การศึกษาหาประสิทธิภาพระยะสั้นของยาด๊อกซาโซซิน ในการรักษาโรคต่อมลูกหมากโต โดยวิธีการแบบสุ่มปิดฉลาก เปรียบเทียบกับยาหลอก

อนุพันธ์ ตันติวงศ์

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THE SHORT TERM EFFECTIVENESS OF DOXAZOSIN IN TREATMENT OF BENIGN PROSTATIC HYPERPLASIA (BPH). A RANDOMIZED DOUBLE -BLIND PLACEBO-CONTROLLED TRIAL

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วัตถุประสงค์ : เพื่อเปรียบเทียบอัตราการดีขึ้นของอาการโรคต่อมลูกหมากโตที่ไม่มีภาวะแทรกซ้อน ในชายอายุ 50 ปีขึ้นไป ซึ่งรักษาโดยยาด๊อกซาโซซินกับรักษาด้วยยาหลอกเป็นเวลา 3 เดือน

รูปแบบ : การทดลองเปรียบเทียบกับยาหลอกแบบสุ่มปิดฉลาก

สถานที่ : ในห้องตรวจระบบปัสสาวะ ภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล

ประชากร : ผู้ป่วย 32 คน อายุ 50 ปีขึ้นไป ซึ่งมีคะแนนอาการ IPSS $\geq$ 8, อัตราการไหลปัสสาวะสูงสุด $\leq$ 15 มล.ต่อวินาที ไม่เป็นมะเร็งต่อมลูกหมาก หรือเคยรักษาโรคต่อมลูกหมากโต ได้รับการจับฉลากแบบสุ่มเพื่อรักษาโดยยาด๊อกซาโซซิน 15 คน และยาหลอก 17 คน

วิธีการ : ผู้ป่วยได้รับยาด๊อกซาโซซินหรือยาหลอก ขนาด 1 มก.ก่อนนอนในวันที่ 1-3, 2 มก. ในวันที่ 4-10 และ 4 มก. ในวันที่ 11-21 เมื่อมาตรวจติดตามที่ 3 สัปดาห์ ผู้ป่วยถูกประเมินความรู้สึกในการถ่ายปัสสาวะในครั้งนี้ โดยให้เปรียบเทียบกับการถ่ายปัสสาวะก่อนการได้ยา และใช้คำถามประเมินโดยรวมเพียง 1 คำถาม แสดงผลการศึกษาหลัก หากตอบว่าอาการดีขึ้นมากผู้ป่วยจะได้รับยาขนาด 4 มก.ต่อไปจนครบ 3 เดือน แต่ถ้าอาการยังไม่ดีขึ้นมาก ผู้ป่วยจะได้รับยาเพิ่มขึ้นเป็น 8 มก.จนครบ 3 เดือน ผู้ป่วยจะมาติดตามและประเมินด้วยคำถามเดียวกันเมื่อครบ 3, 6, 9 และ 12 สัปดาห์

ผล : กลุ่มได้ยาด๊อกซาโซซิน หรือยาหลอกมีอาการโดยรวมดีขึ้น 84.6% และ 80.0% ตามลำดับ เมื่อนำผลประเมินที่มาตรวจติดตามครั้งสุดท้ายมารวมกัน แต่ถ้าประเมินที่ 6 สัปดาห์ ผลดีขึ้นเป็น 83.3% และ 66.7% ในกลุ่มยาด๊อกซาโซซิน และยาหลอกตามลำดับ การเปลี่ยนแปลงของคะแนนอาการ IPSS และอัตราการไหลสูงสุดของปัสสาวะในกลุ่มยาด๊อกซาโซซินดีกว่ากลุ่มยาหลอกเพียงเล็กน้อย อาการแทรกซ้อนจากยาจริงพบมากกว่า แต่ผลเปรียบเทียบในทุกด้านทางสถิติ ไม่พบมีความแตกต่างกันเลยทั้งสองกลุ่ม

สรุป : การศึกษาครั้งนี้ซึ่งจำกัดด้วยจำนวนผู้ป่วย พบว่าประสิทธิภาพระยะสั้นของยาด๊อกซาโซซิน ไม่แตกต่างทางคลินิก และทางสถิติจากยาหลอก ทั้งในการประเมินโดยรวม หรือคะแนนอาการ หรืออัตราไหลสูงสุดของปัสสาวะ แต่ถ้ารวมผลทั้งสามเข้าด้วยกันน่าจะทำให้ผลการศึกษาเชื่อถือได้มากขึ้น และอาจเห็นประสิทธิภาพของยาด๊อกซาโซซินได้

ภาควิชา การพัฒนาสุขภาพ ลายมือชื่อนิสิต.....

สาขาวิชา การพัฒนาสุขภาพ ลายมือชื่ออาจารย์ที่ปรึกษา.....

ปีการศึกษา 2543 ลายมือชื่ออาจารย์ที่ปรึกษาร่วม.....

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KEYWORD: BENIGN PROSTATIC HYPERPLASIA / DOXAZOSIN / EFFECTIVENESS / RANDOMIZED CONTROLLED TRIAL ANUPAN TANTIWONG: THE SHORT TERM EFFECTIVENESS OF DOXAZOSIN IN TREATMENT OF BENIGN PROSTATIC HYPERPLASIA (BPH) : A RANDOMIZED DOUBLE-BLINDED PLACEBO-CONTROLLED TRIAL. THESIS ADVISOR: PROF. CHITR SITTHI-AMORN, M.D., Ph.D., THESIS CO-ADVISOR; ASSOC.PROF. NIRUN VANPRAPAR, M.D., M.Sc. 36 pp. ISBN 974-13-0026-3

Objective : To compare the percentage of symptom improvement between Doxazosin and placebo after three-month treatment of symptomatic uncomplicated BPH in men age $\geq$ 50 years old.

Design : Randomized double-blind placebo-controlled trial

Setting : Urological out-patient unit in a tertiary care medical school hospital.

Patients : Thirty-two patients aged 50 years or older with international prostate symptom score (IPSS) $\geq$ 8, peak flow rate $\leq$ 15 ml/sec and without prostate cancer or concurrent treatments for BPH were randomly allocated into 15 cases in Doxazosin group and 17 cases in Placebo group.

Interventions : Patients received Doxazosin or placebo 1 mg at bedtime on D1 to D3, 2 mg on D4 to D10 and 4 mg on D11 to D21. At 3-week follow up visit, the global subjective assessment which was the main outcome was evaluated by one question in order to compare the voiding feeling at that time with the time before treatment. If the subjective symptom was "much improved", the dose maintained until the end of study. If not, the dose was titrated to 8 mg and maintained until the end. The duration of treatment was three months. The global subjective assessment was done in every visits at 3, 6, 9 and 12 week.

Result : By the global subjective assessment, the symptom improvement rate was 84.6% in Doxazosin group and 80.0% in Placebo group when the outcome was evaluated at the last visit of each patient. When the outcome was analyzed at 6 weeks, the improvement rate was 83.3% and 66.7% in Doxazosin and Placebo group respectively. The change in IPSS and peak flow rate in Doxazosin group was better than in Placebo group. The adverse effect in Doxazosin group was higher. There was no statistical significance in the difference of all outcomes between both groups.

Conclusion : This limited study shows that the effectiveness of Doxazosin was not clinically and statistically different from Placebo in term of symptom improvement or IPSS or peak flow rate, but the combination of these outcomes may obtain more reliable result and demonstrate effectiveness of Doxazosin.

Department..Health Development..... Student's signature .....

Field of study..Health Development..... Advisor's signature .....

Academic year..2000..... Co-advisor's signature .....

