CHAPTER 3

RESEARCH DESIGN AND RESEARCH METHODOLOGY

3.1 Research questions

3.1.1 Primary research question

In case of first episode of lateral epicondylitis, has oral celecoxib 200mg/day any difference in efficacy when compare with local injection mixture of triamcinolone (10mg/ml) 1 ml. and 1% lidocaine (10mg/ml) 1 ml. without adrenaline in terms of success rate (pain VAS (visual analog scale) and pain pressure threshold at lateral epicondyle) at 1 month?

3.1.2 Secondary research question

What are the side effects of celecoxib and steroid injection for the treatment of lateral epicondylitis patients during 3 months period?

3.2 Research objective

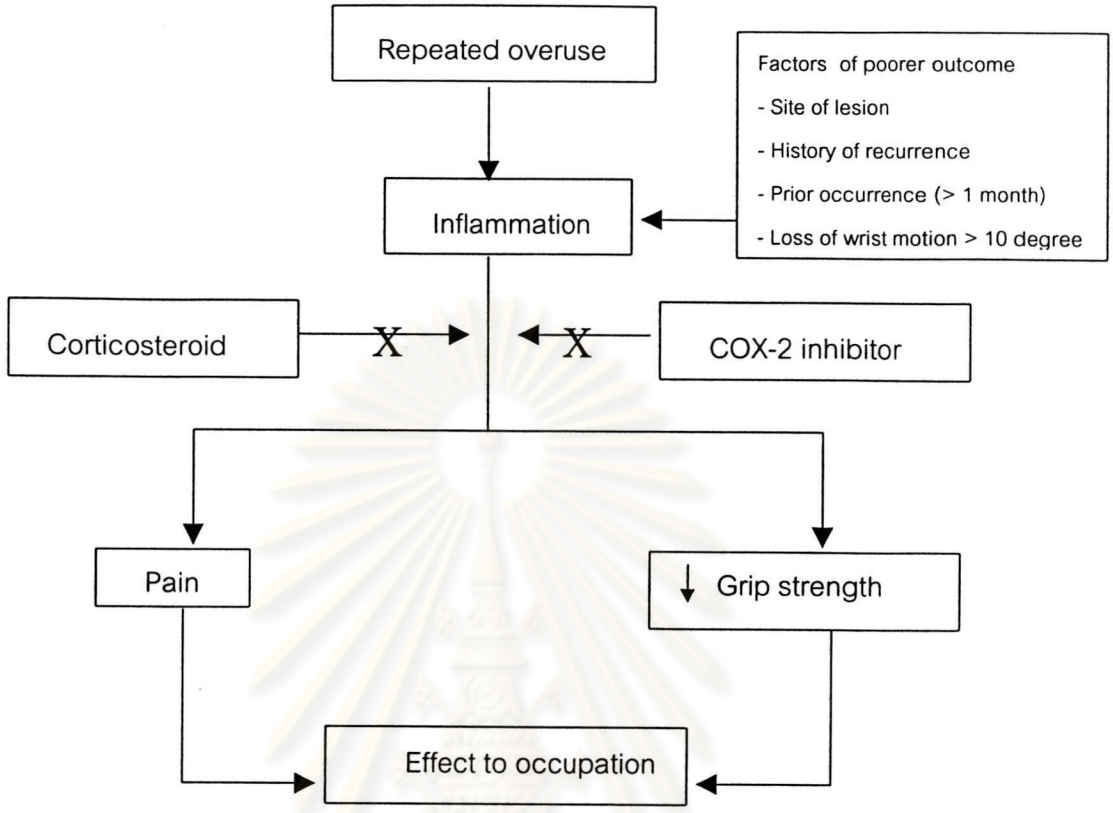
To compare the efficacy between celecoxib 200mg/day and local injection mixture of triamcinolone (10mg/ml) 1 ml. and 1% lidocaine (10mg/ml) 1 ml. without adrenaline in the treatment of lateral epicodylitis patients.

3.3 Statistical hypothesis

Null hypothesis : There is no difference between success rate of celecoxib and local steroid injection group for treatment of lateral epicondylitis during 1 month period.

Alternative hypothesis : There is difference between success rate of celecoxib and local steroid injection group for treatment of lateral epicondylitis during 1 month period.

3.4 Conceptual framework



3.5 Key words

Celecoxib, steroid injection, lateral epicondylitis

3.6 Operational definition

3.6.1 Success of treatment was determined when pain VAS after treatment decreased by ≥ 50% of initial value and pain pressure threshold at lateral epicondyle did not differ from normal side more than 20%.

