CHAPTER III

RESEARCH METHODOLOGY

3.1 RESEARCH QUESTIONS

3.1.1 Primary Research Question

3.1.1.1 Can vessel sealing system tonsillectomy (VSST) change intraoperative bleeding in comparison with cold knife tonsillectomy (CKT)?

3.1.1.2 Can VSST change operative time in comparison with CKT?

3.1.1.3 Can VSST change postoperative pain in comparison with CKT?

3.1.2 Secondary Research Question

3.1.2.1 Does VSST have any postoperative adverse effects (bleeding & others) in comparison with CKT?

3.2 OBJECTIVES

3.2.1 Primary Objectives

3.2.1.1 To compare intraoperative blood loss between VSST and CKT.

3.2.1.2 To compare operative time between VSST and CKT.

3.2.1.3 To compare postoperative pain between VSST and CKT.

3.2.2 Secondary Objectives

3.2.2.1 To compare postoperative adverse effects (bleeding & others) between VSST and CKT.

3.3 HYPOTHESIS

3.3.1 Research Hypothesis

3.3.1.1 There is difference of intraoperative blood loss between VSST and CKT.

3.3.1.2 There is difference of operative time between VSST and CKT.

3.3.1.3 There is difference of pain on postoperative day 0-7 between VSST and CKT.

3.3.2 Statistical Hypothesis

$\overline{D}_1$ = Mean of difference between intraoperative blood loss of unilateral CKT and VSST (Intraoperative blood loss of unilateral CKT – Intraoperative blood loss of unilateral VSST)

Null hypothesis $\overline{D}_1 = 0$

Alternative hypothesis $\overline{D}_1 \neq 0$

$\overline{D}_2$ = Mean of difference between operative time of unilateral CKT and VSST (Operative time of unilateral CKT – Operative time of unilateral VSST)

Null hypothesis $\overline{D}_2 = 0$

Alternative hypothesis $\overline{D}_2 \neq 0$

Pain scores on postoperative day 0-7 between VSST side and CKT side.

Null hypothesis

Pain scores on postoperative day 0-7 from CKT side = VSST side

Alternative hypothesis

Pain scores on postoperative day 0-7 from CKT side ≠ VSST side

3.4 CONCEPTUAL FRAMEWORK

The conceptual framework of this study was shown. (Fig 1)