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LIST OF ABBREVIATIONS

BPH	Benign Prostatic Hyperplasia
IPSS	International Prostate Symptom Score
PF	Peak Flow
QOL	Quality of Life
SD	Standard Deviation
SE	Standard Error

CHAPTER 1

BACKGROUND AND RATIONALE

1. BACKGROUND AND RATIONALE

With the present economic crisis in Thailand and other Asian countries, the most cost-effective treatment should be chosen. BPH (Benign Prostatic Hyperplasia), the most common benign neoplasm in the aging male, has a high prevalence that increases progressively with age. In Thailand as in other countries in Asia, the prevalence of symptomatic BPH (symptom score $\geq$ 8 out of 35) is 31% , 50% and 65% in the age groups of 50 to 59, 60 to 69 and 70 to 79 years, respectively.[1] The symptoms of BPH may consist of weak stream, frequency of urination during daytime and / or bedtime, urgency, hesitancy, intermittency and incomplete voiding. Although this condition is rarely lifethreatening, it can significantly impair the quality of life, disturb the patient's day-to-day functioning and cause discomfort and health worries. [2]

There are many modalities of treatment for BPH based on patient's preference and clinical need. [3] Transurethral resection of the prostate (TUR -P) is the most common surgical treatment for BPH with complications such as recurrent acute retention, chronic retention, recurrent urinary tract infection, vesical stone and renal failure. For symptomatic, uncomplicated BPH, there are two alternative forms of treatment. The first one is watchful waiting or conservative treatment which is an appropriate strategy for the majority of patients especially for patients with mild to moderate BPH. The second one is medical treatment which is now very popular for treatment of moderate to severe BPH patients. There are no definite or recommended criteria or indications to select between two treatment modalities and it is acceptable to select either of them but we do not know which one is more effective and in which condition.

There are two main groups of drug, 5-alpha reductase inhibitor and alpha blocker. Finasteride is a 5-alpha reductase inhibitor that blocks conversion of testosterone to dihydrotestosterone and reduces the size of the prostate gland. Since its maximal effect requires six months or more [3] and its cost is about 40 Baht per day, it is not suitable for study. In the alpha blocker group, there are many kinds of drug such as prazosin, terazosin, doxazosin and alfuzosin which are available in Thailand. The maximal effect of these drugs can be demonstrated within four weeks. There is no evidence to suggest that any one alpha blocker is more effective than the other.[3] Although prazosin is cheap, it is just a short acting alpha blocker that has to be taken twice a day and the prevalence of orthostatic hypotension is rather high. Therefore, we have selected doxazosin in our study, which is a long acting alpha blocker with a better tolerance and compliance than the short acting one[4] and being the cheapest one in the long acting alpha blocker group and it is in the National Essential Drug List.

The real effectiveness of doxazosin and its clinical significance is questionable. In the 29 placebo controlled studies, the difference of peak flow rate of the alpha blocker compared to placebo is 1.47 ml/sec (15.8%).[4] It means that the effect size is rather small. The median probability of symptom improvement based on global subjective assessment in placebo is 45% and 90% CI is 26-65%.[5] In alpha blocker treatment, the median probability is 74% and 90% CI is 59-86%. Although the mean improvement between placebo and alpha blocker is quite different but the range of confidence interval are wide and overlapping. There has not been any kind of randomized controlled trial on BPH treatment in Thailand and if we want to do a cost effectiveness study we need a randomized controlled trial for effectiveness study in our situation, so we decide to conduct this study.

We design a randomized double-blind placebo-controlled trial because there is a considerable symptomatic improvement with placebo,[7] and we want complete blindness in our study. At the same time, the outcome of the placebo is comparable to the outcome of watchful waiting or conservative treatment. The median probability in symptom improvement of watchful waiting is 42% and 90% CI is 31-55%.[5]

Finally the natural history of BPH and the outcome of medical treatment is unpredictable. Sometimes patients feel better, sometimes they feel worse. So if we conduct a short term study, we may demonstrate the factors which predict the outcome and can select the most appropriate treatment.

In natural history of BPH, symptom can change from time to time and within a short period. So the drug which can demonstrate the maximum effect in a short period after administration will be useful in treatment according to the nature of the disease. It means that the doctor can modify the course of treatment which is suitable and cost effective to each individual.

In conclusion, an important rationale for conducting this study is to demonstrate the real effectiveness of drug compared to watchful waiting in treatment of symptomatic uncomplicated BPH in Thai. The result of the study will be benefit to Thai patients in selecting their appropriate treatment.

CHAPTER 2

LITERATURE REVIEW

BPH is characterized by a group of symptoms usually referred to as prostatism or lower urinary tract symptoms. For most patients , these symptoms are the dominant aspect of the disease and the motivating factor in seeking medical attention. More than 90% of all surgical procedures performed for BPH in the United States was done for symptoms or a combination of symptoms and other indications.[6] Of all the direct treatment outcome, symptom improvement is of the greatest concern of the patient.

In the past, improvement of symptom was evaluated by global subjective assessment by either the patient or his physician. There are three categories of changes in symptom status "improved " " unchanged " and " worse " [5]. About 40% of the patients were reported with global improvement after the placebo treatment and the same following watchful waiting . Improvement in alpha blocker treatment was 74% and in finasteride treatment was 67%. By this assessment we could not determine the magnitude of symptom improvement in each individual. In this study, we still use global subjective assessment as a main outcome because it mostly represent the real patient's concern.

In the present, symptom scores were reported in most of the studies. Many symptom scores has been developed in the last 20 years such as Boyarsky system in 1976 , Madsen and Iversen system in 1983 and AUA symptom index in 1992. The AUA symptom index is clinically sensible , reliable, valid and responsive. It is practical for use in clinical practice and for inclusion in research protocols[9]. The international consultation on BPH has developed IPSS (International Prostate Symptom Score) by modification of the AUA symptom index and adding one question of quality of life score. This has been recommended for worldwide use as an initial and outcome evaluation of BPH.[10]

Some studies demonstrated the mean pretreatment and posttreatment symptom scores. They compared them with the total score and reported as a percentage of the total score. The difference of percentage of score in pre and post treatment is the magnitude of effect of the treatment. By this measurement, the mean improvement in score in alpha blocker group was 48% compared with 32% in placebo group.[5]

Most of the studies nowadays evaluate the outcome of treatment in term of symptom score and report the improvement of symptom score in percentage of the group and compare the difference in percentage of improvement between treatment and placebo. In review article in 1995[4] Eri reported the weighted average improvement in overall symptom score was 38.7% for patients receiving alpha blocker and 24.8% for those receiving placebo with the difference being 13.9%. There is no definite criteria to determine the symptom score improvement in each individual and we can not relate this objective treatment outcome with the subjective feeling of the patients, so we can not determine the clinical significance of the treatment. In the second and third International Consultation on BPH in 1993 and 1995, the BPH consultation committee has proposed a tentative concept and response criteria for evaluation of efficacy,[7,8] but it is not clear and acceptable now.

From the third international consultation on BPH, the BPH consultation committee also highly recommended a peak or maximum urinary flow rate (Qmax), voiding diary (frequency volume chart), digital rectal examination, urinalysis, renal function assessment and PSA for initial evaluation in BPH patients. [11]

Peak urinary flow rate is an indirect treatment outcome determined in many studies. Although it is recommended in the initial diagnostic assessment and during or after treatment to determine response,[11] but because of the great intraindividual variability and the volume dependency, the correlation between peak flow rate and scores on individual questions were poor.[12] In our study we will assess urinary flow rate as a secondary outcome.

In review article in 1995,[4] Eri suggested that there was a dose-response relationship for alpha blocker. High dose increased the flow rate and decreased the symptom score but also increased the chance of adverse effects. So titration of the dose is recommended. He also reported that four weeks has been proposed as the minimum duration of treatment required to obtain full effect of alpha blocker.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 RESEARCH QUESTIONS

3.1.1 Primary research question :

Does Doxazosin have additional 25 percent of symptom improvement than placebo in three months treatment of symptomatic uncomplicated BPH in men age $\geq$ 50 years old ?

3.1.2 Secondary research questions :

(1) Is Doxazosin more effective than placebo in term of decreasing symptom score, increasing quality of life and increasing peak flow rate?

(2) What are the adverse effects of Doxazosin?

3.1.3 Research objectives

(1) To determine the effectiveness and adverse effects of Doxazosin in short term treatment of symptomatic uncomplicated BPH and compare these outcomes with outcomes of placebo or watchful waiting treatment.

(2) To determine the appropriate dose in treatment of BPH.

(3) To determine the reliable measurement of effectiveness of treatment.