Rationale for determining success of treatment

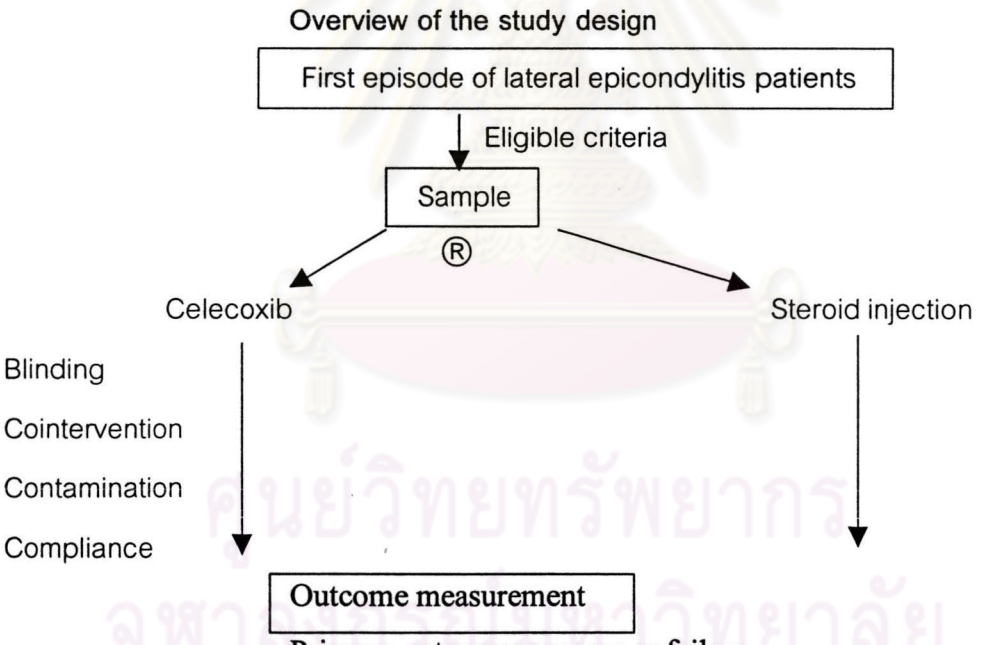
There was no single outcome that represented the sign and symptoms of the disease. From the literature that compared between the pain score before and after treatment, if VAS decreased by 50% of initial value, the further analgesic did not required.[28] So we used decreasing of VAS more than 50% to represent the success in treatment of pain. And from the study of normal pain pressure threshold (PPT), the normal PPT did not differ more than 20% between both sides of the body.[29] So it was considered to be success if the PPT of the affected side was more than 80% of the normal side.

3.6.2 The diagnostic criteria for lateral epicondylitis were:[12]

1. typical history of lateral elbow pain, characteristically aggravated by (overhand) gripping or effort of the arm, especially by active extension of the wrist, often mitigated by rest,
2. tenderness at distinct palpation on the lateral epicondyle of humerus, and
3. pain (increase) with dorsal extension of the wrist against resistance.

3.7 Research design

This study was conducted as randomized controlled trial, single blinded (evaluator) study comparing the efficacy of oral celecoxib and steroid injection for treatment of lateral epicondylitis. We followed and assessed the patients in both groups at 1 month, 2 months, and 3 months period.



3.8 Target population

The patients with lateral epicondylitis.

3.9 Sample population

The patients with lateral epicondylitis at Srinagarind hospital, Khonkaen General hospital and 2 private clinics in Khonkaen province.

3.10 Eligible criteria

3.10.1 Inclusion criteria

The patients who satisfy all of the following criteria were enrolled into the study;

1. First episode lateral epicondylitis patients who were more than 20 years old.
2. Informed about the study and signed the informed consent form.

3.10.2 Exclusion criteria

The patients who satisfy one or more of the following criteria were not enrolled into the study;

1. History of inflammatory arthritis or gross structural abnormality of elbow.
2. Allergy to NSAIDs and steroid.
3. Recent gastroduodenal ulcer (within 6 weeks).
4. Pregnancy and breast feeding.

