure

3.2 Objectives

To compare the efficacy of pupillary dilatation between 1%tropicamide with 2.5%phenylephrine hydrochloride and 1%tropicamide with 10%phenylephrine hydrochloride in dark irides.

To compare the adverse effects between 1%tropicamide with 2.5%phenylephrine hydrochloride and 1%tropicamide with 10%phenylephrine hydrochloride in dark irides.

3.3 Research Hypothesis

The combination of 1%tropicamide and 2.5%phenylephrine hydrochloride does not differ, in terms of dilatation efficacy, more than 1mm in pupillary size from the combination of 1%tropicamide and 10%phenylephrine hydrochloride in dark irides.

3.4 Operational definition

Dark irides: The irides which give the “black” colour to the eye colour, e.g. irides of Asian or African ethnic groups.

Efficacy of Pupillary Dilatation: Pupil size at 30 minutes after the first set of eyedrops.

Range of equivalence: -1 mm to +1mm. The reason why this range was chosen was because it was the size of papillary size difference that did not have clinical significance. In other words, a pupil size of 6.5 mm would have the same clinical implication a pupil size of 7.5 mm.

3.5 Research Design

The study was carried out as a randomized double-blind controlled trial. The randomization process ensured that the allocation of treatment is independent of the characteristics of the patients. It also increased the level of internal validity of the statistical methods of analysis applied since it was based on the assumption of random samples. The blind process was applied to the intervention giver, patients, and outcome assessors.

3.6 Research Methodology

3.6.1 Population & Sample

Target Population: Out Patient Department (OPD) patients who required a dilated fundus examination.

Sample Population: OPD patients at the Department of Ophthalmology, King Chulalongkorn Memorial Hospital who required a dilated fundus examination and met the inclusion criteria.

3.6.2 Inclusion Criteria

a) Age 16-80
b) Have dark irides
c) Agree to participate and sign the informed consent

3.6.3 Exclusion Criteria

a) History of hypertension, DM, or heart diseases
b) History of intraocular surgery or laser surgery
c) History of iritis, anterior or posterior synechiae, Horner's syndrome, Adies' pupil or any other pupillary abnormality.
d) History of using eyedrops in the past month
e) History of ocular injury
f) History of previous attack of acute angle closure glaucoma or high risk patients, e.g. shallow anterior chamber

3.6.4 Outcomes

The main outcome was the horizontal pupil size at 30 minutes. The secondary outcomes were blood pressure, heart rate, and intraocular pressure changes.

3.6.5 Sampling method

The convenient method was used. Everyday the research assistant would attend the dilating room, where patients received dilating drops following a doctor's order for papillary dilatation. The research assistant would then determined whether or not the patient fit the inclusion criteria.

3.6.6 Allocation and Concealment

The patients who met the above selection criteria were randomized into either group A or B.

Group A: 1%tropicamide combined with 2.5%phenylephrine hydrochloride every 10 minutes x 3 times

Group B: 1%tropicamide combined with 10%phenylephrine hydrochloride every 10 minutes x 3 times

The randomization was done by using a randomization table. After an eligible patient agreed to participate in the study and had signed the informed consent, the research assistant then telephoned the statistician, who handled the randomization, and asked which bottle of eyedrops to give to the patient.

3.6.7 Preparation of the drugs

Both 2.5% Phenlyephrine Hydrochloride and 10% Phenylephrine Hydrochloride were prepared by a pharmacist at Chulalongkorn Hospital. They were in identical bottles and labelled in running numbers. The code control sheet was sealed in an envelop and was given to the statistician who did the randomization. The code would be revealed in the following situations:

1) at the end of the study

2) when the end pupil size of a patient did not satisfy the doctor who took care of the patient. Then the code would be broken. And if it showed that the eyedrops that the patient received was the 2.5% Phenylephrine hydrochloride, the doctor would be informed as such and given an option of the conventional 10% Phenylephrine hydrochloride.

3.6.8 Blinding

The eyedrops were given by the research assistant who was blind to which treatment was being given. This was achieved by masking both treatment in identical bottles labelled in running numbers.

The patients were not informed as to which arm of the randomized grouping they were in.

The assessors of outcomes were also blind against guessing treatment arm from complications, e.g. rise in blood pressure, by seperating the assessors of the main outcome (pupil size at 30 minutes) and complications. The data collection forms were also seperated.

