CHAPTER 3

RESEARCH METHODOLOGY

RESEARCH QUESTIONS AND OBJECTIVES

Primary research question:

Does budesonide aqueous nasal spray at once daily dose of 200 micrograms have the same effectiveness in controlling nasal symptoms comparing with once daily dose of 400 micrograms for the treatment of Thai adults with perennial rhinitis during three-week period?.

Secondary research questions:

1. What are the adverse reactions of using budesonide aqueous nasal spray at once daily dose of 200 and 400 micrograms for the treatment of Thai adults with perennial rhinitis during a three-week period?.
2. What is the cost-effectiveness of once daily budesonide 200 micrograms comparing with 400 micrograms?.

Research objectives

1. To compare the short-term effectiveness of budesonide aqueous nasal spray between once daily dose of 200 micrograms and 400 micrograms for the treatment of Thai adults with perennial rhinitis during a three-week duration.
2. To compare the short-term adverse reactions of budesonide aqueous nasal spray between once daily dose of 200 micrograms and 400 micrograms for the treatment of Thai adults with perennial rhinitis during a three-week duration.

3. To compare the cost-effectiveness of budesonide between two dosages for Thai adults with perennial rhinitis.

HYPOTHESIS

There is no difference in the effectiveness of budesonide aqueous nasal spray between once daily dose of 200 and 400 micrograms for controlling nasal symptoms in Thai adults with perennial rhinitis during a three-week period.

OPERATIONAL DEFINITIONS

1. Perennial rhinitis is the chronic inflammatory reactions of nasal mucosa. It is characterized by intermittent or continuous nasal symptoms (sneezing, nasal congestion, nasal discharge) resulting from an allergic reactions or nonspecific irritations without seasonal variation. The symptoms usually persist throughout the year.

2. Individual nasal symptom (sneezing, nasal stuffiness, nasal discharge) score:

   0 = no symptom

   1 = mild symptom (not troublesome)

   2 = moderate symptoms (frequently troublesome but not sufficient to interfere with normal daily activity or night time sleep)

   3 = severe symptoms (sufficiently troublesome to interfere with normal daily activity or night time sleep)

3. Overall nasal symptom rating scale:

   0 = symptoms are worse comparing with the baseline(run-in period)

1	=	same symptoms comparing with the baseline
2	=	symptoms can be minor controlled comparing with the baseline
3	=	symptoms can be substantially controlled comparing with the baseline
4	=	symptoms can be totally controlled

4. Cost:

Because budesonide has to be imported and it is quite expensive, cost of treatment will be evaluated in health provider's point of view. If this study proves that both dosages have the same success rate, cost-effectiveness analysis will be analyzed as cost-minimization because it is a very safe drug and the side effects usually rarely occur. So only the cost of the drug and the unit/cost will be used. If it shows that daily dose of budesonide 400 micrograms is more effective than 200 micrograms, it will be useless to evaluate the economic cost because the doctors will not change their practice.

RESEARCH DESIGN

This study was conducted as a stratified randomized double-blind parallel trial comparing the effectiveness of two different dosages of budesonide aqueous nasal spray for controlling nasal symptoms in adult patients with perennial rhinitis . The design overview is shown below.

DESIGN JUSTIFICATION

1. Clinical trial was needed because the aim of the study was to compare the effectiveness of topical nasal budesonide at daily dose of 200 and 400 micrograms for controlling nasal symptoms and to compare their adverse effects in the treatment of perennial rhinitis in Thai adults.