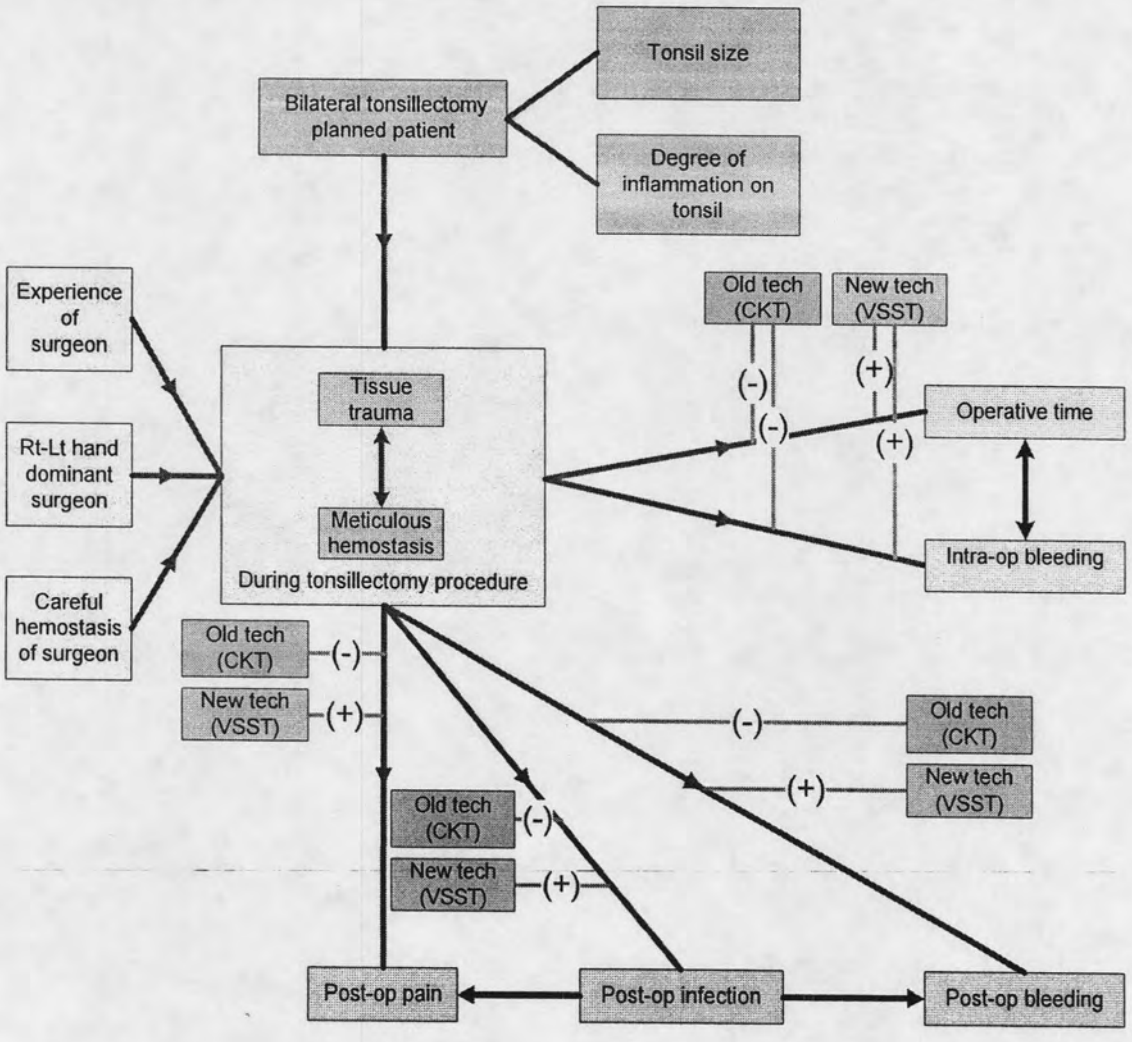


Figure 1: Conceptual framework

3.5 KEYWORDS:

PALATINE TONSIL/ VESSEL SEALING SYSTEM/ INTRAOPERATIVE PERIOD/ POSTOPERATIVE PERIOD/ HEMORRHAGE

3.6 OPERATIONAL DEFINITIONS

3.6.1 Cold Knife Tonsillectomy (CKT)

- Cold knife tonsillectomy (CKT) is a standard tonsillectomy technique.
- Cold knife tonsillectomy is usually performed by incision of the anterior pillar with a sickle knife blade. The peritonsillar plane is located and the tonsil is then dissected toward the inferior pole by blunt dissection. The inferior pole is snared and ligated. The tonsil specimen is removed, and the fossa is packed with gauze and then removed. Bipolar cautery is used to secure hemostasis.

3.6.2 Vessel Sealing System Tonsillectomy (VSST)

- Vessel sealing system tonsillectomy (VSST) is a new technique for tonsillectomy. Vessel sealing system (VSS) is a new bipolar vascular sealing system, with integrated active feedback control. The tissue is grasped and compressed by the handpiece. After the instrument is removed, the seal is visible as a semitransparent window, which can safely be divided.
- Tonsil is grasped with an Allis clamp and retracted toward the midline. Dissection of the tonsil toward the inferior pole is performed by the VSS handpiece. The inferior pole is coagulated, and the tonsil specimen is removed. VSS is also used for hemostasis.

3.6.3 Operative time

- Operative time (minutes) is the duration of tonsillectomy operation on one side of tonsil starting at the time of incision and at the time of complete hemostasis.

3.6.4 Intraoperative Blood Loss

- Amount of intraoperative blood loss is measured from amount of fluid including blood and saliva (milliliters) in the container and gauze. Wet gauze containing blood will be measured by increased weight and calculated to be milliliters of blood.

3.6.5 Postoperative Pain

- Postoperative pain is patient's feeling of pain or discomfort at the surgical area of tonsillectomy, measured by Faces Pain Scale–Revised. It does not include pain or discomfort on other areas e.g. headache.

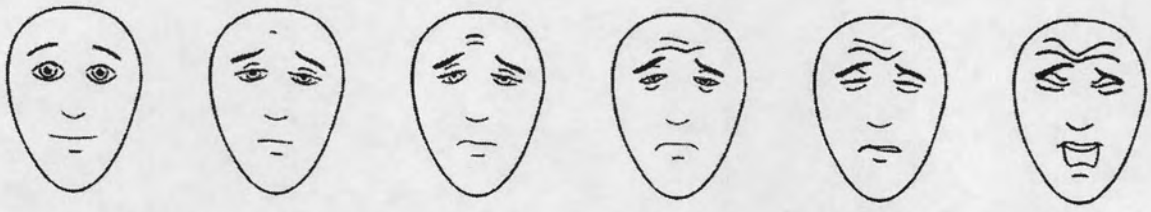
3.6.5.1 Faces Pain Scale – Revised (FPS-R) (English Version) (Fig 2)

- In the following instructions, say "hurt" or "pain," whichever seems right for a particular child.
- "These faces show how much something can hurt. This face [point to left-most face] shows no pain. The faces show more and more pain [point to each from left to right] up to this one [point to right-most face] – it shows very much pain. Point to the face that shows how much you hurt [right now]."
- Score the chosen face 0, 2, 4, 6, 8, or 10, counting left to right, so '0' = 'no pain' and '10' = 'very much pain.' Do not use words like 'happy' and 'sad'. This scale is intended to measure how children feel inside, not how their face looks.

3.6.5.2 Faces Pain Scale – Revised (FPS-R) (Thai Version) (Fig 2)

- ในคำชี้แจงต่อไปนี้ ให้ใช้คำว่า "เจ็บ" หรือ "ปวด" ตามความเหมาะสมแก่ผู้ป่วยเด็กแต่ละคน
- "รูปหน้าต่อไปนี้จะแสดงให้เห็นว่ามีความปวดมากเท่าไร รูปหน้านี้ (ซ้ายสุด) แสดงว่าไม่ปวดเลย รูปหน้าถัดมาแสดงว่าปวดมากขึ้น มากขึ้น (ชี้รูปหน้าจากซ้ายมาขวา) จนถึงรูปหน้านี้ (ชี้รูปขวาสุด) แสดงว่าปวดมากๆ ให้หนูชี้รูปหน้าที่แสดงว่าหนูปวดมากแค่ไหน (ตอนนี้)"
- ให้คะแนนตามรูปหน้าที่เลือก 0,2,4,6,8,10 ตามลำดับจากซ้ายไปขวา คะแนน 0 = ไม่ปวดเลย คะแนน 10 = ปวดมากๆ ไม่ควรใช้คำว่า "สุข" หรือ "เศร้า" การให้คะแนนนี้มีจุดประสงค์เพื่อวัดว่าผู้ป่วยเด็กมีความปวดมากแค่ไหน ไม่ใช่การให้คะแนนจากการดูลักษณะสีหน้าของเด็ก