3.1.4 Hypothesis

If the percentage of symptom improvement of Doxazosin treatment = D, percentage of symptom improvement of placebo treatment = P

Ho : D = P

Ha : D > P

3.2 OPERATIONAL DEFINITIONS

(1) Symptom improvement : defined as any level of improvement in global subjective assessment. So percentage of symptom improvement is a percentage of patient who has symptom improvement in each group. This is a primary outcome.

(2) Global subjective assessment : consisted of five categories ,much improved, slight improved, unchanged, slightly worse and much worse. This assessment was done by the patients at each visit compared to the feeling about his urination before treatment. (Appendix)

(3) IPSS or International Prostate Symptom Score : is a standard questionnaire recommended by WHO to evaluate the symptoms of BPH patients. It consists of 7 questions with 5 scores in each question. The maximum total score is 35 points. (Appendix)

(4) Urinary flow rate : is an indirect outcome most commonly used objectively to determine the efficacy of BPH treatment. It is measured by uroflowmeter in unit of ml./sec. Each peak and mean flow rate is determined from a total voided volume $\geq$ 150 ml.

(5) Quality of life : is evaluated by one question QOL-IPSS questionnaire recommended by WHO. It has 7 levels with score 0 - 6. (Appendix)

(6) Adverse effects of the drug: consists of dizziness, headache, syncope, fainting, orthostatic hypotension, fatigue and other. (Appendix)

(7) Symptomatic uncomplicated BPH : defined as a patient who has lower urinary tract symptoms similar to BPH and has no complication of BPH such as retention of urine, hematuria, vesical stone, urinary tract infection and renal failure. (Appendix)

(8) Individual symptom score: is a score for each symptom of IPSS such as nocturia, frequency and hesitancy. Each symptom is evaluated by scores from 0 to 5.

(9) Intention to treat analysis : The main outcome (Global subjective assessment) was analysed according to the treatment assigned at the beginning.

- The patient who could not take the medicine due to adverse effect was considered as failure of treatment.
- The patient who lost follow up at the beginning was considered as failure of treatment.
- The patient who lost follow up after 3 weeks was considered according to the outcome of the last visit.

3.3 RESEARCH DESIGN

A randomized double – blind placebo – controlled trial

3.4 THE SAMPLE

3.4.1 Target population :

The target population was all symptomatic uncomplicated BPH patients who fit the eligible criteria.

3.4.2 Sample population

The sample population was BPH patients who attended urological out-patient unit in Siriraj hospital in 1998-2000.

3.4.3 Eligible Creteria

Inclusion Criteria :

- Men 50 years of age and older, ambulatory condition.
- Have voiding problem
- IPSS $\geq$ 8
- Peak flow rate $\leq$ 15 ml/sec. in a total voided volume $\geq$ 150 ml.
- Prostatic enlargement as determined by digital rectal examination (DRE).
- The patient has given written informed consent for participation

Exclusion Criteria :

- Suspected prostate cancer due to elevation of PSA and/or abnormal DRE.
- Complicated BPH for which TUR-P is indicated (e.g., urinary retention, bladder stones, recurrent urinary tract infection or gross hematuria and renal failure).
- Pharmacologic treatments that affect voiding function or BPH. except discontinuation of the drugs at least one month before entering the study. (There is no exception for finasteride treatment.)
- Previous prostate surgery, TUR-P or minimally invasive surgery.
- Any known causes other than BPH for urinary symptoms or reduction in flow rate. (e.g., neurogenic bladder, bladder neck contracture, urethral stricture, acute or chronic prostatitis, bladder malignancy)
- Hypotension (sitting BP. less than 90/60) or orthostatic hypotension

3.3.4 Sample size estimation

Because the main outcome is the percentage of symptom improvement of two independent groups, i.e. Doxazosin group and placebo group. The formula for sample size calculation is

$$n/group = \frac{2 (Z\alpha + Z\beta)^2 \ \pi (1 - \pi)}{(P_t - P_c)^2}$$

$$\pi = \frac{P_t + P_c}{2}$$

Specify α - error = 5%

β - error = 10%

$Z\alpha$ = 1.96 (two - tail)

$Z\beta$ = 1.28

Pt (percent improvement of Doxazosin) = 0.7

Pc (percent improvement of placebo) = 0.45

Outcome difference = .25

$$n / group = \frac{2 (1.96 + 1.28)^2 \times 0.575 \times 0.425}{(0.25)^2}$$

= 82

Dropout rate = 10%

n / group = 90 cases

3.4.5 Randomization

A computer - generated randomization schedule provided balanced blocks of patient numbers for each treatment group. Patients were randomized in blocks of four.

3.4.6 Stratification

In order to make sure that the number of patient with different severity balanced in both groups, before randomization the patient was stratified according to the severity of the disease.

There were two parameters which determined the severity, IPSS and peak flow rate. They were independent and not related to each other.

IPSS was stratified into three levels: 8-12, 13-19 and 20-35.

Peak flow rate was stratified into two levels : 12-15 and <12 ml/sec.

There was 6 strata in this study.

3.5 INTERVENTION

The first visit was a screening visit. Screening or initial evaluation consisted of adequate medical history, IPSS, voiding diary, physical examination and digital rectal examination, urinalysis, renal function assessment, serum PSA and uroflowmetry.

In the next visit, if a patient fit the eligible criteria he was stratified into one of six strata and randomly allocated into one of the two treatment groups, doxazosin and placebo. The drug was titrated from small dose to high dose in order to prevent the adverse effects as recommended by the drug company. Patients took 1 mg.placebo or 1 mg doxazosin at bedtime on D1 to D3, 2 mg placebo or doxazosin on D4 -D10 and 4 mg placebo or doxazosin on D11 to D21. (D = day)

Patients returned to visit a doctor on D22 and was evaluated for efficacy. Patients with an adequate response maintained at the same dose for the duration of the study. Patients who did not respond adequately were titrated to the next dose of 8 mg doxazosin or placebo.

An adequate response is defined as having a “much improved” in global subjective assessment in the first or 3-week follow up visit.

How to analyse in this condition analyse by the dose that he could maintain. If some adverse effects such as fainting occur, the dosage should be reduced by one dose level or the patient may discontinue the drug but must contact the investigator.

The patients were followed up at week 3, 6, 9 and week 12. Symptoms, adverse effects including blood pressure in sitting position and urinary flow rate were evaluated. At each visit, pills were counted to assess compliance. Concurrent medication was determined. The importance of drug compliance and concurrent medication was stressed.

The treatment period was three months and the outcomes of the treatment was evaluated at the end of the study.

3.6 OUTCOME MEASUREMENT

3.6.1 Baseline data : consists of age in years, IPSS (total score and individual symptom score), quality of life score, peak and mean flow rates (ml/sec), and serum PSA or prostate specific antigen (ng/ml). The baseline characteristics of patient in the doxazosin and placebo groups will be reported in terms of mean and standard deviation.

3.6.2 Outcomes : at the end of study, the following outcomes will be evaluated :

Therapeutic response : consists of post treatment peak flow rate, IPSS and QOL score. The absolute change (pre - post) and relative change (pre-post /pre) will be calculated. Global subjective assessment will be done. The symptom improvement which is the main outcome will be evaluated according to the operational definition.

Adverse events : consist of complications of BPH and adverse effects of drugs during the treatment period.

3.7 DATA COLLECTION

A medical history, demographic data and complete physical examination is to be completed by physician at Visit 1 or screening visit. IPSS and quality of life questionnaire should be completed by the patient. If the patient can not do this by himself, a trained resident or nurse will be responsible for interviewing. Urinary flow rate was determined using a uroflowmeter at screening. The peak flow rate will be read manually from the printout. All baseline data will be recorded in case record form (CRF) and transferred into the data base in computer.

At a follow up visit, evaluation of the treatment response, adverse effects and complications of BPH will be done and recorded in the CRF.

In the last visit, outcome evaluation will be done . All variables will be recorded in the CRF and computer.

3.8 DATA ANALYSIS

An intention-to-treat analysis was used in evaluating results. The outcome of patient who has to discontinue study treatment due to adverse effects or other problems will be evaluated at the end of the study. For the dropout patients, the reasons for dropout and the outcome will also be reported.