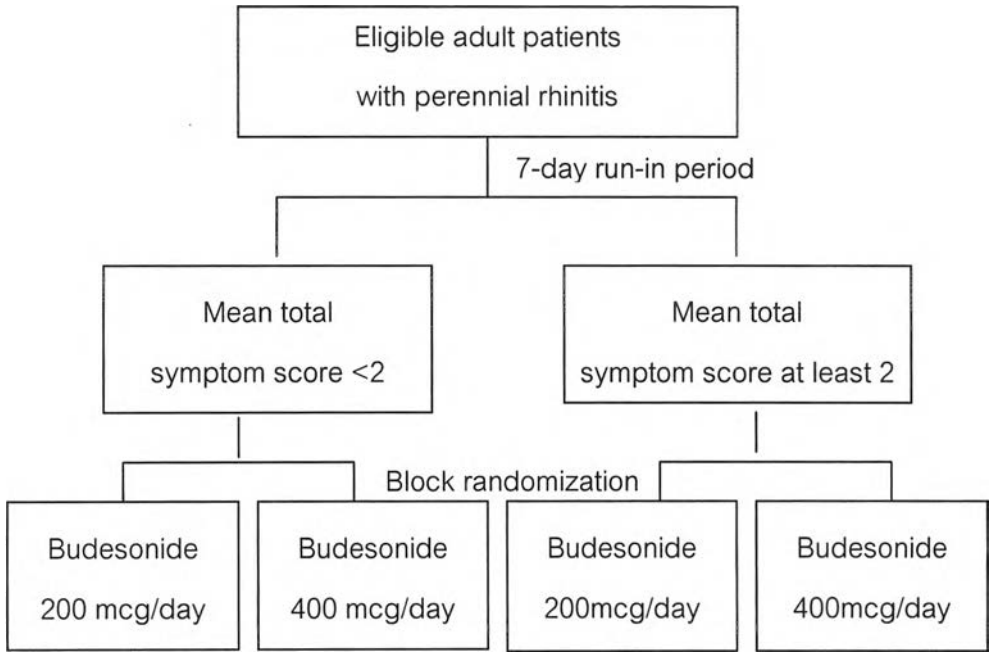
2. Stratification into two groups would balance the prognostic factor , the severity of nasal symptoms.

3. Randomized controlled studies would avoid selection and allocation bias and make a balance between the two treatment groups; so that the measured or unknown prognostic factors and other characteristics of the subjects at the time of randomization would be on the average or balanced between the two groups. Block randomization was used in order to achieve balance over time in the number of subjects who were randomized to each sequence.

4. Double-blind would avoid an expectation and assessment bias, from both the researcher and the patients.

The important factor which might influence the symptoms of perennial allergic rhinitis was the concentration of allergen and irritant exposure which might be seen from the severity of the symptoms. Therefore, patients were grouped according to the severity of symptoms.

Figure 1. Design overview



TARGET POPULATION

The target population of this study was Thai adults with perennial rhinitis whose ages were at least 16 years old. Both males and females were eligible.

SAMPLE POPULATION

The sample population was Thai adults with perennial rhinitis who attended the outpatient department of Otolaryngology, Srinagarind hospital.

INCLUSION CRITERIA

1. Thai patients with symptoms of perennial non-infective rhinitis for at least 1 year preceding the study.
2. Patients with age at least 16 years old.
3. Patients who usually had at least two of the following nasal symptoms: nasal stuffiness, nasal discharge, sneezing. They had to have the above nasal symptoms of at least 4 days in one week.
4. Patients who gave written informed consent.
5. Only literate patients were included because they had to read and filled up the daily record card.
6. Patients who stopped the following drugs before the study .
    - 6.1 Immunotherapy at least 1 year.
    - 6.2 Astemizole at least2 months.
    - 6.3 Corticosteroid therapy at least 4 weeks.
    - 6.4 Terfenadine, cetirizine and loratadine at least 2 weeks.
    - 6.5 First-generation antihistamine at least 3 days.
    - 6.6 Any decongestant at least 3 days.

EXCLUSION CRITERIA

Patients who had the following conditions were excluded from the study.

1. Pregnant or lactating women. Although teratogenic effects and fetal anomalies in human have not been proven, it was safer not to use this drug in these patients.
2. Immunocompromised hosts such as diabetes mellitus, leukemia, liver disease were excluded because the first pass metabolism of budesonide occurs in the liver and

the response to the drug in immunocompromised hosts may not be as in normal population.

3. Patients with nasal or paranasal sinus diseases which had the nasal symptoms mimicking perennial rhinitis such as rhinosinusitis, nasal polyps, nasal or paranasal sinus tumors, marked nasal septal deviation.

4. Patients with other diseases that might need intermittent or continuous medications that had the effect on nasal symptoms (antihistamine, decongestant, steroid, anticholinergic drugs): bronchial asthma, allergic dermatitis, concomitant respiratory tract infection.