The data collection forms comprised of three seperate forms:

1) Demographic data: Filled by research assistant

2) Pupil size (Primary outcome): Filled by the assessor of the main outcome

3) Blood pressure, Heart rate and Intraocular pressure: Filled by research assistant

3.6.9 Exit from the protocol

The patients would exit the protocol in one of the following circumstances:

1) Upon completion of the protocol, ie. the measurement of the primary outcome was done.

2) The patient had severe adverse reaction before the completion of the protocol.

3) The patient decided to exit the study.

3.6.10 Sample Size

Since this study was an equivalence trial the method of sample size calculation would be different from a comparative study.(19) In the confidence interval approach, equivalence is concluded if the interval falls entirely within two pre-specified (-1mm to +1mm in this study) tolerance limits. The formula(19) used to estimate the sample size in this study was:

$n = 2s^2/\Delta^2[z(1-(alpha)) + z(1-ß/2))]^2$ Power = 2(Phi) (/(square root)s^2(2/n)) - z(1-(alpha)) - 1

A pilot study was required for an estimation of variance. The result of the pilot study are shown in the Chapter IV.

With the alpha error of 0.05 and beta error as 0.2, a sample size of 60 patients per group was estimated from the formula. However, because of the expected amount of patients per days was quite large, together with the cost-effectiveness of hiring research assistants, a sample size of 100 patients per arm was the target. The additional patients would pose little extra burden to the research team. And we considered that it would be worth the more power it provided.

3.6.11 Measurement

Variables: Independent Variable = Intervention given
Dependent Variable = Pupillary size at 30 mins

3.6.11.1 Instrumental Design

A slitlamp biomicroscope (Fig 1) was used to measure the pupil size. A scale with resolution up to 0.1mm is built-in most of the slitlamps. (Fig2) In this study, Haag-

Striet slitlamp biomicroscope model 900 was used. The pupil size was measured horizontally at 30 minutes after the drops. Each day before measurement the instrument was standardized.

Figure 1. The photo shows how the pupil size is measured.

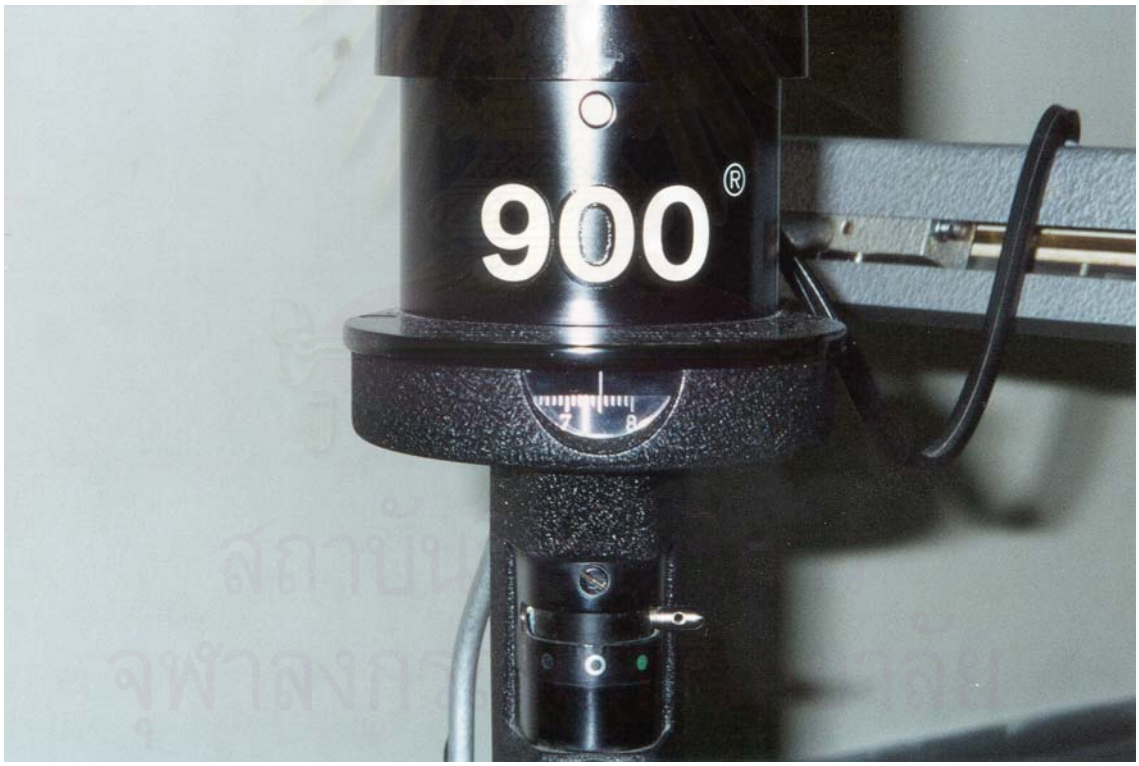

Figure 2. The scale on the slit-lamp.