Translation credit: Wimonrat Krisanaprakornkit & Duenpen Horatanaruang, Department of Anesthesiology, Srinagarind Hospital, Khon Kaen University, Khon Kaen, Thailand



0 2 4 6 8 10

Figure 2: Faces Pain Scale – Revised (FPS-R)

3.6.6 Postoperative Bleeding

- Postoperative bleeding or hemorrhage is bleeding from the surgical area of tonsillectomy occurring after the procedure was completely done. It may be immediate (within 24 hours) or delayed (after 24 hours until completely healed wound) bleeding.

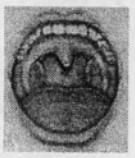
3.6.7 Postoperative Adverse Effects

- Postoperative adverse effects are undesirable reactions possibly related to the intervention. It may be immediate (within 24 hours) or delayed (after 24 hours until completely healed wound).

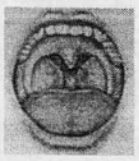
3.6.8 Tonsil Size

- Tonsil size is graded by standard classifications into 5 grades: grade 0, 1, 2, 3, and 4. If the difference is equal or more than 2, it will be defined as much different in size. (Fig 3)

Tonsil size grade 0



Tonsil size grade 1



Tonsil size grade 3

Tonsil size grade 2

Tonsil size grade 4

Figure 3: Tonsil size classification

3.7 RESEARCH DESIGN

Randomized, paired-control study (Fig 4)

