CHAPTER II

RESEARCH DESIGN

Research Questions

1. Primary Research Questions

1.1 Is it efficacious in reducing the prevalence of residual muscle relaxation to less than 25% of the control group (the group that muscle relaxants are administered at fixed time interval - the standard way of muscle relaxant administration in Thailand), if we use peripheral nerve stimulator instead of fixed time interval to guide muscle relaxant administration during anesthesia?

1.2 Is it efficacious in reducing the prevalence of residual muscle relaxation to less than 25% of those who received long acting relaxants (the standard drug in Thailand), if we use newer (intermediate acting) muscle relaxants instead of long acting ones during anesthesia?

2. Secondary Research Questions

2.1 Does peripheral nerve stimulator (PNS) have the same effect in reduction of the prevalence of

residual relaxation for both long acting (standard) and intermediate acting (new) relaxants?

2.2 Is the operative condition better or worse if the peripheral nerve stimulator (PNS) is used instead of fixed time interval to guide the muscle relaxants administration?

2.3 Is the operative condition better or worse if the newer drug (intermediate duration of action) is used instead of the standard (long acting) muscle relaxant?

2.4 From the provider's viewpoint, is the use of peripheral nerve stimulator to guide muscle relaxant administration or a newer relaxant more cost effective in reducing the prevalence of residual relaxation?

2.5 Can newer relaxant or peripheral nerve stimulator help to reduce the postoperative respiratory complications when compared to long acting relaxant given at fixed time interval?

Objectives

1. To compare whether there is a difference in the prevalence of postoperative residual relaxation among these four groups of patients which are:

Group I who receive long acting muscle relaxant (pancuronium) at fixed time interval,

Group II who receive long acting muscle relaxant (pancuronium) guided by a peripheral nerve stimulator,

Group III who receive intermediate acting muscle relaxant (vecuronium) at fixed time interval,

Group IV who receive intermediate acting muscle relaxant (vecuronium) guided by a peripheral nerve stimulator.

If there is a difference in the prevalence of postoperative residual relaxation, then to see whether the prevalence in group II, III and IV are less than 25% of that in group I.

2. To compare whether there is a difference in operative conditions among these four groups of patients.

3. If there is a significant difference in the prevalence of residual relaxation, to calculate the marginal cost effectiveness for economic evaluation of each technique.

4. To compare the prevalence of postoperative respiratory complications, such as hypoxia, airway obstruction and aspiration pneumonitis among these four groups of patients.

Hypothesis

1. Using peripheral nerve stimulator will help adjust the administered amount of muscle relaxant according to what the patient needs, so the risk of overdose and the postoperative residual relaxation will be reduced.

2. A newer (intermediate acting) relaxant has a more reliable action and also shorter duration of action than the standard (long acting) relaxant, so using the newer relaxant instead of the standard relaxant should reduce the risk of postoperative residual relaxation.

Research Design

The design of this study is a 'Randomized controlled trial'. As both kinds of muscle relaxants and peripheral nerve stimulator are also currently in use, so the randomized allocation of patients to either group will not pose an ethical problem. In this study there are 2 factors of interest, each of 2 levels (using peripheral nerve stimulator/using fixed time interval; a newer drug/a standard drug) which might affect the outcome (prevalence of residual relaxation). In addition these 2 factors might not be independent from each other, this means that the effect of both factors acting at the same time might not be a simple additive effect. In

order to demonstrate the effect of interaction, we use the 'Balanced factorial design' (Cox, 1958). This study will have 4 groups of patients as in Fig. 2.1.

Research Methodology

1. Population and Sample (Fig. 2.1)

1.1 The target population of this study is all patients who have general anesthesia with muscle relaxants.

1.2 The sample selection (the studied population):

1.2.1 Inclusion criteria:

- Patients who are scheduled for gynecological operation under general anesthesia with muscle relaxants at Siriraj Hospital.

- Patients who are scheduled for an operation lasting more than one hour.

- Age 16-60 years.

1.2.2 Exclusion criteria:

- Known severe systemic disease.

- Known neuromuscular disease such as myasthenia gravis.

- Pregnant women.