3.6.11.2 Validity

The slitlamp is widely used as a tool for measurement of the anterior segment geometry of the eye.21 The scale on the slitlamp is a tried-and-true measurement of linear length. In fact, it has been used as a gold standard against many other instruments. However in this study we had established the precision of the slitlamp measurement against a micrometer and a vernier both of which had the resolution up to 0.01mm. (Fig 3,4) (results in Table 1) We used five objects of various sizes and measured them using the slitlamp, vernier and micrometer.

Figure 3. Micrometer

Figure 4. Vernier

Table 1. Validity test

Micrometer (mm)	Vernier (mm)	Slitlamp Biomicroscope (mm)
4.2	4.2	4.2
5.7	5.7	5.7
6.9	6.9	6.9
7.3	7.3	7.3
8.4	8.4	8.4

In conclusion, the scale for linear measurement in the slitlamp biomicroscope was precise up to 0.1mm resolution.

3.6.11.3 Reliability

The reliability was tested in two conditions:

1) The reliability of the instrument

2) The reliability of the method used

3.6.11.3.1 The reliability of the instrument(in vitro)

The test was performed by measuring a series of lines on a paper using the slitlamp.(Fig 5) Each line was measured twice. The results are shown in Table 2.

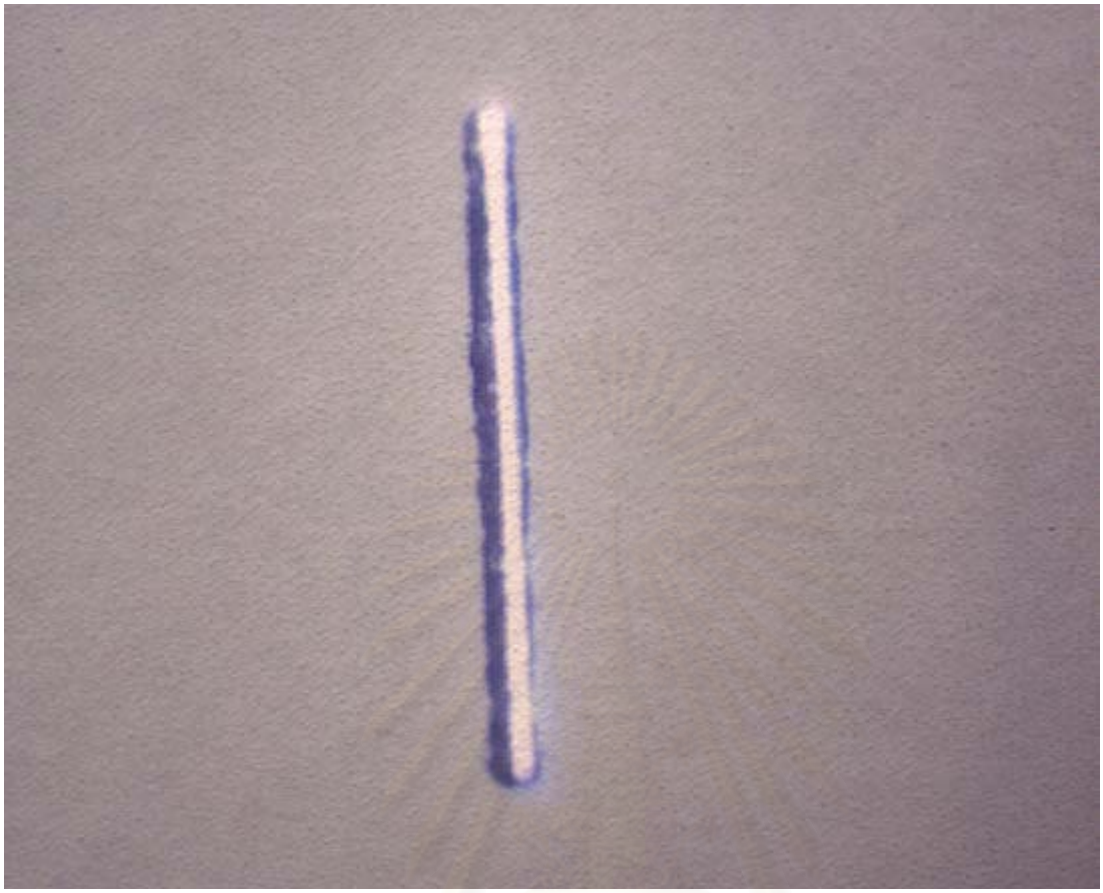

Figure 5. The blue line was the line to be measured. The white line was the light from the slit-lamp.

Table 2 Reliability test (in vitro)

Measurement I	Measurement II
5.9	5.9
6.4	6.4
6.7	6.7
6.8	6.8
7.0	7.0
7.3	7.3
7.4	7.4
7.7	7.7
7.9	7.9
8.2	8.2

3.6.11.3.2 The reliability of the method used (in vivo)

Even though the instrument produced prefect repeatability (within 0.1mm resolution) when used to measure the lines on a paper, it might not have the same level of reliability when used to measure a pupil size in a patient. Eye movement and blinking could cause an error in measurement. So we tested the reliability of the measurement in real patients. Ten patients were measured. The results are shown in Table 3

Table 3. Reliability test (in vivo)

Measurement I	Measurement II
5.7	5.7
6.1	6.1
6.3	6.3
6.6	6.6
7.0	7.0
7.2	7.2
7.4	7.4
7.7	7.7
7.7	7.7
8.2	8.2

3.6.12. Data Collection

After the first set of eyedrops, the following parameters would be measured.

1) Pupil size: If both eyes received the dilating drops in one patient, the mean was used to represent the pupil size of that patient. It was measured before the instillation of the first set of drops and then at 30 minutes.

2) Blood pressure was measured each time before the instillations.

3) Pulse rate was measured each time before the instillations.