5. Patients who took rescue drugs during the run-in period.

SAMPLE SIZE

The formula for calculating the sample size depends on the types of outcome measurement and the study design (whether the two groups are dependent or independent). Since the final primary outcome measurements were repeated ordinary data (as discussed in the paragraph of outcome measurement), the following sample size formula should be used.[33]

$$N/group = 2V(\bar{P},n_o,S,c)(Z_\alpha + Z_\beta)^2 / (P_1 - P_2)^2$$

$\bar{P} = (P_1 - P_2)/2$

n_o = number of repeated measurements per subject

S = variance of responses among different subjects

c = conditional correlation among repeated measurement

$$V(\bar{P},n_o,S,c) = \bar{P}(1-\bar{P}) / (S+1) + \bar{P}(1-\bar{P})S / [n_o(S+1)] \times$$
$$[1+2(n_o-1)\,c/n_o + 2(n_o-2)\,c^2/n_o + \ldots\ldots + (1)c^{no-1}/n_o]$$

Since there was no previous study of budesonide nasal spray for perennial rhinitis using repeated measures of ordinal data, it is difficult to determine the above important parameters. As the sample size for a single measurement per subject is larger than sample size for repeated measurements per subject, the traditional sample size formula will be used in order to see whether it is feasible for this study or not.[34]

Because this study is the equivalent trial, the following formula will be used. [34]

$$N/group = \frac{2P(100-P)[Z_\alpha + Z_\beta]^2}{\Delta^2}$$

P = overall percentage of success to be expected if the treatments are equivalent[9] = 90%

Δ = equivalence for the difference in percentage of success rate = 10%

α = 0.05 (one tail), $Z_{\alpha = 1.65}$

β = 0.10, Z_β = 1.28

$$N / group = \frac{2 \times 90(100-90)[1.65+1.28]^2}{10 \times 10}$$

= 155

Estimated dropouts = 10%

So the total number of patients/group

= N/(1-R)

= 155/(1-0.1)

= 172 patients

INTERVENTION

The eligible patients were stratified into two groups according to the baseline severity of nasal symptoms as mean total symptom score of less than 2 and at least 2.

Then each group was randomly allocated to be treated either by once daily budesonide 200 or 400 micrograms administered nasally at night. Those receiving budesonide 200 micrograms/day used the drug from the bottle containing budesonide 50 micrograms per puff and those using 400 micrograms/day used the drug from the bottle containing 100 micrograms per puff. So each patient used 2 puffs for each nostril once daily at night. The bottles of both strengths were similar in appearance, colour of the drugs and weight. The patients were advised to use the drugs continuously for 3 weeks. They were allowed to use Hista-oph (antazoline HCL 0.05%, tetrahydrozoline HCL 0.04%, Benzalkonium chloride 0.015%) 1-2 drops for each eye every six hours only if they had eye itching.

SAMPLING TECHNIQUE

After 7-day run-in period, the eligible patients were stratified into two treatment groups according to the severity of average total nasal symptom score: less than 2 and at least 2. Then each subgroup was randomly allocated in blocks of four patients by using random number to generate into the 200 and 400 micrograms/day budesonide groups.

CO-INTERVENTION

The patients were instructed not to buy any anti-cold or anti-allergic drugs themselves. If they had any problem , they could contact the researchers by telephone easily or were allowed freely to come to meet the researchers at the hospital. If they had to go to see other doctors for other diseases , the notes to the other doctors of not permitting the following drugs were required : any antihistamine, decongestant, anti-

cold remedies, any local nasal application, steroid. The co-intervention was assessed by asking the patients and telling them to take any remaining drugs to the researcher every visit.

CONTAMINATION

Each bottle of budesonide was labeled with the code number. Each patient was given only one bottle. Because in Thailand budesonide could be bought over the counter, so the patients were explained not to buy any nasal applications by themselves. If they had lost the drug or the bottle was broken, they should notify the researchers in order to get another one.

COMPLIANCE

Before allocation, the patients were instructed on how to use the nasal spray correctly and how to record nasal symptoms into the daily diary card. Before giving the drug to the patient, everyone had to practice to use the drugs correctly . Moreover they were informed of the purpose of the study. Only those who were likely to follow the study protocol were included. Once daily nasal spray was very easy to comply with. The compliance was assessed by asking the patients directly and by weighing the bottles of the drug before giving to the patients and the last visit. The four-puff weight for each strength of budesonide was equal to 0.2 grams.