Comparability of the two treatment groups in respect to baseline and demographic characteristics will be assessed using mean and standard deviation for age, IPSS, QOL- score, peak flow rate and PSA.

For outcome data of the two groups, the mean and standard deviation will be described for post treatment IPSS, QOL- score and peak flow rate.

The primary outcome will be determined by symptom improvement according to the operational definition . Comparison of the percentage of symptom improvement of the two groups will be computed by Chi-square test and 95% confidence interval will be reported. The null hypothesis will be rejected if p - value is less than 0.05.

The result of global subjective assessment in each group will be compared by using histogram to demonstrate the trend of improvement.

The secondary outcomes will be evaluated and compared between two treatment groups as follows :

The absolute and relative change of pre - post treatment IPSS, QOL and peak flow rate in each group will be calculated and described in terms of mean and standard deviation. The difference of pre and post outcome values in each group will be compared using paired t - test. The difference of pre-post treatment change between two treatment groups will be compared by using unpaired t-test.

The intermediate outcomes (IPSS and peak flow rate) at 3, 6 and 9 weeks will be evaluated to determine the starting point and the progression of the effect.

The incidence of adverse effects and complications of BPH will be reported in proportion and the difference between two groups will be calculated by the chi -square test and reported in p - value.

3.9 ETHICAL CONSIDERATIONS

The problems which relate to ethical consideration in this study are the placebo treatment and the adverse effects of Doxazosin. In symptomatic, uncomplicated BPH patient, both conservative or watchful waiting which is similar to placebo, and medical treatment are acceptable as treatment depending on the patient's preference.

The adverse effects of doxazosin in our experience and literature are usually mild and transient such as dizziness, headache and fatigue. In our study we try to prevent the adverse effects by careful dose titration, and patients can contact the investigator or discontinue the drug whenever he feels unwell.

In our study, the patients will be explained about the study and the drug and will be asked to sign a consent form, and they are completely free to refuse to participate or drop out at anytime they want without any effects on later treatment.

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with ICH GCP. The trial will also be conducted in compliance with the protocol that has received prior institutional review board or ethic committee approval.

3.10 LIMITATIONS

(1) Preparation of placebo which was similar to active drug was not possible. In this situation we assigned a research assistant to provide the drug and counted the pill in follow up visit. This person did not involve in assessment or treatment of the patient.

(2) Answering IPSS and QOL questionnaire was impossible for someone who could not read. So the research assistant who was blinded to the study performed a structured interview .

(3) Voided volume of at least 150 ml for uroflowmetry was a problem for some patients. So we explained and encouraged them to drink more water and postpone urination as long as possible.

3.11 BENEFITS OF THE STUDY

The study of the effectiveness is an important step. The result can be applied to determine the cost effectiveness in some particular situations or settings such as in private hospital or in district hospital. The effectiveness of doxazosin can also be applied to other alpha blocker drugs. The outcome of placebo group is similar to outcome of conservative treatment or watchful waiting.

Because not every patient will response to both treatments, doxazosin or placebo, it would be helpful if it could be predicted in some way which patients would benefit from the treatment. The correlation analysis between each symptoms, total score or peak flow rate with the outcomes should be performed.

If we know the relationship between subjective assessment and objective assessment ie. symptom score or peak flow rate, we can set up a definite criteria to assess the treatment outcome more appropriately.

If Doxazosin is more effective than placebo with clinically significance, but the cost is high, we can conduct further study to find out another alpha blocker which costs less but has the same effectiveness or to find out the more cost effective way for long term treatment of BPH.

3.12 OBSTACLES

(1) The limitation of time and number of patients was an important obstacles. We had expected to recruit about 10 cases per month. Because of unexpected job of the researcher and the number of the patients who fit the criteria was low so the study could not finish on schedule.

(2) Poor compliance of the patients and cointervention of treatment was prevented or reduced by good doctor – patient relationship and good monitoring.

CHAPTER 4

RESULTS

4.1 DEMOGRAPHIC DATA OF THE SUBJECTS

The numbers of patients who fulfilled the eligible criteria and were recruited in the study were 15 for Doxazosin group and 17 for the placebo group. The demographic data of the patients including age, IPSS, QOL-score and peak flow rate of both groups was shown in Table 4.1 These baseline data were not statistically different ($P > 0.05$) between the two groups.

Table 4.1 Demographic data of Doxazosin and Placebo group in terms of mean $\pm$ 2SE (SD).

	Doxazosin group (n=15)	Placebo group (n=17)
Age *(year)*	64.1 $\pm$ 2.8 (5.2)	66.8 $\pm$ 3.0 (6.2)
IPSS *(score)*	16.0 $\pm$ 2.8 (5.6)	13.7 $\pm$ 1.4 (3.0)
QOL *(score)*	3.4 $\pm$ 0.6 (1.1)	3.1 $\pm$ 0.8 (1.2)
Peak flow *(ml/sec)*	9.4 $\pm$ 1.4 (2.8)	9.9 $\pm$ 1.4 (2.9)

The severity of the patients in this study was determined by the IPSS score and the peak flow rate and was divided into 6 strata. The most common subgroup was subgroup which IPSS was 13-19 and peak flow rate was less than 12 ml/sec. This subgroup contributed to 43.8% of the total subjects. The number of patients in each strata was shown in Table 4.2.

Table 4.2 Number of Cases in each Strata.

Strata (IPSS, PF)	Number (%)
1. (8-12, 12-15)	4 (12.5)
2. (8-12, <12)	7 (21.9)
3. (13-19, 12-15)	2 (6.3)
4. (13-19, <12)	14 (43.8)
5. (20-35, 12-15)	2 (6.3)
6. (20-35, <12)	3 (9.4)

The treatment had started at the day of randomization. There were four follow up visits at 3,6,9 and 12 weeks respectively. The number of patients who came to each visit was shown in Table 4.3. Eighteen patients or 56.3% had completed follow up. Four patients lost follow up at the first 3 weeks. In this situation, the outcome of these cases was considered as "the same" or failure of treatment. The number of patients who lost follow up at 6,9,12 weeks was 1,5,4 respectively. The patients who lost follow up did not come back again until the end of the study. The average duration from the start of treatment to the last visit was 8.2 weeks in Doxazosin group and 9.5 weeks in Placebo group. Two patients in Doxazosin group dropped out at 6 and 9 weeks due to untolerated adverse effect and the outcome of treatment was analysed as failure of treatment. Other two in the same group were in the process of study at the time of analysis.

Table 4.3 The number of patients in each visit according to treatment group.

	Doxazosin Gr.	Placebo Gr.
Randomization	15	17
3 wks FU.	13	15
6 wks FU.	12	15
9 wks FU.	9	13
12 wks FU.	7	11

4.2 COMPARING THE DOSAGE

The dosage of drugs given in this study was titrated from 1, 2 and 4 mg within 10 days or within the 1st follow up visit. At the 1st follow up visit, the dosage was titrated to 8 mg. of Doxazosin or Placebo if the patient was not much improved. The percentage of 2, 4 and 8 mg dosage in Doxazosin group was 7.1, 21.4 and 71.4% respectively and the dosage in placebo group was 11.8% in 4 mg and 88.2% in 8 mg. The percentage of maximum dosage at 8 mg was not statistically different between two groups. ($P > 0.370$)

4.3 COMPARING THE GLOBAL SUBJECTIVE ASSESSMENT AND SYMPTOM IMPROVEMENT RATE

The global subjective assessment was the main outcome in this study. It was divided into 5 categories "much improved", "slight improved", "same", "slightly worse" and "much worse". The result of overall assessment in both groups at 6 weeks, 12 weeks and at the last follow up visit of each patient according to the patients in each visit was shown in Table 4.4.

Table 4.4 Percent of patients in each category of global subjective assessment in Doxazosin and Placebo group according to patients in each visit.