4) Intraocular pressure: This was measured at 0 and 30 minutes.

The nurse who gave the drops and the evaluators had separate lists of patients. Each recorded the relevant data into their own lists. At the end of the day, all data would be keyed into the computer database. The data entering process was done independently by two research assistants. Then these two copies of database were compared against each other to ensure data accuracy.

CHAPTER IV
ETHICAL CONSIDERATION

The potential complications of dilating drops and the objectives of the study were explained to the patients in details. It was made clear that the treatment of interest, 2.5%phenylephrine hydrochloride, had a potentially less complications, albeit a possibility of being less effective. The equal chance of receiving either drops was pointed out. The medical equipment and personnel to properly handle the complications were set ready on site.

Insofar as the ethical considerations were concerned, the patients were fairly treated because:

1) The treatment of interest had a potentially less harmful effect when compared to the conventional treatment.

2) Appropriate measures were prepared to handle complications.

3) The treatment of interest had some evidence to support the belief that it might be as effective as the conventional treatment.

4) There was an exit way for the “treatment of interest” group to receive the conventional treatment, if the outcome was not satisfactory.

5) Informed consent was a prerequisite to enter the study and the patients had the right to exit the study at any time without affecting the quality of care.

The protocol and details of the study were submitted to the Ethics Committee of the Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand for approval. It was approved on the 28th of September 2000 and the number of Study Protocol Approval Form was 210/2000.

CHAPTER V
RESULTS

4.1 Pilot Study

The pilot study was done in 10 patients. The results are shown in the Table 4.

Table 4. Pilot study in 10 patients

Patients No.	Pupil size at 30 minutes (mm)
1	6.6
2	8.5
3	8.7
4	8.4
5	7.8
6	7.6
7	7.5
8	7.8
9	8.3
10	7.4

The mean pupil size was 7.87 mm and the standard deviation was 0.62.

4.2 Main study

A total of 196 patients were enrolled comprising of 119 females (60.7%) and 77 males (39.3%). The mean + SD age of the patients was 46 + 15 years (range 18 to 80 years). The demographic data is shown in Table 5. There was no premature exit from the protocol. No code had to be broken before the end of the study.