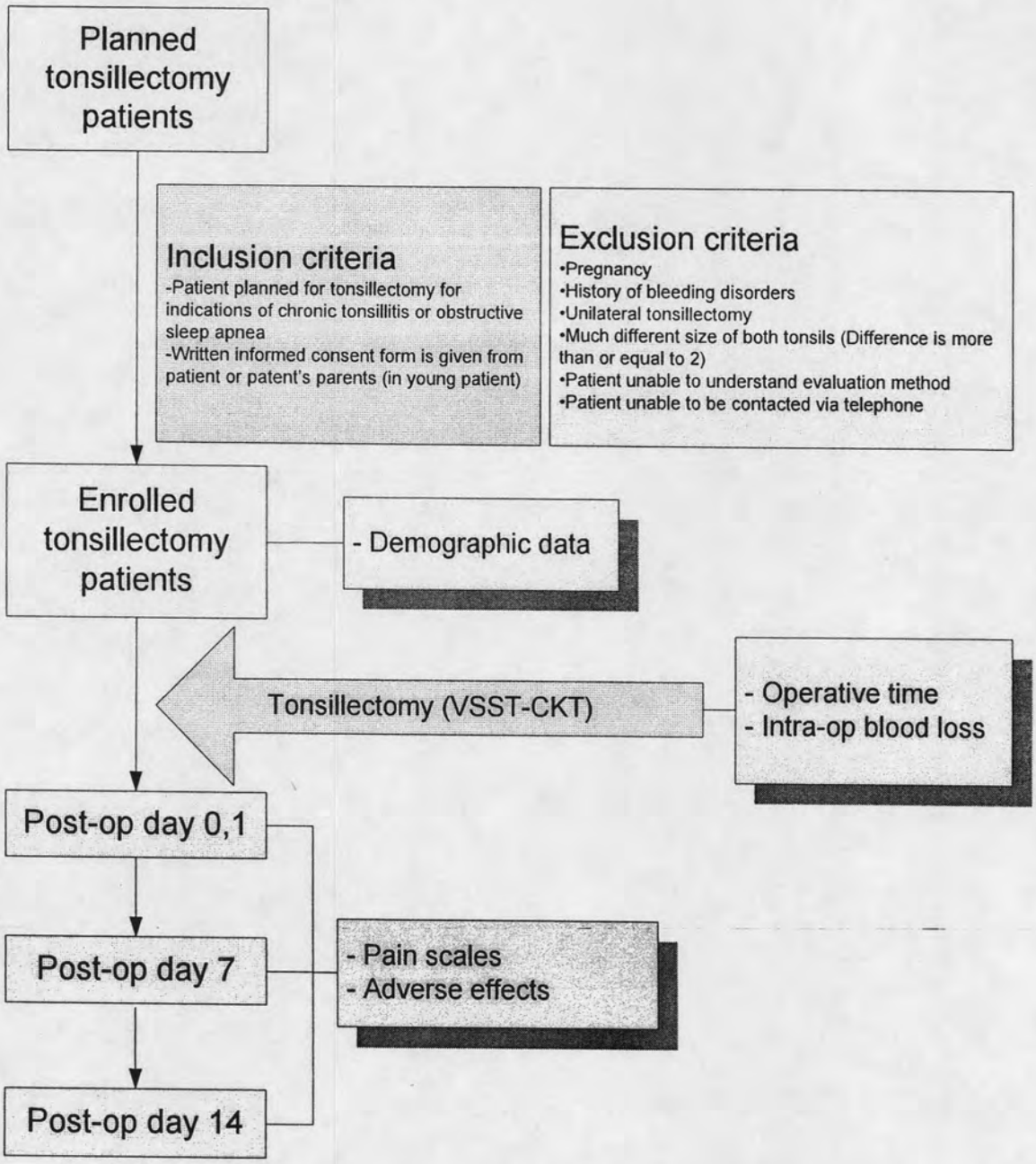


Figure 4: Flow chart of research administration

3.8 RESEARCH METHODOLOGY

3.8.1 Population and Sample

3.8.1.1 Target Population

Patients planned for tonsillectomy

3.8.1.2 Sample Population

Patients planned for tonsillectomy at department of Otolaryngology, King Chulalongkorn Memorial Hospital who are in eligible criteria.

3.8.1.3 Evaluation before enrollment

- The patient was informed about the details of the study protocol by principle investigator and the 1st research assistant.
- The patient was interviewed and examined for baseline demographic data and enrollment criteria.
- The patient was counseled how to assess "postoperative pain by Faces Pain Scale–Revised" & "Adverse Effects" and to follow the protocol correctly.

3.8.2 Inclusion Criteria

- Patient planned for tonsillectomy for indications of chronic tonsillitis or obstructive sleep apnea
- Written informed consent (or assent) form is given from patient or patient's parents (in case of pediatric patient)

3.8.3 Exclusion Criteria

- Pregnancy
- History of bleeding disorders
- Unilateral tonsillectomy
- Much different size of both tonsils (If the difference is more than or equal to 2, it will be defined as much different in size in this study)
- Patient unable to understand evaluation method
- Patient unable to be contacted via telephone

3.8.4 Sample size calculation

- Sample size calculation is based on the difference of intraoperative blood loss between paired groups. The equation for sample size estimation is

  n/group = $[(Z_{\alpha/2}+Z_{1-\beta})^2 * \sigma^2] / \delta^2$

  α = 0.05 (Two-tailed)

  $1-\beta$ = 0.90

  $Z_{\alpha/2}$ = 1.96

  $Z_{1-\beta}$ = 1.28

  δ = 20 milliliters

  σ^2 (variance of the within pair diff) from pilot study = 20^2

  n/group = 10.5

- Sample size calculation is based on the difference of operative time between paired groups. The equation for sample size estimation is

  n/group = $[(Z_{\alpha/2}+Z_{1-\beta})^2 * \sigma^2] / \delta^2$

  α = 0.05 (Two-tailed)

  $1-\beta$ = 0.90

  $Z_{\alpha/2}$ = 1.96

  $Z_{1-\beta}$ = 1.28

  δ = 5 minutes

  σ^2 (variance of the within pair diff) from pilot study = 6^2

  n/group = 15.1

- Sample size calculation is based on the proportion of unequal pain scores from CKT side and VSST side. "nQuery Advisor" version 6.01 is used. (Fig 5)

  α = 0.05 (Two-tailed)

  $1-\beta$ = 0.90

  Subjects in the pilot study were able to feel the difference of pain from each side of tonsillectomy and gave the pain scale for each side.

  Proportion of unequal pain scores on postoperative day 0-7 from pilot study = 0.8 – 0.9

  n/group = 13

- Sample size of 20 subjects will be used for this study.