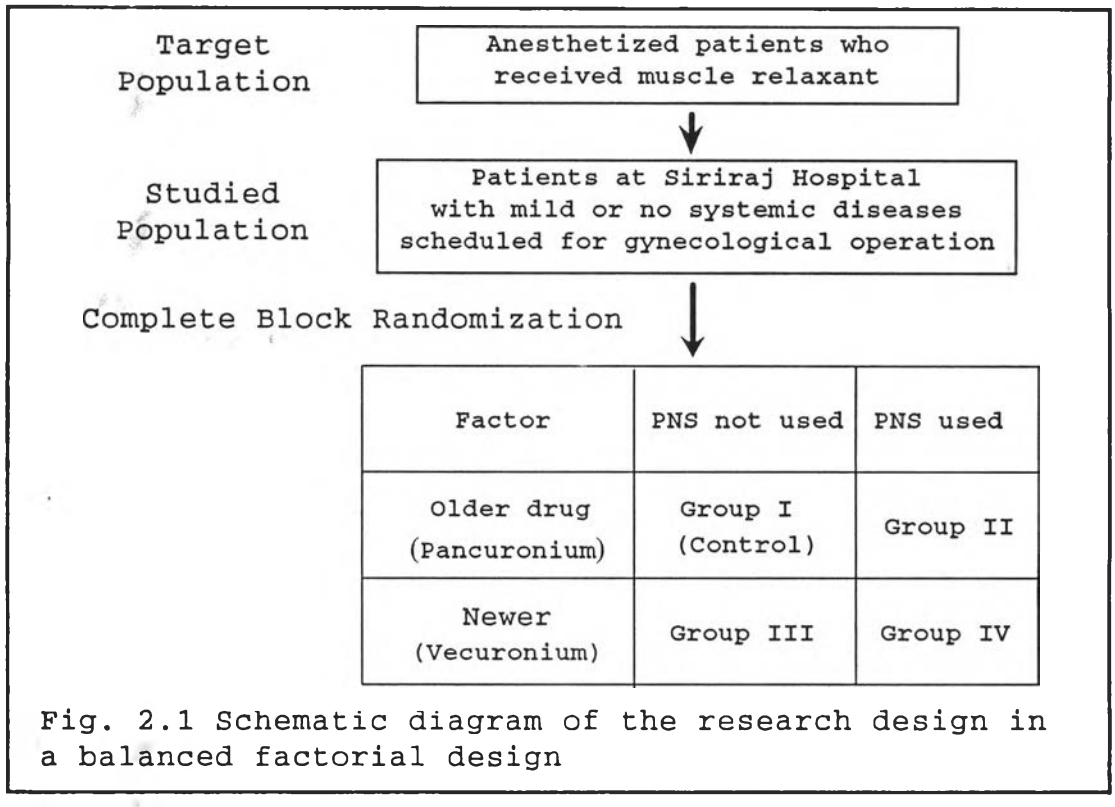

Fig. 2.1 Schematic diagram of the research design in a balanced factorial design

1.3 Sample size calculation:

The main outcome measurement in this study is the prevalence of the postoperative residual relaxation which is the dichotomous outcome. There are 2 factors that might affect the outcome of the study. These factors are whether or not a peripheral nerve stimulator is used to guide muscle relaxants administration and the types of muscle relaxant. Each factors consists of 2 levels. As it is possible that there is an interaction between factors and the research questions are on the individual factor effect, so the sample size must be large enough to cover the subgroup

analysis among each of the four groups shown in Fig. 2.1. The sample size of this study can be calculated from the main outcome to answer the primary research questions. The expected clinical significant differences are the same for both primary research questions which is 75% reduction of the prevalence of the postoperative residual relaxation from the control groups. The formula for sample size calculation in this case is (Feinstein, 1977):

$$n = \frac{1}{\Delta^2}[Z_\alpha\sqrt{2\bar{p}(1-\bar{p})} + Z_\beta\sqrt{p_2(1-p_2)+p_1(1-p_1)}]^2$$

When n equals the number of patients in each group shown in Fig. 2.1, p_1 equals the prevalence of postoperative residual relaxation in the group of patients who received the standard muscle relaxant by fixed time interval and p_2 equals the prevalence of postoperative residual relaxation in the group of patients who received an intervention.

H_0: $p_1 \leq p_2$

H_1: $p_1 > p_2$

α = 0.05 $\quad Z_\alpha$ = 1.645

β = 0.20 $\quad Z_\beta$ = 0.842

As from previous study (Worawut Lapisatepun et al., 1992) the prevalence of postoperative

หอสมุดกลาง สถาบันวิทยบริการ
จุฬาลงกรณ์มหาวิทยาลัย

residual relaxation equals 34%, so p_1 = 0.34 and then q_1 = 1 - p_1 = 0.66.