	Doxazosin			Placebo		
	I	**II**	**III**	**I**	**II**	**III**
Symptom improvement	84.6	88.9	84.7	66.7	81.8	80.0
- much improved	30.8	55.6	38.5	26.7	36.3	33.3
- slight improved	53.8	33.3	46.2	40.0	45.5	46.7
Same	15.4	11.1	15.4	33.3	18.2	20.0
n	12	7	13	15	11	15

Note : I = 6-week visit

II = 12-week visit

III = last follow up visit

Because of operational difinition, the symptom improvement rate was the combination of "much improved" and "slight improved" categories. The symptom improvement rate (success rate) in each group was analyzed at 6 weeks, 12 weeks and at the last visit of each patient. The difference in success rate which was the research question was shown in Table 4.5. The statistical significance of the difference between two groups was evaluated by Fisher's Exact Test and was shown in the same table.

Table 4.5 The symptom improvement rate (Success rate) in Doxazosin group and Placebo group, calculated by the number of patients in each visit and by intention to treat basis.

	Doxazosin	Placebo	Difference in Success Rate	P-Value (2-sided)
At 6 weeks	84.6 (12)	66.7 (15)	17.9	0.396
At 12 weeks	88.9 (7)	81.8 (11)	7.1	1.000
At last visit	84.7 (13)	80.0 (15)	4.7	0.572
Intention to treat	66.7 (15)	70.6 (17)	-3.9	0.555

Note : Number in parenthesis was the number of patients in each visit.

4.4 COMPARING THE SECONDARY OUTCOMES

The secondary outcomes were IPSS, QOL and peak flow rate. The result of pre and post treatment, the absolute change of these outcomes from pre to post and P-value of statistical analysis were shown in Table 4.6. In the process of statistical analysis, the distribution of data was first analyzed by Kolmogorov Smirnor test. All the data of secondary outcomes were normal distribution.

Table 4.6 Mean ± 2SE of the pre, post, absolute change of IPSS, QOL and peak flow rate in Doxazosin group and Placebo group and P-value between group and within group.

	Doxazosin	Placebo	P-value
IPSS			
- Pre Treatment	16.0 ± 2.8	13.7 ± 3.0	0.169
- Post Treatment	10.2 ± 3.0	10.3 ± 1.8	0.913
- Absolute change	↓ 5.2 ± 0.8	↓ 3.3 ± 1.8	0.251
- P-value	0.002	0.003	
QOL			
- Pre Treatment	3.4 ± 0.6	3.1 ± 0.8	0.530
- Post Treatment	2.8 ± 0.8	2.3 ± 0.6	0.238
- Absolute change	↓ 0.5 ± 0.4	↓ 0.6 ± 0.8	0.863
- P-value	0.026	0.206	
Peak flow			
- Pre Treatment	9.4 ± 1.4	9.9 ± 1.4	0.628
- Post Treatment	10.9 ± 1.8	10.6 ± 1.8	0.811
- Absolute change	↑ 1.2 ± 1.8	↑ 0.9 ± 1.6	0.816
- P-value	0.228	0.272	

From the Table 4.6, only the change in IPSS and QOL in pre and post treatment in Doxazosin group and change of IPSS in Placebo group were statistically significant different.

4.5 COMPARING THE ADVERSE EFFECT

The adverse effect which probably related to the drug was dizziness, headache or fainting. In Doxazosin group, the incidence of this adverse effect was 28.6% but only 12.5% in Placebo group. The difference in adverse effect was 16.1% without statistically significance (P=0.378). In 4 patients who had adverse effect in Doxazosin group, one had fainting at 2 mg dose and another one had at 8 mg dose. Both of them dropped out from the study because of the adverse effect. The complication of BPH during 3 months treatment in both group was not occurred.

4.6 COMPARING THE CORRELATION OF OUTCOMES

Table 4.7 and 4.8 showed the three outcomes of the treatment and their correlation in Doxazosin group and Placebo group respectively. The three outcomes were global subjective assessment, the change of IPSS before and after treatment (dif. ipss) and the change of peak flow rate before and after treatment (dif.pf). The correlation of three outcomes was the direction of the outcomes. If the global subjective assessment was improved, the change of IPSS was decreasing or improvement of IPSS and the change of peak flow rate was increasing, it meant positive correlation. If three outcomes went to the opposite direction it meant negative correlation. From Table 4.7, it showed 7 in 13 or 53.8% of positive correlation of three outcomes. In "much improved" group there was 4 in 5 or 80% of positive correlation while there was 3 in 6 or 50% in "slight improved" group had positive correlation. From Table 4.8, it showed only 4 in 15 or 26.7% of positive correlation. In "much improved" group, there was only 1 in 5 or 20% had positive correlation and 3 in 7 or 42.9% had positive correlation in "slight improved" group.

Table 4.7 The global subjective assessment, the absolute change of IPSS, peak flow rate and voided volume in Doxazosin group.

	dox.no	treat	global	difipss	difpf	difvol	correlation
1	1	DOXAZOSIN	much improved	-8.00	4.80	-18.00	Yes
2	3	DOXAZOSIN	same	-1.00	.30	27.00	No
3	5	DOXAZOSIN	slight improved	2.00	-4.60	-125.00	No
4	7	DOXAZOSIN	slight improved	.00	-	-	No
5	9	DOXAZOSIN	much improved	-5.00	1.70	-1.00	Yes
6	11	DOXAZOSIN	-	-	-	-	
7	14	DOXAZOSIN	slight improved	-8.00	.50	-125.00	Yes
8	15	DOXAZOSIN	much improved	-4.00	1.50	95.00	Yes
9	18	DOXAZOSIN	much improved	-7.00	8.30	97.00	Yes
10	23	DOXAZOSIN	-	-	-	-	
11	26	DOXAZOSIN	slight improved	-2.00	.40	-103.00	Yes
12	28	DOXAZOSIN	much improved	-15.00	.00	20.00	No
13	31	DOXAZOSIN	same	-4.00	-.10	-42.00	No
14	32	DOXAZOSIN	slight improved	-13.00	-.90	-107.00	No
15	33	DOXAZOSIN	slight improved	-3.00	1.90	-30.00	Yes

Note : Minus sign in difipss means improvement of IPSS post treatment and minus sign in difpf means decreasing of peak flow rate post treatment.

Table 4.8 The global subjective assessment, the absolute change of IPSS, peak flow rate and voided volume in Placebo group.

	dox.no	treat	global	difipss	difpf	difvol	correlation
1	2	placebo	Slight improved	-3.00	2.30	-50.00	Yes
2	4	placebo	Slight improved	-2.00	-3.50	-54.00	No
3	6	placebo	Slight improved	-2.00	-.50	-20.00	No
4	8	placebo	Much improved	-9.00	-1.80	-11.00	No
5	10	placebo	Same	1.00	2.80	258.00	No
6	12	placebo	-	-	-	-	
7	13	placebo	-	-	-	-	
8	16	placebo	Slight improved	-3.00	2.40	98.00	Yes
9	19	placebo	Slight improved	.00	5.50	81.00	No
10	20	placebo	Same	-2.00	-.60	-26.00	No
11	21	placebo	Much improved	-3.00	-2.60	15.00	No
12	22	placebo	Much improved	.00	1.30	-4.00	No
13	24	placebo	Same	-4.00	3.00	141.00	No
14	25	placebo	Slight improved	-2.00	-2.90	-	No
15	27	placebo	Much improved	-12.00	-.40	154.00	No
16	29	placebo	Much improved	-8.00	6.30	-15.00	Yes
17	30	placebo	Slight improved	-1.00	1.80	153.00	Yes

Note : Minus sign in difipss means improvement of IPSS post treatment and minus sign in difpt means decreasing of peak flow rate post treatment.

4.7 COMPARING THE COMBINATION OF OUTCOMES

Because there was no one ideal outcome to demonstrate the effectiveness of the treatment and in the treatment, the outcome should have positive correlation.

The combination of the outcomes which is an alternative way to evaluate the effectiveness of the treatment was proposed after the study. The three considered outcomes were the global subjective assessment, the change of IPSS and the peak flow rate post treatment. There is no difinite or standard criteria for combination, but the direction of every outcome in the combination should go in the same improvement direction. We propose three criteria or model, they are: -

A. The success of the treatment is the combination of (1)Global Subjective Assessment at any level of improvement, (2)improvement of IPSS $>$ 3, (3)improvement of peak flow rate $\geq$ 3 ml/sec. The magnitude of improvement of IPSS and peak flow rate was proposed by the 3rd International Consultation on BPH.