Table 5. Demographic data

	2.5% Group (n = 100)	10% group (n = 96)
Gender (Male/Female)	39/61	38/58
Age (Mean, SD, Range)	46.5, 16, 20-80	45.8, 14.3, 18-72

4.2.1 Primary outcome analysis

The mean pupil size at 30 minutes of the 2.5% group was 7.35 mm (SD = 0.90) and the 95% confidence interval was 7.17-7.53 mm. For the 10% group, the mean pupil size was 7.58 mm (SD = 0.77) and the 95% CI was 7.42-7.74 mm. The mean difference of the pupil size between the two groups was 0.22 mm (p=0.058) and the standard error of mean was 0.12. The 95% CI of the difference in pupil size was –0.46 to 0.007 mm.

4.2.2 Secondary outcomes analysis

The blood pressure, heart rate and intraocular pressure before the drops are shown in the Table 6.

Table 6. Baseline data of the secondary outcomes

	2.5% Group	10% Group
BP (mmHg)	131/73	127/70
HR (beat/min)	74 $\pm$ 12	74 $\pm$ 11
IOP (mmHg)	16.1 $\pm$ 3.5	15.5 $\pm$ 3.5

For the secondary outcomes analysis, the ANCOVA model was used. The results are shown in the Table 7.

Table 7. Secondary outcomes analysis

	F	Sig
Systolic pressure	1.150	0.285
Diastolic pressure	0.084	0.772
Heart rate	0.410	0.523
IOP	0.741	0.391

Since we also measured the blood pressure and heart rate at the 10 and 20 minutes as well as at the 30 minute, we performed the repeated measurement analysis to see if there was any changes in blood pressure and heart rate. The result is shown in the Table 8-13.

Table 8. Repeated measurement analysis for systolic blood pressure- Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Eta Squared
SYS	Sphericity Assumed	6734.145	3	2244.715	56.501	.000	.226
	Greenhouse-Geisser	6734.145	2.862	2352.869	56.501	.000	.226
	Huynh-Feldt	6734.145	2.924	2302.712	56.501	.000	.226
	Lower-bound	6734.145	1.000	6734.145	56.501	.000	.226
SYS * DRUG	Sphericity Assumed	132.737	3	44.246	1.114	.343	.006
	Greenhouse-Geisser	132.737	2.862	46.377	1.114	.342	.006
	Huynh-Feldt	132.737	2.924	45.389	1.114	.342	.006
	Lower-bound	132.737	1.000	132.737	1.114	.293	.006
Error(SYS)	Sphericity Assumed	23122.319	582	39.729			
	Greenhouse-Geisser	23122.319	555.247	41.643			
	Huynh-Feldt	23122.319	567.342	40.756			
	Lower-bound	23122.319	194.000	119.187			

Table 9. Repeated measurement analysis for systolic blood pressure- Pairwise Comparisons

(I) SYS	(J) SYS	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
1	2	6.474	.614	.000	4.837	8.112
	3	7.203	.693	.000	5.355	9.051
	4	6.535	.696	.000	4.680	8.390
2	1	-6.474	.614	.000	-8.112	-4.837
	3	.729	.583	1.000	-.826	2.283
	4	6.083E-02	.625	1.000	-1.605	1.726
3	1	-7.203	.693	.000	-9.051	-5.355
	2	-.729	.583	1.000	-2.283	.826
	4	-.668	.601	1.000	-2.269	.933
4	1	-6.535	.696	.000	-8.390	-4.680
	2	-6.083E-02	.625	1.000	-1.726	1.605
	3	.668	.601	1.000	-.933	2.269

Based on estimated marginal means

* The mean difference is significant at the .05 level.

a Adjustment for multiple comparisons: Bonferroni.

Table 10 Repeated measurement analysis for diastolic blood pressure – Tests of Within-Subjects Effects

Source		Type III Sum of Squares	df	Mean Square	F	Sig.	Eta Squared
DIAS	Sphericity Assumed	583.066	3	194.355	7.101	.000	.035
	Greenhouse-Geisser	583.066	2.827	206.256	7.101	.000	.035
	Huynh-Feldt	583.066	2.888	201.906	7.101	.000	.035
	Lower-bound	583.066	1.000	583.066	7.101	.008	.035
DIAS * DRUG	Sphericity Assumed	122.194	3	40.731	1.488	.217	.008
	Greenhouse-Geisser	122.194	2.827	43.225	1.488	.219	.008
	Huynh-Feldt	122.194	2.888	42.314	1.488	.218	.008
	Lower-bound	122.194	1.000	122.194	1.488	.224	.008
Error(DIAS)	Sphericity Assumed	15928.811	582	27.369			
	Greenhouse-Geisser	15928.811	548.419	29.045			
	Huynh-Feldt	15928.811	560.236	28.432			
	Lower-bound	15928.811	194.000	82.107			