3.11 Sample size

The equation for sample size estimation of two independent groups, proportional variable by using this formula.[30]

$$N = \frac{[z_{1-\alpha/2}\sqrt{\{2\bar{P}(1-\bar{P})\}} + z_{1-\beta}\sqrt{\{P_A(1-P_A)+P_B(1-P_B)\}}]^2}{\delta^2}$$

where $\delta = P_A - P_B$ and $\bar{p} = (P_A + P_B)/2$

P_A = 90% (Improvement rate of patient's global assessment of change in local steroid injection group)

P_B = 70% (Improvement rate of patient's global assessment of change in celecoxib group (assumed comparable with naproxen))

We assumed that patient 's global assessment could represent our outcome variables; pain VAS , pain pressure threshold at lateral epicondyle.

$$\bar{P} = (P_A + P_B)/2 = (0.9 + 0.7)/2 = 0.8$$

Type 1 error = 5%

Type 2 error = 20%

$$Z_{1-\alpha/2} = 1.96(\text{two tailed test})$$

$$Z_{1-\beta} = 0.84$$

$$N = \frac{[1.96\sqrt{2(0.8)(0.2)} + 0.84\sqrt{0.9(0.1)+0.7(0.3)}]^2}{(0.2)^2}$$

n/group = 61.6

Drop out rate (R) = 20%

N/group = n/(1-R) = 61.6/(1-0.2) = 77

So sample size in each group were 77 cases.

3.12 Allocation technique

All the subjects were randomly allocated to be treated with celecoxib or steroid injection using the permutation block randomization.

3.13 Intervention

The patients who met the eligible criteria were randomly allocated into 2 groups;

Group 1 (Celecoxib group) received oral celecoxib (200mg/day) once daily for 3 weeks

Group 2 (Injection group) received injection mixture of triamcinolone (10mg/ml) 1 ml. and 1% lidocaine(10mg/ml) 1 ml. in one syringe into the tender site at the lateral humeral epicondyle

The patients in both groups were given the oral and written instructions to avoid undue strain on the arm for the first two weeks. All patients were instructed to apply ice to

the area of injection once home for 15-20 minutes.[10] Stretching and strengthening exercise were initiated after the pain subsided.[9 10] They were instructed to observe any symptoms relate to the side effects. They were given a diary for record pain after injection (first 5 days) and gastrointestinal symptoms for 3 weeks. They received the acetaminophen plus codeine 30 tablets for pain rescue.

The patients were followed up at 1 months, 2 months and 3 months. If the treatment was failure, the patients received the injection mixture oftriamcinolone (10mg/ml) 1 ml. and 1% lidocaine(10mg/ml) 1 ml in both groups.

3.14 Outcomes variables and measurement

Primary outcome

success of treatment or failure

The treatment was determined as success when met both of the following criteria

-Pain score VAS (Visual Analog Scale) decreased by $\geq$50% of initial value

-Pain pressure threshold at lateral epicondyle measured by pain pressure threshold meter differed from normal side not more than 20%.

Secondary outcome

1.Side effects of treatment

-GI side effect: The patients were instructed to record dyspepsia, abdominal discomfort, abdominal pain, nausea/vomiting and GI bleeding in diary in first 3 weeks.

-Post injection pain : The patients were instructed to record pain and its severity in diary in first 5 days.

-Local skin atrophy was observed at each visit.

2. Grip strength measured by hand dynamometer (mean from 2 times) compared with baseline.

3. Pain score VAS (Visual Analog Scale) compared with baseline.

4. Pain pressure threshold compared with baseline.

5. Number of acetaminophen plus codeine used

6. Duration of pain free symptoms, which defined after the successful of treatment occurred until the recurrent occurred.

- About instruments which measure the outcomes

Trained nurse who didn't know the treatment of the patients did all outcomes measurement.

Pain score was recorded by a 10 cm horizontal visual analog scale(VAS). The patients were instructed to mark at that scale. The patients were asked with the question: "How much pain do you feel in your elbow in daily activities such as tooth brushing, bathing, dressing, desk-work and carrying bags etc."

Pain pressure threshold was measured by pain pressure threshold meter (PTM) or algometry. The pain pressure threshold meter, commercially available through Pain Diagnostic and Treatment, is a force gauge fitted by a rubber disk with a surface of 1 $cm.^2$ A known force (pressure) can be applied on the lateral epicondyle through this rubber disk. The gauge is calibrated in Newtons (N) or in kg/ cm^2, with a range to 10 Kg and 0.1 kg divisions. Before the study PTM was test for intra rater reliability. The coefficient was 0.97

Grip strength will be measured by grip strength dynamometer, T.K.K. 5001 Grip-A, produced by Takei Japan. It has a range from 0-100 kgf and 0.5 kgf. division. Before the study grip strength dynamometer was test for intra rater reliability. The coefficient was 0.95.