B. The success of the treatment is the combination of three outcomes in A and the result of these outcomes must be in the same improvement direction at any magnitude.

C. The success of the treatment is the combination of
   (1) global subjective assessment at any level of improvement
   (2) Improvement of IPSS at any score (Post IPSS - Pre IPSS < 0)
   (3) Improvement of peak flow rate (Post PF - Pre PF > 0) when the voided volume in post treatment did not increase more than 100 ml.

The result of success rate according to three criteria was shown in Table 4.9. The statistical method used in comparison of two treatment was Fisher's Exact Test.

Table 4.9 Success rate of Doxazosin and Placebo group according to criteria of combination of outcomes.

Criteria of combination	Doxazosin	Placebo	Difference in success rate	P-value (1-sided)
A	16.7	6.7	10.0	0.414
B	58.3	26.7	31.6	0.102
C	58.3	20.0	38.3	0.049

CHAPTER 5

DISCUSSION

This study has turned to be a pilot study because of many obstacles but the result gives a lot of information and this information is very useful in development of a further study in the future.

COMPARISON OF DEMOGRAPHIC DATA

The baseline data of two treatment groups showed some differences especially in age and IPSS, but the peak flow rate and QOL was the same. There was no statistical difference of the data. The difference came from a small number of subject and a wide range of age and IPSS compared to peak flow rate. In the main study which the population will be 6 times more or about 180 cases, the difference in baseline data will decrease. The method of stratification was also helpful in this situation.

The number of drop out or loss follow up was quite high in this study and most of them or 10 in 14 patients had no reason. This situation showed that the project management and monitoring was weak. So in a further study, the researcher should be careful in selecting the participant and should take time to explain the process of the study. When the participant does not show face in the appointment visit, the researcher should take action immediately by calling him by phone.

Although the percentage of complete follow up was only 56.3% but the average duration of follow up was more than 8 weeks. Because duration of treatment which can demonstrate the maximum effect was 4 weeks, so the follow up period was long enough.

COMPARISON OF DOSAGE

The dosage of Doxazosin or Placebo was titrated from 1 mg to 4 mg and in the first follow up visit, the dose will increase up to 8 mg if the response was not much improved. The dosage in Placebo group was a little bit higher than in Doxazosin which is reasonable. But the dosage in Doxazosin group was quite high compared to clinical practice where normal dosage is 2 or 4 mg. This means that the doctors undertreat the patients, so the result of this study may impact the practice in this point.

One reason that can explain the cause of high percentage in 8 mg treatment is the design of treatment. This study designed to increase the dose up to 8 mg. at 3-week follow up visit if the response was not adequate. Three weeks of treatment seem to be too short to see the maximum effect of treatment because the patient received 4 mg dose only 10 days while it took about 4 weeks to demonstrate the maximum effect. In a further study, the adequate response of treatment should be evaluated at 6-week follow up visit. It means that a patient will receive 4 mg treatment for at least 4 weeks which it will be long enough to show the maximum response.

COMPARISON OF GLOBAL SUBJECTIVE ASSESSMENT

Depending on the global subjective assessment, the effectiveness of Doxazosin compared to the Placebo was not as good as we had expected. Although the symptom improvement rate in Doxazosin group was high but in Placebo group the improvement rate was high too. The high improvement rate in Placebo group showed that the placebo effect was higher than we thought.

The high improvement rate in Placebo group may be explained in many ways. First is the Thai's culture. They try to satisfy other people especially if the patients respect the doctors very much. Second is the frequency of follow up visit. In placebo group, the improvement rate was increased in 12-week visit more than in 6-week visit. But in Doxazosin group, this phenomenon did not occur, so the placebo effect may not increase by the frequency of follow up. Third is the degree of improvement. Slight improvement was a little bit better than the same according to the patient's feeling. So if the researcher regroups the improvement or success outcome by considering "same" and "slight improved" as in the

same group. By this way, the improvement rate in both treatment group dropped to about 30-40% and there was no difference between two treatments. So in the further study we should define the effectiveness of treatment by the "much improved" group in global subjective assessment.

In clinical practice, most of the doctors evaluate the result of medical treatment by overall subjective assessment as in this study. So this study showed that this method of assessment was too sensitive and may mislead the treatment. The doctors need more other evidences to conclude the result and further management.

The improvement rate in each group was analysed according to the duration of follow up ie. 6-week FU, 12-week FU and at the last FU visit of each patient. In Doxazosin group, the improvement rate at six weeks seems to favor this group and showed the maximum improvement rate but evaluation at the last visit does not, this result confirms that Doxazosin shows the maximum response within 6 weeks. In Placebo group, the improvement rate seems to increase according to the frequency of follow up. This is another kind of bias. In a further study, the frequency of follow up should decrease or the duration of follow up should be longer than 3 week in order to prevent this bias.

COMPARISON OF OTHER OUTCOMES

Although the magnitude of absolute change of IPSS in Doxazosin group was higher than Placebo group but there was no statistical significance. The reason may be due to small sample size. The initial IPSS which was higher in Doxazosin group than in Placebo group may also effect the response of treatment, because the patients who had the more severe symptoms had tendency to improve more. So it was difficult to conclude that Doxazosin was more effective by this outcome only.

In this study, no correlation between IPSS, global subjective assessment and peak flow rate in some patients had been observed especially in Placebo group. These outcomes had a lot of variation in each individual for example, IPSS may be different from the truth due to misunderstanding, miscommunication and poor memory. So if the patient can record voiding chart or voiding diary correctly, this measurement will be helpful and more reliable.

The QOL was the same between two treatment groups because there was a little difference between the effectiveness of these groups and the change in QOL needs a long period of time. So the treatment was not effect on quality of life as a whole.

The peak flow rate was an objective evidence but unfortunately, it depends on the voided volume and the voiding situation. In this study, I found a few patient in Placebo group had improvement in peak flow rate due to increasing of voided volume. So in the further study, we should measure uroflowmetry at least two times in one visit, if it is possible, and then the researcher can select the peak flow rate of the same voided volume for comparison.

COMPARISON OF ADVERSE EFFECT

There were two patients in Doxazosin group who had fainting which related to the drug. This adverse effect impact on the result of treatment because these patients had to drop out from the study before the maximum improvement was obtained and there were considered as failure of treatment.

COMPARISON OF THE COMBINATION OF OUTCOMES

Because there is no ideal individual outcome for evaluation the effectiveness of medical treatment for BPH as demonstrated in the result of this study. The outcomes in Doxazosin group seem to be more correlated than the outcomes in Placebo group. So the combination of these outcomes in the positive correlation basis may be more reliable in evaluation of effectiveness of the treatment as demonstrated by the three models of combination in the result chapter.

There is no standard recommendation for combination of outcomes in world literature now. So in a further study, the researcher should define the combination criteria which is reliable and applicable before the study start.

CHAPTER 6

CONCLUSION

Although the improvement rate, global subjective assessment, IPSS and peak flow rate in Doxazosin group were a little bit higher than Placebo group but the hypothesis could not be proved from this study. A further study should be continued because the result may have impact on clinical practice in at least two issues, one is about the effective dosage of Doxazosin and another one is about the global subjective assessment of clinical response of Doxazosin treatment.

In the further study, the effectiveness of treatment should be determined in term of the combination of more than one outcomes and the researcher should try to develop more objective outcome such as voiding diary and 2 to 3 times uroflowmetry in each visit.

The management of the project such as time table, research assistant and monitoring is very important and is the key for success of the study too.

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APPENDICES

CRF-1

ชุมชน..... **PROSTATE EVALUATE FORM** DN.....

ID..... HN.....

Name.....Age.....Tel.....

Date of visit ...../...../..... Treatment ..... Started date...../...../.....

Type of visit : 1-screening 2-randomization 3-FU.....mths. 4-final evaluation

---

Chief complaint : 1= Normal 2= Not sure 3= Having symptom.....