The null hypothesis is rejected when p_2 = ¼ X 0.34 = 0.085, so q_2 = 1 - p_2 = 0.915 and Δ = 0.34 - 0.085 = 0.255.

$$\bar{p} = \frac{p_1 + p_2}{2} = \frac{0.34 + 0.085}{2} = 0.2125$$

$$1 - \bar{p} = 1 - 0.2125 = 0.7875$$

So n = 30.77.

As the outcome of this study is a dichotomous outcome, so this number would need the correction for continuity analogous to that Yates' correction in chi-square tests (Feinstein, 1977).

$$n' = \frac{n}{4}[1 + \sqrt{1 + (\frac{8}{n\Delta})}]^2$$

So the sample size for each group equals 45 and the total amount of patients in this study will be 180 patients.

2. Measurement

2.1 Hypothetical Framework

2.1.1 The outcome variables

Postoperative residual relaxation (curarization) can be measured by using a special kind of peripheral nerve stimulator - an 'accelograph'. This equipment will give the TOF stimulation over the motor nerve, which usually is the ulnar nerve. Then the response of movement caused by contraction of the muscle supplied by that motor nerve, which usually is the movement of the thumb, will be detected. The comparison of the fourth movement (T_4) to the controlled movement (T_1) is used for the diagnosis of residual relaxation. Normally we diagnose the patient to have 'residual relaxation when $\%T_4/T_1$ is less than 70% (Viby-Mogensen, 1990)'. There are several ways for measuring the responses of muscle to motor nerve stimulation, such as measurement of muscular electrical activity, measurement of the force of muscle contraction and measurement of the acceleration of muscular movement. Measuring electrical activities is not popular because force or power of the muscle is more important clinically and it is also more difficult to measure especially in the operating room environment. Measuring the force is usually accepted as the 'gold standard', but the equipment needed for its measurement is quite complicated, so it is reserved for laboratory research. As the force needed for movement of any object is directly related to the acceleration of that movement (Newton's law), measuring the acceleration

will represent the force (Jensen, Viby-Mogensen and Bang, 1988; Viby-Mogensen et al., 1988). There were many studies already done to show the validity and reliability of this new equipment (May, Neilsen and Werner, 1988; Werner et al., 1988; Silverman et al., 1992).

This measurement will be done at three points of time related to time of reversal (at 5, 15 and 30 minutes after reversal). The 5 and 15 minute data sets represent the onset and peak action of reversal drug respectively. However the 30 minute data set will be chosen as the main outcome measurement because this period of time is more likely to be related to clinical problems in the recovery room, as it is the time that the recovery room personnel may pay less attention to the patient.

The numbers and kinds of movement of the patients (spontaneous respiration, hiccup, bucking, gross movement of limbs) will be observed and recorded every 5 minute during operation. This is to reflect the operative condition.

The respiratory complications are probably the most interesting variable because they are actually the undesired endpoints of the residual muscle relaxation. But the problem is that the prevalence of

all these events is much lower than the residual relaxation, so choosing this variable as the main outcome of the study will demand a very large sample size and limit the feasibility of this study. In addition, the respiratory complication may occur from other reasons e.g., respiratory depression from opioid analgesic drugs or aspiration, so it is less specific than accelograph. However, because of its importance, it will be observed and recorded. It is also important to know that this kind of clinical observation by different physicians may yield different results (Godfrey et al., 1969). Hypoxia which is the most important problem related to the respiratory system will be measured by both clinical observation and using the pulse oximeter. The use of pulse oximeter is a very sensitive tool for detecting hypoxia but it does not point out what the cause of that hypoxia is.

The amount of relaxants given, the duration of the operation and the cost of a peripheral nerve stimulator will also be recorded. These data will be used for further cost analysis. Cost comparison among different technique can be measured as the marginal cost over the control as other factors are common in all techniques.

2.1.2 The administrative variables

The hospital number, the admission number, the identification serial number including name and surname of the patient will be recorded for administration purpose.

2.1.2 The baseline variables

These variables will be recorded as the baseline data:

- age,
- body weight and height,
- history of previous recovery from general anesthesia,
- history of jaundice, renal problems and previous serious illnesses,
- laboratory investigation, e.g., hemoglobin, hematocrit, BUN, creatinine and electrolytes.

2.1.4 The intervention variables

The types of muscle relaxants given and whether or not the peripheral nerve stimulator is used, will be assigned to patient according to the complete block randomization (15 blocks of 12 patients). These data, the numbers of twitch count and the amount of drugs given to the patient will be recorded as the intervention variables.