Table 11. Repeated measurement analysis for diastolic blood pressure-Pairwise comparison

Pairwise Comparisons

Measure: MEASURE_1

(I) DIAS	(J) DIAS	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
1	2	2.193	.557	.001	.707	3.678
	3	2.015	.582	.004	.464	3.567
	4	1.514	.571	.052	-8.343E-03	3.036
2	1	-2.193	.557	.001	-3.678	-.707
	3	-.177	.482	1.000	-1.462	1.108
	4	-.679	.500	1.000	-2.010	.653
3	1	-2.015	.582	.004	-3.567	-.464
	2	.177	.482	1.000	-1.108	1.462
	4	-.501	.468	1.000	-1.748	.745
4	1	-1.514	.571	.052	-3.036	8.343E-03
	2	.679	.500	1.000	-.653	2.010
	3	.501	.468	1.000	-.745	1.748

Based on estimated marginal means

* The mean difference is significant at the .05 level.

a Adjustment for multiple comparisons: Bonferroni.

Table 12. Repeated measurement analysis for heart rate- Tests of Within-Subjects Contrasts

Source	HR	Type III Sum of Squares	df	Mean Square	F	Sig.	Eta Squared
HR	Linear	1454.143	1	1454.143	77.153	.000	.285
	Quadratic	193.072	1	193.072	17.717	.000	.084
	Cubic	4.044	1	4.044	.404	.526	.002
HR * DRUG	Linear	5.455	1	5.455	.289	.591	.001
	Quadratic	6.144E-02	1	6.144E-02	.006	.940	.000
	Cubic	.701	1	.701	.070	.792	.000
Error(HR)	Linear	3656.407	194	18.847			
	Quadratic	2114.177	194	10.898			
	Cubic	1942.435	194	10.013			

Table 13. Repeated measurement analysis for heart rate- Pairwise Comparisons

(I) HR	(J) HR	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
1	2	2.340	.359	.000	1.382	3.297
	3	3.365	.410	.000	2.271	4.459
	4	3.719	.431	.000	2.569	4.869
2	1	-2.340	.359	.000	-3.297	-1.382
	3	1.026	.329	.013	.148	1.904
	4	1.380	.337	.000	.482	2.278
3	1	-3.365	.410	.000	-4.459	-2.271
	2	-1.026	.329	.013	-1.904	-.148
	4	.354	.326	1.000	-.514	1.222
4	1	-3.719	.431	.000	-4.869	-2.569
	2	-1.380	.337	.000	-2.278	-.482
	3	-.354	.326	1.000	-1.222	.514

Based on estimated marginal means

* The mean difference is significant at the .05 level.

a Adjustment for multiple comparisons: Bonferroni.

CHAPTER VI
CONCLUSION

In this study, the clinical equivalence of the efficacy of pupillary dilation between 2.5% Phenylephrine Hydrochloride and 10% Phenylephrine Hydrochloride when combined with 1% Tropicamide was defined as the difference of less than + 1mm (-1mm to +1mm). The reason for choosing 1 mm difference for equivalence was because it was the difference that could be detected by naked eye and it was the least amount of difference that could effect the fundus examination.

The result from this study showed that the 95% CI was –0.46 mm to 0.007 mm. Both lower limit, -0.46mm and the upper limit, 0.007 mm, lied entirely within the range of equivalence. Therefore, the combination of 2.5% Phenylephrine Hydrochloride with 1% Tropicamide was clinically equivalent to the combination of 10% Phenylephrine Hydrochloride with 1% Tropicamide in terms of papillary dilatation in patients with dark irides.

As for the secondary outcomes, which were mainly the side effects from the eyedrops, there were no differences detected. The blood pressure, heart rate and intraocular pressure were comparable between both groups. The reason for this might be because our sample was too small to detect the differences in secondary outcomes. Moreover, patients with hypertension or heart diseases who might be more susceptible to adverse effects, were excluded from this study.

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VITAE

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