OUTCOME MEASUREMENT

Effectiveness outcome measurement

As reviewed from published articles, there was no standard outcome measurement for rhinitis. However the outcome assessment for chronic non-infective rhinitis (perennial rhinitis) usually measured in 3 different ways

Subjective assessment

1. **Patient's subjective assessment by using symptom rating scales and treat it as continuous data:**

Nasal symptoms will be assessed by the patients recording individual nasal symptoms into the daily diary card. These symptoms will be recorded after wake up early in the morning and before bed time because these are the two periods that the patients usually have the most evidence of symptoms. Each symptom may be scored by using visual analogue scale or by 4-point symptom scale (0 = no symptom, 1 = mild, 2 = moderate, 3 = severe). Then all nasal symptoms will be summed up and averaged into total nasal symptom score and using as continuous data.

The pitfall of using this symptom score is its reliability, which has not been tested before and there are no good rationale for using this score as continuous data. However, this type of measurement was the most commonly used in the published articles about rhinitis.

2. **Patient's overall subjective assessment on rating scale:**

Patients will assess themselves at the end point of the trial on four or five rating scale as: 0 = worse, 1= the same, 2= symptoms can be minimally controlled, 3=

symptoms can be substantially controlled, and 4 = symptoms can be totally controlled. This assessment is easy to understand but it may not be so sensitive to compare the effectiveness between two treatments because the assessment will be done only at one occasion only at the end point. In order to make it more sensitive, this study will use repeated measurements which means that the patients will assess themselves everyday after treatment. For the clinical meaningful, those whose overall symptoms are substantially or totally controlled will be in the success group and those whose overall symptoms are less than substantially controlled will be in the failure group.

3. Physician assessment:

Two physicians will assess the outcome at the endpoint by examining the nasal cavities and describing the nasal sign as

0 = when there is no edema or mild edema and no nasal secretions

1 = when there is mild/moderate edema with a little nasal secretions

2 = when there is severe/total nasal obstruction, or profuse nasal secretions or both

Success = score 0

Failure = score 1 or 2

This type of assessment is quite unreliable because

3.1 For the rhinologists' viewpoint, the nasal mucosa especially at the inferior turbinate of normal people is bulking because it contains cavernous tissue. Frequently the nasal findings may not correlate with the patients' nasal symptoms.

3.2 Most patients with perennial rhinitis have the peak nasal symptoms early in the morning and at night and will usually be better during the day time. So it is unreliable to assess during the day time.

Objective assessment

1. Rhinomanometric or rhinometric assessment

by using instruments called rhinomanometer or rhinometer to measure the nasal resistance or nasal volume. Though this is an objective method, it is impractical to assess the patients' daily symptoms because it is usually used in a single occasion at the OPD during the day time which will not correspond to the symptoms of the patients because mostly the symptoms usually occur early in the morning and at night. Moreover it can measure only the degree of nasal stuffiness, not the nasal discharge and sneezing. Previous studies showed that this objective assessment showed poor correlation with subjective assessment of the nasal airway.[3,35]

2. Nasal peak inspiratory flow rate

The same reason as above.

Conclusions

The outcome variables were nasal symptoms which were frequently experienced by the patients at night and early morning. So most of the outcome variables could not be seen by the researcher. To overcome this issue, the patients had to record their symptoms themselves by using symptoms diary card. This study will use the following outcome measurements to assess the effectiveness of the treatment

Primary outcome measurement for effectiveness:

The patients assessed the global nasal symptoms by themselves once daily at night before the next nasal actuation, comparing each day with the average run-in period.

Secondary outcome measurement for effectiveness

The patients also recorded the individual nasal symptom by assessing each nasal symptoms according to the operational definition as no symptom(0), mild (1), moderate (2) and severe(3) before bedtime and early morning.

Adverse reaction assessment

Adverse reaction were assessed by using the closed- and open-ended questionnaires, structured interview and physical examinations. Adverse reactions recorded in the questionnaires were epistaxis, nasal stinging, nasal itiching ,sneezing, dry nose, dry throat and others. These were reported as categorical data.