3.15 Data collection

General baseline data, demographic data were recorded at first visit. Including :

Administrative data

- Identification number
- Name
- Address

Demographic data

- Age
- Sex
- Occupation
- Dominant hand

Baseline data

- Duration of pain
- Range of motion of wrist (flexion and extension)
- Pain score VAS
- Grip strength of the affect side
- Pain pressure threshold of both sides

At each visit, pain score VAS, pain pressure threshold, grip strength and local skin atrophy were recorded by well-trained nurse who doesn't know the group allocation of patients. Other data that were recorded were number of rescue drug used, duration of pain free symptoms, GI side effects (dyspepsia, abdominal discomfort, abdominal pain, nausea/vomiting, GI bleeding) and post injection pain.

Control measure for reliability and validity of the data

:The evaluator was trained and assessed for intra-rater reliability before beginning the study. The evaluator measured the pain pressure threshold and grip strength of the 15 normal subjects The coefficient was 0.97, which accepted for good reliability.

:During the study, the patients were informed about the measurement procedure and instrument clearly before each measurement.

3.16 Data processing and data analysis

1. Intention to treat analysis was performed. All hypotheses tests were two tailed with $\alpha = 0.01$.

2. Baseline demographic data was presented by using the mean and standard deviation as an index localization dispersion of continuous data and described by percent in category data

3. Fisher's Exact test was used to compare success rate between two treatments.

4. Survival analysis (the product limit method; Kaplan-Meier method) was used. Duration of pain free symptom after each treatment was used as survival time. The two survival curves were compared by Log Rank test.

5. Repeated ANCOVA were used for test statistically significant differences in pain score VAS, pain pressure threshold and grip strength between two treatment at each follow up. As baseline data were covariances.

6. Side effects of each treatment were presented in percentage.

3.17 Ethical considerations

1. Risk

Local corticosteroid injection is one of the common treatment for lateral epicondylitis, has been accepted efficacy and few side effects. It can make post injection pain within 48 hours. Local skin atrophy can occur but it isn't a serious side effect.

Celecoxib is COX-2 inhibitors. It has less side effects especially gastrointestinal ulcers and has no effect on platelet aggregation.

2. Benefit

Celecoxib is COX-2 inhibitors. Its efficacy is comparable with naproxen or diclofenac. Its gastroduodenal side effects are comparable with placebo.

3. Informed consent

The informed consent documents were used to explain in simple terms regarding the risks and benefits to the patients before the patients were recruited into the study. The informed consent document contained a statement that the consent was freely given, that the patient was aware of the risks and benefits of entering into the study, and that the patient was free to withdraw from the study at any time.

Each patient had to understand the nature of the study and sign an informed consent document. The patients were free to withdraw from the study at anytime they want.

The investigator was responsible to see that informed consent was obtained from each patient and for obtaining the appropriate signatures and dates on the informed consent document prior to the performance of any protocol procedures and prior to the administration of study drug.

4. Confidentiality

All the patients' data were kept confidential.

5. Ethical review

The Institute Ethical Committee reviewed the protocol before the study. An informed consent document approved by the Institute Ethical Committee was signed prior to the patient's participation in this study by the patient. The patient and investigator were provided with copies of the signed informed consent document.

3.18 Limitations

This study was conducted for the first episode patients. So it could not generalize to every patients, or chronic patients

3.19 Benefits of the study

Lateral epicondylitis is the common cause of elbow pain. It causes pain, decrease grip strength and disability. Local corticosteroid injection gives good improvement but also give some injection site problems. The injection technique needs experience and skill.

If celecoxib (200mg/day) is effective in the treatment of lateral epicondylitis, it might be a better choice for any physician, not only orthopedist because it doesn't need injection skill, can avoid injection site problems and has lower GI side effects when compare with conventional NSAIDS.

3.20 Obstacle

After 3 months of study, the government implied the universal coverage policy (30- Baht project). This policy indicated the patients had to stay or be treated within their community hospitals. So the number of patients dropped from 90-100 cases/year to 40 cases/2.5 years. This made this study couldn't collect enough cases in the assigned time.

The study was planed to do in the 4 sites, but it's difficult to convince patients to follow up at Srinagarind hospital (due to limitation of instrument), even though we gave them the transportation cost to make the follow up more convenience.