CHAPTER 5

RESEARCH METHODOLOGY

5.1 Research Design

Randomized double-blinded controlled trial.

5.2 Setting

Bhumibol Adulyadej Hospital, tertiary level hospital and school of medicine affiliated with Chulalongkorn University located in the north of Bangkok.

5.3 The Sample

5.3.1 Target Population

Women undergo elective simple total abdominal hysterectomy for benign condition.

5.3.2 Sample Population

The patients participated in these research were the women who were undergoing simple total abdominal hysterectomy for benign condition in Bhumibol Adulyadej Hospital between March 1996 to March 1997.

5.3.3 Eligible criteria

Inclusion criteria

1. Elective simple abdominal hysterectomy.
2. Informed consent

Exclusion criteria

1. Known medical complications that might make the patient to infection e.g. diabetes mellitus.
2. Immunocompromized host e.g. poor nutritional status, positive anti HIV.
3. Indication of hysterectomy due to infectious condition or known to require antibiotics before surgery.
4. History of penicillin allergy.

5.3.4 Sample size estimation

Sample size calculated by equation comparing two independent nominal data.

$$n = \frac{2(Z\alpha + Z\beta)^2 \pi(1-\pi)}{(P_1 - P_2)^2}$$

The proportion of patient that had infectious morbidity in non-prophylaxis group was about 15%[4]. And the proportion in prophylaxis group, if it worked well, wound be decreased to 5%.

To use α = 0.05; then $Z\alpha$ = 1.645

To use one-tailed test because the antibiotic prophylaxis wound be used in practice only in the case of its efficacy was more than placebo.

Power of study = 80% ; then $Z\beta$ = 0.84

To used data from Department of Obstetric and Gynecology statistic[4] , then

P1 was the infection rate in non-prophylactic group = 0.15

P2 was the infection rate expected in prophylactic group = 0.05

$$\pi = \frac{P1 + P2}{2}$$

$$= \frac{2(1.645+0.84)^2 (0.1)(0.9)}{(0.15 - 0.05)^2}$$

$$= 110.7$$

n/group = 111

The total number of patients were needed in the study were at least = 222

5.4 Experimental Maneuver

5.4.1 Sample Collection

The patients who scheduled for simple total abdominal hysterectomy and passed eligibility criteria were invited to participated the research protocol. All eligibility patients were explained the risk and benefit of research protocol (appendix 1.), then informed consent were signed. The patient was admitted to the gynecological ward for scheduled hysterectomy in the next morning. The preoperative preparation as in research protocol was done in the night prior to the operation. Randomization process was done in operation room. Drug or placebo was injected intravenously 15 - 30 minutes before the operation. After standard general anesthesia, standard abdominal

hysterectomy was performed. After the operation and two hours in the recovery room, the patient was transferred back to the ward, the post operative care was followed the research protocol (appendix 1.) The outcomes measurement were start here by the observers. The outcomes were collected from patient's chart to data recorded form.

5.4.2 Randomization

The twenty three set of blocks were used. Each block contains ten patients, five patients in placebo group and five in treatment group. Permutation method was used to defined sequence in each block. The probability of possible sequences were listed. Then thirty three of them were selected to use in this research. The number of sequence assigned in each block were written in a paper and put in a sealed envelope. The numbers corresponded to the numbers in the sealed envelope were on the vials containing cefazolin and other sterile, non medicated powder placebo. The sealed envelope and vials contain cefazolin and placebo were kept in the operating room. The randomization was done 1/2-1 hour just before the operation, and intervention was started immediately after

randomization. The code was kept in the office without broken until the end of research.

5.4.3 Blindness

The cefazolin sodium vial containing 1 g. of white crystal power, when reconstituted with normal saline, it turn to straw color solution. The placebo vial was prepared to look like medicine vial and also turn to straw color when mixing with normal saline. The labeled code number were attached to the vial by pharmacist and brought to the operation room. So this was a double-blinded trial, the patients and the surgeons did not know which vial contained cefazolin or placebo. The code wound not be broken until the end of the research.

5.4.4 Drop out

Because all data collection for each subject wound be finished when patients were still in the hospital, and random allocation process started just before operation, drop out was expected to be minimal in this trial.

5.5 Measurements

5.5.1 Outcome variables

Variables to be measured were

1. General data

1.1 Patient age

1.2 Menstrual status (pre- or postmenopausal)

1.3 Operative diagnosis

1.4 Surgeon name(skill)

1.5 Operative time

1.6 Amount of blood loss

2. Infectious morbidity data

3. Febrile morbidity data

5.5.2 Outcome validity

Main outcome, infectious morbidity, febrile morbidity had their strictly criteria according to textbook and to acceptance of gynecological staffs. Infectious morbidity was evaluated by their categories below.

Abdominal wound infection was any wound which had serous or serosanguous discharge was diagnosed as infection. This diagnosis was made when wound drainage purulent material or serous fluid from which potential pathogen was disclosed by culture and/or gram stain. Tissue induration, warm and erythema were present and the incision was more tender than the previous examination. Wound which patient complained of extraordinary pain and had hyperemia or redness of skin was also diagnosed to be infected.