BPH complication : 0= No 1= Yes specify.....

Other causes of voiding dysfunction : 0= No 1= Yes: specify.....

Associated disease : 0= No 1= Yes specify.....

Symptoms	IPSS score	Voiding chart score	Total no. of symptom	Voiding chart record
1. Incomplete emptying				No. of record day.....
2. Daytime frequency				A. No. of daytime voiding.....
3. Intermittency				B. Total daytime volume.....
4. Urgency				C. No. of nocturia.....
5. Weak stream				D. Total nocturia volume.....
				A+C =.....time, B/A=.....D/C=.....
6. Hesitancy				Bothersome Symptom
7. Nocturia				No. Yes. 1 2 3 4 5 6 7
Total Score			QOL (QUALITY OF LIFE) SCORE.....	

BIS (BPH Impact Score): 1=P=..... 2=M=..... 3=S=..... 4=Total=.....

Risk behavior : 0= No 1= Yes (specify).....

Physical exam: 0= Normal 1= Abnormal.....BP____/_____(sitting) BP_____/_____(supine)

Investigation : 0= No 1= Yes..... 0=Normal 1= Abnormal.....

DRE : Width.....FB 1= Normal 2=BPH 3=CaP 4=Suspicious CaP 5=Other.....

TRUS: W.....cm. D.....cm. L.....cm. Vol.....cc. PSA-D.....ng/ml/cc.

UROFLOW : Vol.....cc, PF.....MF..... RU.....cc. pattern.....

Vol.....cc, PF.....MF..... RU.....cc. pattern.....

BLOOD : PSA.....ng/ml Creatinine.....mg/dl. Other.....

URINE : 0= Neg. 1= Pos. Wc .....Rc.....Other.....

Overall assessment : compared to : 1= previous visit 2= before Tx, by : 1=patient 2=doctor

1=much improved 2=slight improved 3=same 4=slight worse 5=much worse

Adverse event : 0=No 1=Yes : Spceify.....

Previous Dose.....mg. Next dose.....mg. Next visit...../...../.....

Remark:.....

.....

.....

Cross X over one which is unknown or not done

CRF-2

ELIGIBLE CRITERIA

Name.....Age.....Date...../...../.....

HN.....DN.....ID.....

Inclusion Criteria :

- Men ≥ 50 years, ambulatory condition. Yes No
- Have voiding problem Yes No
- IPSS ≥ 8 Yes No
- Peak flow rate ≤ 15 ml/sec. in a total voided volume ≥ 150 ml. Yes No
- Prostatic enlargement as determined by DRE. Yes No
- The patient has given written informed consent for participation Yes No

Exclusion Criteria :

- Suspected prostate Ca. due to elevation of PSA and/or abnormal DRE. Yes No
- Complicated BPH for which TUR-P is indicated Yes No
- Pharmacologic treatments for BPH. Yes No
- Previous prostate surgery,TUR-P or minimally invasive surgery. Yes No
- Any known causes other than BPH for symptoms or reduction in PF. Yes No
- Hypotension (sitting BP.less than 90/60) or orthostatic hypotension. Yes No

If all "Yes" in inclusion criteria and all "No" in exclusion criteria,
The patient can be recruit in the study.

Stratification

IPSS = _____classified as S_1 (8-12) S_2 (13-19) S_3 (20-35)

PF = _____classified as F_1 (12-15) F_2 (<12)

Strata = A (S_1F_1) B (S_1F_2) C (S_2F_1) D (S_2F_2) E (S_3F_1) F (S_3F_2)

Randomization : ☐ No ☐ Yes Strata_____ No_____

N.B. Any drugs that affect voiding function but not for treatment of BPH such as urecholine, dicomin should not be prescribed during the study. If the patients have used these drugs more than two weeks before treatment, they should continue through the end of the study.

CRF-3

RECORD OF NEGATIVE OUTCOME

lame.....DN.....

OUTCOME	Before Treatment	At ___ Wk Date...../...../.....		At___ Wk Date...../...../.....		At____ Wk Date...../...../.....	
		Start	Stop	.Start	Stop	Start	Stop
dverse event (1)							
NAD	.....	.....		.....		.....	
zziness	.....	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Headache	.....	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Syncope	.....	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Palpitations	.....	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Tiredness	.....	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Nausea	.....	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Dypsnea	.....	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Impotence	.....	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
BP (sitting / supine)	...../.....	__/___	__/___	__/___	__/___	__/___	__/___
Other_____	.....	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
PH Complication (2)							
No	.....	.....		.....		.....	
Acute retention	.....	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Dysuria	.....	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
Hematuria	.....	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
other_____	.....	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__	__/__/__
mpliance (3)							
= good 1. not good		_____		_____		_____	
left / total		_____/_____		_____/_____		_____/_____	
intervention (4)							
= No 1 = Yes	_____	_____		_____		_____	
ecify_____	_____	_____		_____		_____	
	_____	_____		_____		_____	

แบบฟอร์มหนังสือยินยอม

วันที่.....

ข้าพเจ้า.....อยู่บ้านเลขที่.....หมู่.....

แขวง.....เขต.....จังหวัด.....

ได้รับทราบการศึกษาเรื่อง ประสิทธิภาพของยาด็อกซาโซซิน ในการรักษาโรคต่อม-ลูกหมากโต โดยที่ข้าพเจ้าจะได้รับการปฏิบัติดังนี้

1. ได้รับการตรวจเบื้องต้นซึ่งประกอบด้วย การซักประวัติ ตรวจร่างกาย ตรวจทางทวารหนัก ตรวจปัสสาวะ ตรวจความแรงของการถ่ายปัสสาวะ และเจาะเลือดประมาณ 10 ซีซี เพื่อตรวจสารบ่งชี้มะเร็งต่อมลูกหมาก

2. ได้รับการสุ่มเพื่อรักษาด้วยยาด็อกซาโซซิน หรือยาหลอก การรักษาเริ่มด้วยยาขนาด 1 มก. วันที่ 1-3 , 2 มก. วันที่ 4-10 และ 4 มก. ตั้งแต่วันที่ 11 เป็นต้นไปจนครบ 3 เดือน ถ้ามีภาวะแทรกซ้อนจากยาจะลดขนาดยาลงครึ่งหนึ่ง

3. ได้รับการตรวจประเมินผลการรักษา ซึ่งประกอบด้วยการซักอาการถ่ายปัสสาวะ การวัดความแรงของการถ่ายปัสสาวะ และการซักถามภาวะแทรกซ้อน โดยจะมารับการตรวจติดตามเช่นนี้ในสัปดาห์ที่ 3, 6, 9 และ 12 ตามลำดับ

ข้าพเจ้าเข้าใจวัตถุประสงค์ของการศึกษา ตลอดจนประสิทธิภาพและผลข้างเคียงที่อาจเกิดขึ้นจากยาในการศึกษานี้เป็นอย่างดี และได้พิจารณาว่าการศึกษานี้จะเป็นประโยชน์ต่อมนุษย์ชาติ และต่อการสาธารณสุขของประเทศไทย ข้าพเจ้ามีความยินดีที่จะร่วมในการศึกษาดังกล่าว ในระหว่างการศึกษานี้ ข้าพเจ้ามีสิทธิ์ที่จะบอกเลิกการร่วมในการศึกษาเมื่อใดก็ได้ และการบอกเลิกการศึกษาจะไม่มีผลต่อการให้การรักษาพยาบาลโดยแพทย์ผู้ทำการศึกษาในเรื่องนี้ต่อข้าพเจ้าแต่อย่างใด

ข้าพเจ้าได้อ่านและเข้าใจหนังสือยินยอมนี้โดยตลอดแล้ว จึงลงลายมือชื่อไว้เป็นหลักฐานต่อหน้าพยาน

ลงชื่อ.....ผู้ยินยอม
(.....)

ลงชื่อ.....หัวหน้าโครงการวิจัย
(.....)

ลงชื่อ.....พยาน
(.....)

ลงชื่อ.....พยาน
(.....)

แบบประเมินการถ่ายปัสสาวะด้วยตนเอง

ชื่อ ..... **อายุ**.....**ปี** **วันที่ประเมิน**.....