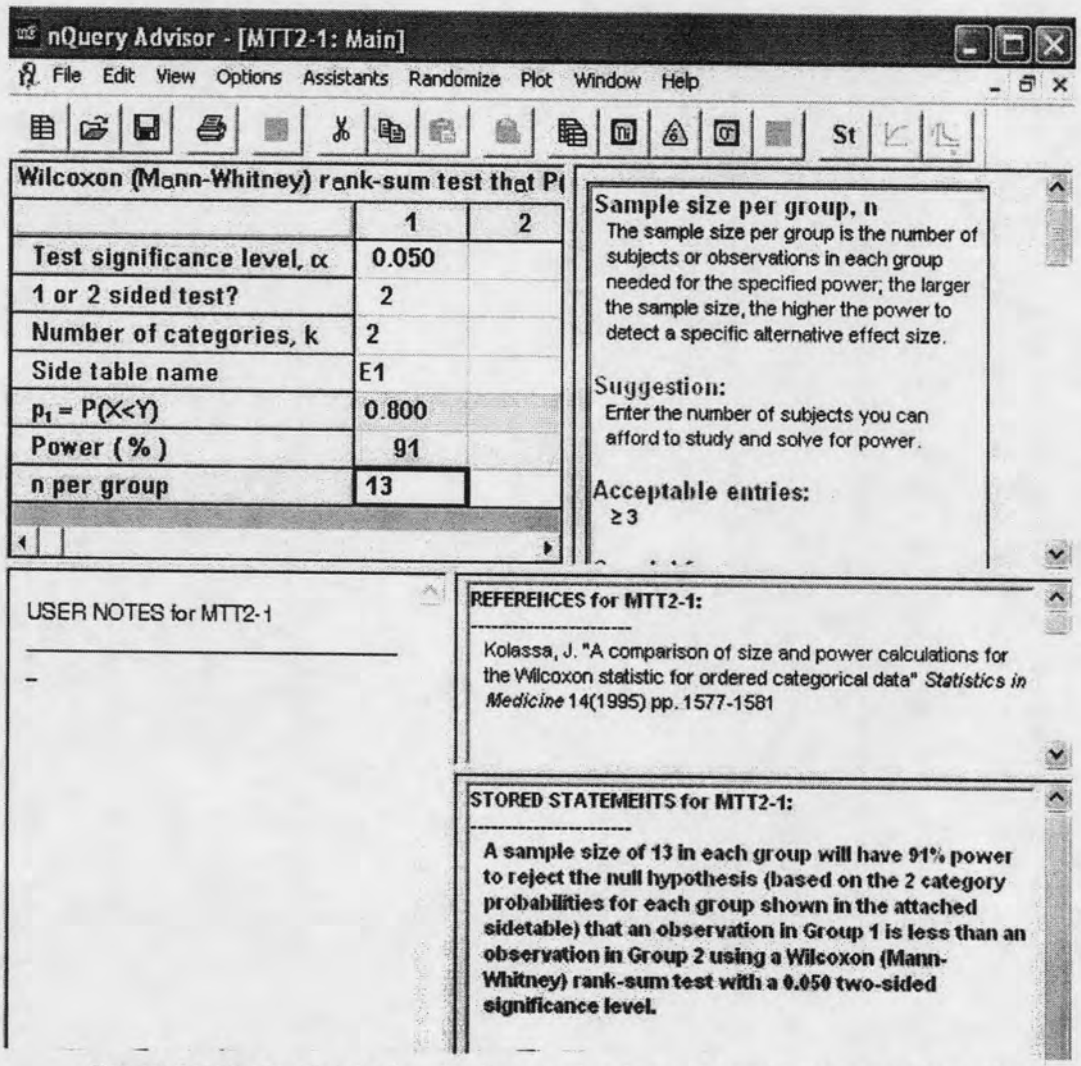


Figure 5: Sample size calculation based on the proportion of unequal pain scores from CKT side and VSST side

using "nQuery Advisor" version 6.01

3.8.5 Randomization and allocation concealment

- Patients planned for tonsillectomy will be enrolled consecutively. Randomization will be performed by mixed block randomization. Intervention by vessel sealing system tonsillectomy will be randomized to "Right or Left" side. VSST will be performed first, and then CKT will be done on the other side. (Fig 6)
  - VSST – Right → CKT – Left
  - VSST – Left → CKT – Right
- The sequence of VSST followed by CKT was aimed to prevent contamination of primary outcome from re-bleeding because the possibility of re-bleeding from VSST is very rare from the investigator's experience.
- Because there will be one surgeon (the principal investigator) involving in the study. One randomization sequence will be generated.
- The allocation will be concealed and blinded to physician, patients and personnel involved in the study.
- The allocation concealment will be used by sequentially numbered opaque sealed envelopes with an enclosed card containing the assignment and the signature of the person preparing the sequence over envelope seals.

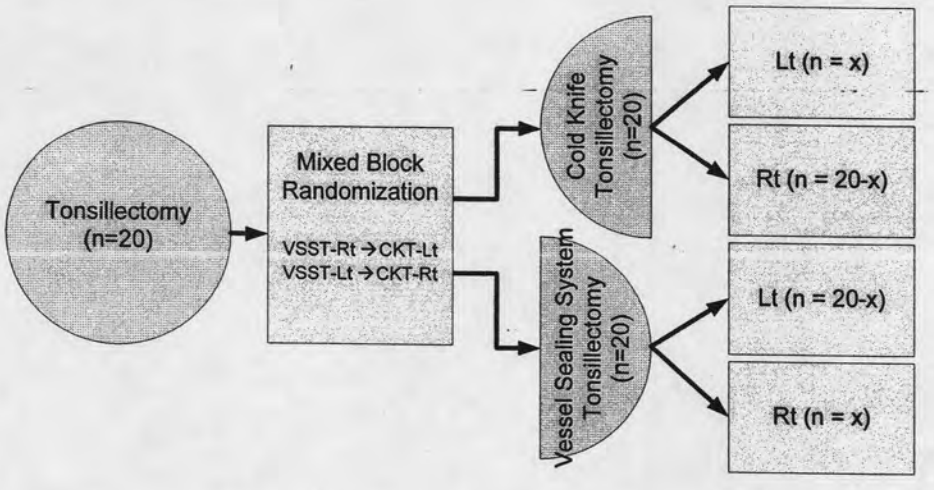


Figure 6: Flow chart of randomized allocation

3.8.6 Surgical procedures and perioperative care

3.8.6.1 Preoperative Care:

- Every patient will be admitted in the hospital.
- Every patient will be interviewed, examined and assessed by ENT residents and anesthesiology residents for perioperative care.
- Every patient will be informed again about the details of the study protocol by principle investigator and the 1st research assistant.
- The patients will be counseled by the 2nd research assistant how to assess "postoperative pain by Faces Pain Scale–Revised" & "Adverse Effects" and how to follow the protocol correctly.
- After written informed consent (or assent) is given, the patient will be enrolled in the study.
- Every patient who gives written informed consent (or assent) will be interviewed and examined again for baseline demographic data and enrollment criteria.
- The 1st research assistant will assign the subject's number, prepare this subject's folder, fill data in the baseline and screening sheet of case report form, get the consecutively assigned concealed randomization envelop and bring it to the operating theater on the surgery day.
- The 1st research assistant will contact operating room nurses for equipment preparation.
- General anesthesia will be done in every case.
- Routine mouth care and normal saline will be used for gargling in the mouth.
- NPO after midnight
- IV fluid will be given to the patient using IV catheter by anesthesiologist team or ward nurses.