Economic evaluation

Cost-effectiveness ratio, marginal cost effectiveness and sensitivity analysis were evaluated.

DATA COLLECTION

The demographic data: sex, age, occupation ,duration of nasal symptoms were recorded. Individual nasal symptom scores were recorded into the daily diary card during the seven-day run in period. After receiving the treatment, the patients recorded each nasal symptom (nasal sneezing, nasal obstruction ,nasal discharge) on a 4-point scale in daily diary cards twice daily before bedtime and early morning throughout the study. They recorded their overall nasal symptom once a day at night as previously described. At each end point (1, 2 and 3 week after completion of using budesonide nasal spray) the patients assessed the overall nasal symptom comparing with the overall

nasal symptoms during the run-in period. Moreover they were instructed to daily record whether they had fever, coloured nasal discharge, myalgia or not because the events of upper respiratory tract infection will worsen the nasal symptoms. The adverse reactions were also recorded everyday. Any co-intervention drug was also recorded by the patients. Follow-up visits was done at the 1st week and 3rd week after treatment. The aim of the 1st week visit was to check the correctness of the daily diary record and the compliance of the patients.

DATA ANALYSIS

Baseline

Demographic data was analyzed by using descriptive statistics as the followings.

Age: Mean +/- SD

Sex: Proportions

Duration of symptoms: Mean +/- SD

Severity of symptoms: Mean +/- SD

Drug's effectiveness

As some patients might not follow the protocol, non-complier, dropouts and got confounder events (URI), the analysis based on the groups as randomized (intention-to-treat analysis) was used to analyze the effectiveness of the treatments. The data was analyzed in two ways, both including and then excluding dropouts, and non-compliant patients.

To compare the effectiveness between budesonide of different dosage, the following statistics were used.

1 Primary outcome measurement

Because the primary outcomes were assessed by using repeated categorical scale everyday, this data was the repeated dependent ordinal variables. So the Generalized Linear Model (GLM) by Generalized Estimating Equations (GEE) was used.[36] However because of the limitation of the statistical software, this primary outcomes were collapsed as binary data and STATA® Statistical Software version 5.0 was used for computations.

Another analysis of this total nasal symptoms score was to analyse as proportion on the five categorical data at each end point (1, 2 and 3 week after applying nasal spray), and on the binary data (success = score 3 or 4, failure = score 0, 1, or 2) at each endpoint using Chi-square for trend and 95% confidence interval of success difference respectively.

2 Secondary outcome measurements: individual nasal symptoms using as continuous data

Although this outcome measurement is the ordered categorical data, this thesis used it as continuous data like all other published ariticles in order to compare the results.

3. Adverse reactions

Because the adverse reactions were assessed as proportion, 95%% confidence interval of the differences of the adverse reactions between the two dosages was performed.

ETHICAL CONSIDERATION

Budesonide is a topical steroid nasal spray which is widely used around the world for chronic non-infective rhinitis and accepted as a safe drug when prolonged used without systemic steroid side effects. Only patients who gave written informed consent were included. They were completely free to withdraw from the study at any time without any prejudice to their further treatment.

LIMITATIONS

1. Since the effectiveness outcome measurement for this study depended only on subjective assessment by the patients themselves, it would be necessary that the patients were free to assess their nasal symptoms without any bias or influence by the researchers.

2. The symptoms of perennial rhinitis would depend on the amounts of allergens and non-specific irritants. These factors were confounders of the result which were out of control. However, these factors would affect the severity of nasal symptoms. We tried our best to balance these confounders between two treatment groups by using stratification and randomization.

BENEFITS OF THE STUDY

Since budesonide is a very commonly used drug for perennial rhinitis but it has to be imported and quite expensive. Thai patients with perennial rhinitis and Thailand will

save more money if the effectiveness of both dosages are the same.

OBSTACLES

The patients might forget to assess and record their nasal symptoms everyday. It was impossible to recall the severity of nasal symptoms many days later. This would lead to the missing and erroneous data. To solve this problem , the patients were told about the importance of their assessments and the researchers would ask their close relatives to help if possible. If they had telephone at home, they would be warned by the researcher assistants every three days during the trial.