Pelvic cellulitis defined as infection in extraperitoneal space primarily lateral to the vaginal cuff including parametrial tissue. The diagnosis was made

when a woman complain of increasing abdominal pain and had increasing tenderness to gentle deep palpation of the lateral vaginal wall. The speculum examination was performed to allow collection of material cephalad to vaginal cuff for culture. A bimanual examination was performed to confirm diagnosis and to detect the presence of pelvic abscess or infected hematoma.

Infected hematoma and pelvic abscess was diagnosed when patient had pelvic pain and fever after 48 hours post operation, speculum and bimanual pelvic examination were performed to detect pelvic cellulitis. This diagnosis was made when infection was present in tissue as previously described in adnexal structure and/or fluctuate tender mass was palpable.

Vaginal cuff abscess. On the fifth postoperative day or when patients complained of abnormal vaginal discharge, speculum examination was performed. The presence of purulent vaginal discharge with neither abdominal pain nor pelvic mass developing more than three

days after surgery with absence of other cause of febrile morbidity was diagnosed vaginal cuff abscess.

Febrile morbidity was defined as temperature 38.0 C (100.4 F) or higher, the temperature to occur on any 2 of the first 10 days post operation, exclusive of the first 24 hours, and to be taken by mouth by a standard technique at least four times daily.

5.5.3 Outcome Reliability

Abdominal wound infection : The photograph of the infected wound in any stage that was tested for validity by the content expert wound be shown to the observer. The reliability test was performed. Kappa test was used to test agreement in the diagnosis of wound infection. The reliability test was performed before the research began.

Pelvic cellulitis : Two residents were perform speculum and bimanual pelvic examination. If their conclusion were the same, pelvic cellulitis was diagnosed.

If they were disagreement, attending staff examination by strictly criteria mentioned above was a final diagnosis.

Infected hematoma and pelvic abscess: Two residents were performed speculum and bimanual pelvic examination. If their conclusion was the same, pelvic cellulitis was diagnosed. If they were disagreement, attending staff examination by strictly criteria mentioned in 5.5.2 was a final diagnosis. If any mass was detected, sonography that shows hypoechogenic or mixed echoic mass or collection in the pelvic cavity wound be done and used to confirm diagnosis and used as a baseline for follow up.

Vaginal cuff abscess: Photography of cuff abscess, after passed the validity test by gynecological staffs, was used to test reliability among observers by kappa test before research was started.

5.6 Data Collection

All data was recorded in the data collection form (appendix 2.) from the patient hospital chart by a third

year resident of obstetrics and gynecology department. All data were filled in the patient's record by attending resident, composed of patient's name, drug code, hospital number, patient's age, menstrual status, preoperative diagnosis, surgeon's name, operative time, amount of blood loss, post operative diagnosis and treatment. Infectious morbidity and febrile morbidity was designated yes or no depended on physician diagnosis according to its criteria.

5.7 Data Analysis

Descriptive statistics of both group were described including, menstrual status, preoperative diagnosis, patient age, urine culture, chest x-ray, result of operative site culture, cause of infectious morbidity, and antibiotic therapy. All continuous data were present in means and standard deviation. Dichotomous data was present in percent.

Chi-square was used to compare two independent proportional data. Febrile morbidity and infectious morbidity, were compared between placebo and treatment

group. Computer assisted calculation was done by Epi Info and SPSS program.

Confounder adjustment by surgeon's name who did the operation, operation time, amount of blood loss, preoperative diagnosis were also be analyzed by Mantel-Haenszel Chi-square procedure and multiple logistic regression analysis.

5.8 Ethical Consideration

1. Every potential subjects were explained about the details of the study. Written informed consent were obtained from every subject.

2. Prophylaxis antibiotic for abdominal hysterectomy was still a controversial issue.

3. Penicillin allergy was asked from every patient. Awareness and preparation of prompt treatment of hypersensitivity reaction were arranged.

4. Even though cefazolin was a broad spectrum antibiotic and may change vaginal flora, it was not routinely used in treatment of post hysterectomy infection

in this hospital. So the infection that might be occurred after failed prophylaxis could be treated with other antibiotics.

5. Antibiotics combination were commonly used in treatment of post hysterectomy infection with respect to the cause of infection.

The research protocol was passed the ethical committee of Bhumibol Adulyadej Hospital before beginning.

5.9 Limitation

Result of prophylactic antibiotics was varies substantially in the literature because of their different in criteria used in diagnosis infection. Result was limited to whom applied these valid criteria for diagnosis infection in this thesis.

5.10 Expected benefits and application.

1. To reduced the postoperative infection rate of abdominal hysterectomy.

2. To detect the efficacy of cefazolin in prevention of infection of post abdominal hysterectomy.

5.11 Obstacle and strategies to solve the problem.

There were many surgeons to encounter this research. The ways to manage the patient were very different among them that wound be threaten to the validity and reliability of the result. The researcher closely contacted to them, to reassure that research protocol wound be followed strictly.