3.8.6.2 Intraoperative Care:

- General anesthesia is started and maintained by anesthesiologist.

- Amoxicillin 1 g (or 20 mg/kg) IV or Clindamycin 600 mg (or 10 mg/kg) IV in case of penicillin allergy.
- No antibiotic in case of allergy to both antibiotics.
- Dexamethasone 10 mg (or 0.2 mg/kg) IV
- After GA is started, the assigned randomization envelop will be disclosed to the ENT surgeon (the principal investigator) by the 1st research assistant.
- The used envelop will be destroyed.
- Tonsillectomy procedure will be done by one senior ENT surgeon (the principal investigator) wearing fiberoptic headlight.
- The patient will be in supine position with extension of head and neck (Boyce's position) which is the standard position for tonsillectomy procedure.
- ENT surgeon in sterile dressing and sterile surgical gloves will drape sterile sheets covering on patient's body as the standard of care for surgical procedure.
- Surgical equipment will be set up completely before starting the tonsillectomy procedure.
- Mc Ivor's mouth retractor will be applied to keep mouth open widely enough to get good exposure view for tonsillectomy.
- Gauze will be packed into hypopharynx to prevent fluid including blood or saliva to get down into esophagus or trachea and then normal saline will be used for mouth cleaning before starting the tonsillectomy procedure.
- Then a container for measurement will be installed with suction tube in order to collect fluid including blood and saliva from each tonsillectomy site separately.
- 4x4 gauze will be counted and weighted before and after each tonsillectomy site separately.
- VSST will be done on one side of tonsil as stated in the assigned randomization envelop (Left or Right). The other side will be done by CKT.
- If any problems during each tonsillectomy occur such as hardware problem, the other technique will be replaced. Intention-to-treat basis will be used for data analysis.

- After VSST on the first side is finished, 5-10 minutes are the lag time before CKT will be started in order to observe re-bleeding after operative time is recorded.
- If there is re-bleeding, the operative time will be changed and measured from the same starting time to the time of last complete hemostasis.

3.8.6.3 Postoperative Care:

- Patient will be observed in recovery room until stable, then moved to hospital ward for at least one more night stay.
- Every patient will be reminded about the standard postoperative care including
    - Bed rest for 1 day
    - Voice rest for 1 week
    - Avoid trauma to the throat: coughing, throat clearing, phlegm spitting
    - Cold liquid diet for 3 days then soft diet until postoperative day 7
    - Routine mouth care and normal saline gargled in the mouth after meal
    - Tooth brushing is recommended if possible.
- Antibiotics:
    - Amoxicillin 40 mg/kg/day, twice a day (Erythromycin 30 mg/kg/day, four times a day in case of penicillin allergy), starting with liquid form until capsule or tablet can be taken for 7 days.
    - Other antibiotics may be prescribed if needed but their indications have to be stated in the patient's case report form.
- Analgesics:
    - Paracetamol 500 mg (10 mg/kg/dose), four times a day (not prn), starting with liquid form until tablet can be taken for 7 days.
    - Other pain relieving drugs may be prescribed if needed but their indications have to be stated in the patient's case report form.
- Other medications may be prescribed if needed but their indications have to be stated in the patient's case report form.
- AT hospital ward
    - ENT surgeon (the principal investigator) , investigators and residents will visit and examine the patient as standard postoperative care.

- On postoperative day 0 (surgery day):
    - After the patient fully recovers from anesthesia, the 2nd research assistant will ask the patient about throat pain ratings on each side using Faces Pain Scale – Revised (FPS-R), and whether there is any bleeding or other postoperative adverse effects.
    - Data will be entered into a "Faces Pain Scale – Revised (FPS-R)" and "Adverse Effects" report form.
- On postoperative day 1:
    - The 2nd research assistant will ask the patient about throat pain ratings on each side using Faces Pain Scale – Revised (FPS-R), and whether there is any bleeding or other postoperative adverse effects.
    - Data will be entered into a "Faces Pain Scale – Revised (FPS-R)" and "Adverse Effects" report form.
    - If no other problems occur, most patients will be discharged from the hospital on postoperative day 1.
    - If otherwise, the patient will get appropriate care and that have to be stated in the patient's case report form.

- After discharge from the hospital, every patient will be appointed for follow-up at ENT research clinic at postoperative day 7 and day 14 (or approximately in case of inconvenience)
- At home following surgery, patients or their care givers will be contacted daily until postoperative day14 via telephone by the 2nd research assistant for data collection. Information will be gathered regarding throat pain ratings on each side, and whether there is any postoperative bleeding or other adverse effects. Data will be entered into a "Faces Pain Scale – Revised (FPS-R)" and "Adverse Effects" report form.
- At ENT research clinic:
    - On postoperative day 7:
        - The masked physician will give proper postoperative care.