หอสมุดกลาง สถาบันวิทยบริการ จุฬาลงกรณ์มหาวิทยาลัย

2.2 Instrumental Design

The evidence for selecting main outcome measurement in this study is based upon previous studies (May et al., 1988; Werner et al., 1988; Silverman et al., 1992). In the intervention measurement the observation of twitch count is needed (Viby-Mogensen et al., 1985; O' Hara, Fragen and Shanks, 1986). When the blockade is of fairly high degree, the twitches are so small that there might be some differences in observations. The reliability of this tool for measuring the intervention variable was tested in the pilot study and the intraclass correlation coefficient between three observers (two nurse anesthetists and one anesthesiologist) was high (0.93).

Other outcome measurements used are intraoperative observations of movement and postoperative respiratory complications. These observations are important parts of anesthetic training, so there is no need for special teaching and training of these particular observations for this study, but there might be some disagreements between observers (Godfrey et al., 1969; Department of Clinical Epidemiology and Biostatistics, McMaster University, 1980a; Department of Clinical Epidemiology and Biostatistics, McMaster University, 1980b). This disagreement can be reduced by

clarification of the definition involved (Department of Clinical Epidemiology and Biostatistics, McMaster University, 1980b) and finally testing for agreement.

3. Intervention

After receiving the consent from the patients, we shall allocate them into four groups by complete block randomization to ensure equal numbers in each group as in Fig. 2.1. For the first factor (peripheral nerve stimulator), we shall not use PNS in the first and the third groups of patients and shall use it in the second and fourth groups. For the second factor (type of muscle relaxant), we shall use pancuronium in the first and the second groups and shall use vecuronium in the third and the fourth groups. After randomized allocation into four groups, all groups will have the same standard type of general anesthesia. This comprises:

- premedication: fentanyl 1-2 µg/kg IV before induction of anesthesia,

- muscle relaxation for intubation: pancuronium or vecuronium bromide (blindly) 0.1 mg/kg IV and wait 3 minutes before intubating the patient,

- induction of anesthesia (sleep): thiopental 3-5 mg/kg IV immediately after flushing of the relaxant,

- maintenance of the level of anesthesia by N_2O and O_2 (in the ratio of 4:2 lpm) plus halothane (0.25-1%). Halothane and nitrous oxide are used to provide narcosis for the patient and nitrous oxide also has an analgesic effect. If there are signs of light anesthesia such as hypertension, tachycardia, excessive lacrimation and sweating, then supplemental analgesic drugs (e.g. fentanyl 50 µg) can be given and also the concentration of halothane can be increased.

For the administration of muscle relaxant at fixed time interval

The pancuronium group will receive pancuronium 1/4 of loading dose every 60 minute and also normal saline solution every 30 minutes for blinding of the type of relaxant used.

The vecuronium group will receive vecuronium 1/4 of loading dose every 30 minutes and also normal saline solution every 60 minutes for blinding of the type of relaxant used.

For the administration of muscle relaxant guided by PNS

The patients will receive maintenance drug in a blinded fashion (not labeled) according to the

results of twitch count obtained from peripheral nerve stimulation. The peripheral nerve stimulator used in this study is a simple one that can give only the fixed output of 55 mA. By this stimulator, we stimulate the ulnar nerve transcutaneously at the wrist and observe the response at the thumb of that hand. The mode of stimulation used in this study is a train of four (TOF) stimulation (Ali et al., 1970; Lee, 1975; Viby-Mogensen, 1990) and the observed response is a count of twitches. The stimulation is given to the patient every 5 minutes, starting just after the patient is asleep. The patient will have more loading dose of 1/4 of initial loading dose (0.025 mg/kg) of muscle relaxant (the type will depend on the randomization) if the TOF twitch count is more than one at 5 minutes after the first dose. Then the patient will have the same maintenance dose of 1/4 of initial loading dose when the TOF twitch count is more than one.

If there are any signs of poor relaxation as movements or spontaneous respiration in any groups, the patient will be given more relaxant (1/4 of loading dose) each time.

- Reversal: At the end of the operation and at least 10 minutes after last injection of drugs or normal saline, all the anesthetic agents will be turned

off and 5 minutes after that the patient will received the reversal drugs (atropine 1.2 mg and prostigmine 2.5 mg) intravenously for reversal of the muscle relaxant action. After reversal, the intraoperative observer will attach the accelograph to the patient for measuring the degree of residual relaxation. The blind observer will measure T_4/T_1 ratio by using accelograph at 5, 15 and 30 minutes after reversal.