ก. ท่านคิดว่าการถ่ายปัสสาวะของท่านในช่วงนี้เป็นอย่างไร

☐ ปกติ ☐ ไม่แน่ใจ ☐ ไม่ปกติ คือ_____

ข. ท่านกรุณาประเมินการถ่ายปัสสาวะของท่านในช่วงเดือนที่ผ่านมา **ว่ามีอาการต่อไปนี้หรือไม่ ?** ถ้ามี **ท่านมีอาการบ่อยมากเพียงไร ?** โดย**ให้ท่านวงกลมรอบตัวเลขที่ตรงกับคำตอบของท่าน**

1. ในช่วงเดือนที่ผ่านมาช่วงกลางคืน ท่านลุกขึ้นถ่ายปัสสาวะเพราะปวดปัสสาวะกี่ครั้งเป็นส่วนมาก นับตั้งแต่**นอนหลับแล้ว**จนถึง **ก่อนตื่นนอน** ตอนเช้า

0 = ไม่มีเลย 1 = มี 1 ครั้ง 2 = มี 2 ครั้ง
3 = มี 3 ครั้ง 4 = มี 4 ครั้ง 5 = มี 5 ครั้ง หรือมากกว่า

2. ในช่วงเดือนที่ผ่านมา มีบ่อยไหมที่ท่านรู้สึกถ่ายปัสสาวะเสร็จแล้วยังไม่ถึงสองชั่วโมงก็ต้องถ่ายปัสสาวะอีก

0 = ไม่มีเลย
1 = มีนานๆ ครั้ง (ถ่ายปัสสาวะ 10 ครั้ง จะมีอาการนี้น้อยกว่า 2 ครั้ง)
2 = มีบ้าง (ถ่ายปัสสาวะ 10 ครั้ง มีอาการเพียง 2-3 ครั้ง)
3 = มีบ่อยปานกลาง (ถ่ายปัสสาวะ 10 ครั้ง มีอาการประมาณ 5 ครั้ง)
4 = มีบ่อยค่อนข้างมาก (ถ่ายปัสสาวะ 10 ครั้ง มีอาการ 7-8 ครั้ง)
5 = มีเกือบทุกครั้ง

ตั้งแต่ตื่นนอน จนถึงเข้านอน ท่านถ่ายปัสสาวะประมาณ_____ครั้ง

3. ในช่วงเดือนที่ผ่านมา มีบ่อยไหมที่ท่านปวดอยากจะถ่ายปัสสาวะแล้วจำเป็นต้องกลั้นไว้ระยะหนึ่ง แต่กลั้นไม่ได้อย่างที่ต้องการ

0 = ไม่มีเลย 1 = มีนานๆ ครั้ง 2 = มีบ้าง
3 = มีเกือบทุกครั้ง 4 = มีบ่อยค่อนข้างมาก 5 = มีเกือบทุกครั้ง

4. ในช่วงเดือนที่ผ่านมา มีบ่อยไหมที่ท่าน**ต้องเบ่งหรือรอก่อนจะเริ่มถ่ายปัสสาวะ**ออกมาได้

0 = ไม่มีเลย 1 = มีนานๆ ครั้ง 2 = มีบ้าง
3 = มีบ่อยปานกลาง 4 = มีบ่อยค่อนข้างมาก 5 = มีเกือบทุกครั้ง

5. ในช่วงเดือนที่ผ่านมามีบ่อยไหมที่เวลาถ่ายปัสสาวะท่าน**ไม่ได้ถ่ายรวดเดียวเสร็จ แต่จะต้องถ่ายเป็นขยัก ๆ หรือไหล ๆหยุด ๆ**

0 = ไม่มีเลย 1 = มีนานๆ ครั้ง 2 = มีบ้าง
3 = มีบ่อยปานกลาง 4 = มีบ่อยค่อนข้างมาก 5 = มีเกือบทุกครั้ง

6. ในช่วงเดือนที่ผ่านมา มีบ่อยไหมที่ท่านรู้สึกถ่ายปัสสาวะไม่สุด หรือยังเหลือค้างอยู่หลังถ่ายเสร็จแล้ว

0 = ไม่มีเลย 1 = มีนานๆ ครั้ง 2 = มีบ้าง

3 = มีบ่อยปานกลาง 4 = มีบ่อยค่อนข้างมาก 5 = มีเกือบทุกครั้ง

ท่านมีปัสสาวะหยดหลังถ่ายเสร็จแล้วหรือไม่ ☐ มี ☐ ไม่มี

7. ในช่วงเดือนที่ผ่านมา มีบ่อยไหมที่ท่าน **ถ่ายปัสสาวะไม่พุ่งแรงเหมือนเมื่อปีก่อน ๆ**

0 = ไม่มีเลย 1 = มีนานๆ ครั้ง 2 = มีบ้าง

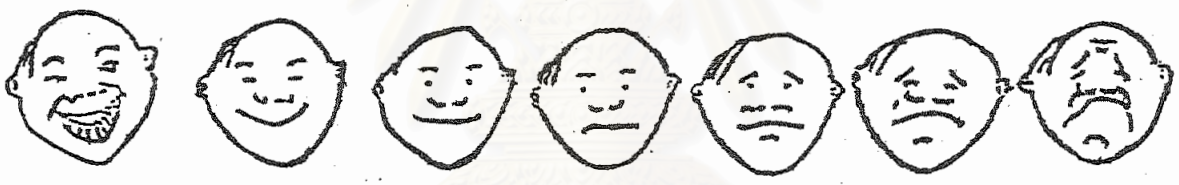
3 = มีบ่อยปานกลาง 4 = มีบ่อยค่อนข้างมาก 5 = มีเกือบทุกครั้ง

ค. ท่านรู้สึกเดือดร้อนกับอาการถ่ายปัสสาวะในข้อ ข.หรือไม่

☐ ไม่เดือดร้อน ☐ เดือดร้อนในข้อ 1, 2, 3, 4, 5, 6, 7 *(วงกลมรอบข้อที่ท่านเดือดร้อน)*

ง. ถ้าท่านมีการถ่ายปัสสาวะเหมือนที่เป็นอยู่ขณะนี้ไปตลอดชีวิต ท่านจะรู้สึกอย่างไร ? ให้วงกลมตัวเลขใต้รูปที่ตรงกับความรู้สึกของท่าน

พอใจมาก ๆ **แย่มาก ๆ**



0 1 2 3 4 5 6

จ. ถ้าเปรียบเทียบกับการถ่ายปัสสาวะเมื่อ_____เดือนก่อน ท่านรู้สึกว่าการถ่ายปัสสาวะของท่านในช่วงนี้เป็นอย่างไร ?

1. ถ่ายปัสสาวะได้เหมือนเดิม
2. ถ่ายปัสสาวะดีขึ้นเล็กน้อย
3. ถ่ายปัสสาวะแย่ลงเล็กน้อย
4. ถ่ายปัสสาวะดีขึ้นมาก
5. ถ่ายปัสสาวะแย่ลงมาก

ฉ. ในช่วง 3 เดือน ที่ผ่านมาท่านมีอาการเหล่านี้หรือไม่ ถ้ามีให้วงกลมรอบข้อนั้น

☐ มี ☐ ไม่มี

1. ปัสสาวะแสบตอนสุด
2. ปัสสาวะขุ่นตอนถ่ายใหม่ๆ
3. ปัสสาวะเป็นเลือด
4. ปัสสาวะไม่ออกต้องสวน
5. อื่นๆ_____

หมายเหตุ ☐ ผู้ป่วยตอบเอง ☐ มีผู้สัมภาษณ์

VITAE

Anupan Tantiwong was born on February 10, 1951 in Bangkok. He got his medical degree from the Faculty of Medicine, Siriraj Hospital, Mahidol University in 1974 and Board of Urology from Thai Medical Council in 1979.

His principle interest in Urological field is prostate disease. Recent years, he has been working on Integrated Health Research Program for the Elderly which supported by The National Research Council.

He enrolled in the Thai CERTC training program in 1997 as funded by the Rockefeller Foundation. Currently, he is working in the Urology Unit, Department of Surgery, Mahidol University.