- If no other problems occur, most patients will get one more week of antibiotic and analgesia as prn.
- Other medications may be prescribed if needed but their indications have to be stated in the patient's case report form.
- If otherwise, the patient will get appropriate care and that have to be stated in the patient's case report form.

- On postoperative day 14:
  - The masked physician will give proper postoperative care.
  - If no other problems occur, most patients will not get any more medication.
  - Other medications may be prescribed if needed but their indications have to be stated in the patient's case report form.
  - If otherwise, the patient will get appropriate care and that have to be stated in the patient's case report form.
- If any serious postoperative adverse effects occur, principle investigators should be informed promptly and then Ethics Committee is informed.

3.8.7 Data management

3.8.7.1 Type of Collected Data

3.8.7.1.1 Baseline (demographic) Variables

- Sex
- Age
- Concomitant operation
- Tonsil size

3.8.7.1.2 Primary Outcome Variables

- Operative time (minutes) will be started at the time of incision and ended at the time of complete hemostasis. After VSST on the first side is finished, 5-10 minutes are the lag time before CKT will be started in order to observe re-bleeding after operative time is recorded. If there is re-bleeding, the operative

time will be changed and measured from the same starting time to the time of last complete hemostasis.

- Amount of blood loss (milliliters) will be measured from amount of fluid including blood and saliva in the container and gauze. Measurement will be started at the time of incision and ended at the time of complete hemostasis in the same manner of operative time.
- Pain score from "Faces Pain Scale – Revised (FPS-R)" report form that the 2nd research assistant will record on post-op day 0-14 by using direct and telephone interview.

3.8.7.1.3 Secondary Outcome Variables

- Postoperative bleeding and other adverse effects from "Adverse Effects" report form that the 2nd research assistant will record on post-op day 0-14 by using direct and telephone interview.

3.8.7.2 Timing of Data Collection

3.8.7.2.1 During Treatment

- Amount of blood loss will be measured from amount of fluid in the container and gauze.
- Operative time will be started at the time of incision and ended at the time of complete hemostasis.

3.8.7.2.2 After Treatment

- The 2nd research assistant will ask the patient about throat pain ratings on each side using Faces Pain Scale – Revised (FPS-R), and whether there is any postoperative bleeding or other adverse effects from post-op day 0-14.

3.8.7.3 Data Collectors

- Two research assistants will be trained in one day about the content & design of the study and how to counsel the patients to follow the protocol.
- The 1st research assistant will counsel the patients who are willing to join the project.

- The 1st research assistant will assign the subject's number, prepare this subject's folder, fill data in the baseline and screening sheet of case report form, get the consecutively assigned concealed randomization envelop and bring it to the operating theater on the surgery day.
- The 1st research assistant will contact operating room nurses for equipment preparation.
- The 1st research assistant will observe, fill and complete the data in a case report form during operation. The complete CRF will be concealed and blinded to physician, patient or other personnel.
- The 2nd research assistant will instruct the patients how to assess "Faces Pain Scale – Revised (FPS-R)" and "postoperative adverse effects"
- The 2nd research assistant, who is blinded to the side of intervention, will interview the patients directly at hospital ward on post-op day 0-1 and by daily telephone call from post-op day 2-14 for "Faces Pain Scale – Revised (FPS-R)" and "Adverse Effects" outcome.

3.8.7.4 Data Collection Procedure

- The tools for data collection during treatment are the following.
    - Containers for measurement of fluid from each tonsillectomy site.
    - A weighing scale for measurement of increased weight in used gauze from each tonsillectomy site.
    - A clock for measurement of operative time.
    - A case report form (CRF) designed to obtain relevant data of intraoperative blood loss and operative time for each unilateral tonsillectomy (appendix.3).
    - A case report form (CRF) designed to obtain relevant data of postoperative throat pain ratings on each side using Faces Pain Scale – Revised (FPS-R) (appendix.5).
    - A case report form (CRF) designed to obtain relevant data of postoperative bleeding or other adverse effects on each side using "Adverse Effects" report form (appendix.4).

- The 1st research assistant will observe, fill and complete the data in a case report form during operation. The complete CRF will be concealed and blinded to physician, patient or other personnel.
- The tonsillectomy procedures (CKT, VSST) will be performed at an ENT operating room of King Chulalongkorn Memorial hospital.
- "Faces Pain Scale – Revised (FPS-R)" report form will be filled by the 2nd research assistant who will interview the patients directly at hospital ward on post-op day 0-1 and by daily telephone call from post-op day 2-14.
- "Adverse Effects" report form will be filled by the 2nd research assistant who will interview the patients directly at hospital ward on post-op day 0-1 and by daily telephone call from post-op day 2-14.

3.8.7.5 Data Editing/Coding

3.8.7.5.1 For baseline (demographic) data

- Sex: Male = 0, Female = 1
- Age: Date of birth in dd/mmm/yy format
- Concomitant operation: No = 0, Yes (specified) = 1
- Tonsil size:
    - Left side: 0, 1+, 2+, 3+ or 4+
    - Right side: 0, 1+, 2+, 3+ or 4+
- Missing items will be reported in percentage, with no substitution value.

3.8.7.5.2 For primary outcome data

- Day of operation in dd/mmm/yy format
- Surgeon initial
- Randomization result:
    - Left side: VSST or CKT
    - Right side: VSST or CKT
- Performed intervention:
    - Left side: VSST or CKT
    - Right side: VSST or CKT

- Intention-to-treat basis will be use if needed.

- Amount of blood loss (milliliters):
  - Left side: Amount of fluid including blood and saliva in the container and gauze from left tonsillectomy procedure
  - Right side: Amount of fluid including blood and saliva in the container and gauze from right tonsillectomy procedure
- Starting time:
  - Left side: Time in hh/mm format
  - Right side: Time in hh/mm format
- Ending time (1^{st}):
  - Left side: Time in hh/mm format
  - Right side: Time in hh/mm format
- Ending time (2^{nd};in case of re-bleeding):
  - Left side: Time in hh/mm format
  - Right side: Time in hh/mm format
- Operative time (minutes):
  - Left side: Time in minutes
  - Right side: Time in minutes
- Primary outcomes of amount of blood loss (milliliters) and operative time (minutes) are rare to be missed because they will be obtained at the time of surgery. The missing data will be substituted with mean of the group if needed.
- There will be some exceptions e.g. the tonsillectomy operation is cancelled by any reasons or the patient wants to withdraw from the study after enrollment. In these settings, the missing data will not be substituted and reported descriptively in "n and percentages".
- For Faces Pain Scale – Revised (FPS-R)
  - For each side of tonsillectomy (Left and Right)
  - For postoperative day 0-14
  - 0, 2, 4, 6, 8, or 10; '0' = 'no pain' and '10' = 'very much pain.'
  - Missing items may be substituted with the L.O.C.F (Last Observation Carried Forward) method if needed.

3.8.7.5.3 For secondary outcome data

- For postoperative bleeding
    - For each side of tonsillectomy (Left and Right)
    - For postoperative day 0-14
    - 0 = None or no need for hemostasis by physician, 1 = Need for hemostasis by physician
    - Missing items may be substituted with the L.O.C.F (Last Observation Carried Forward) method if needed.
- For other postoperative adverse effects
    - For each side of tonsillectomy (Left and Right)
    - For postoperative day 0-14
    - 0 = None, 1 = Yes (specified)
    - Missing items may be substituted with the L.O.C.F (Last Observation Carried Forward) method if needed.

3.8.7.6 Data Entry

- Case report forms for baseline (appendix.1), screening (appendix.2) and operative time & amount of blood loss (appendix.3) will be collected by the 1st research assistant.
- Case report forms for "Adverse Effects" (appendix.4) and "Faces Pain Scale – Revised (FPS-R)" (appendix.5) will be collected by the 2nd research assistant.
- Data from responded case report forms will be transferred into a SPSS file.

3.8.7.7 Data Exploration

- Data exploration and data cleaning process will be done before data analysis.

3.8.7.8 Data Analysis

- Data will be analyzed with SPSS version16 software for descriptive statistics, paired t-test, Wilcoxon signed-rank test.
- Intention-to-treat basis will be used if needed.

3.8.7.8.1 Demographic Data Analysis

- Demographic data will be presented descriptively. (Table 1)

- Sex will be presented as "n and percentages".
- Age will be presented as "mean +/- standard deviation" or "median (IQR)".
- Concomitant operation will be presented as "n and percentages".
- Tonsil size in each group will be presented as "n and percentages".
- Side of tonsillectomy in each group will be presented as "n and percentages".

3.8.7.8.2 Primary Outcome Analysis

- Intraoperative blood loss (IBL) and operative time (OT) of the same technique (from both sides) will be summed and presented as "mean +/- standard deviation".
- Difference of intraoperative blood loss (IBL) and difference of operative time (OT) between both techniques (CKT – VSST) will be presented as "mean +/- standard deviation".
- Paired t-test of difference of intraoperative blood loss (IBL) between both techniques (CKT – VSST) will be done if the paired differences are all identically normally distributed (assumptions of paired t-test are not violated). 95% confidence interval and p-value will be presented. (Table 3)
    - If the assumptions of paired t-test are violated.
        - Intraoperative blood loss (IBL) of the same technique (from both sides) will be summed and presented as "median (IQR)".
        - Difference of intraoperative blood loss (IBL) between both techniques (CKT – VSST) will be presented as "median (IQR)".
        - Non-parametric test (Wilcoxon signed-rank test) of difference of intraoperative blood loss (IBL) between both techniques (CKT – VSST) will be used for analysis. P-value will be presented. (Table 2)
- Paired t-test of difference of operative time (OT) between both techniques (CKT – VSST) will be done if the paired differences are all identically normally distributed (assumptions of paired t-test are not violated). 95% confidence interval and p-value will be presented. (Table 3)
    - If the assumptions of paired t-test are violated.

- Operative time (OT) of the same technique (from both sides) will be summed and presented as "median (IQR)".
- Difference of operative time (OT) between both techniques (CKT – VSST) will be presented as "median (IQR)".
- Non-parametric test (Wilcoxon signed-rank test) of difference of operative time (OT) between both techniques (CKT – VSST) will be used for analysis. P-value will be presented. (Table 2)

- Faces Pain Scale – Revised (FPS-R) of the same technique (from both sides) will be summed and presented as "median of each day (postoperative day 0-14)".
- Non-parametric test (Wilcoxon signed-rank test) and generalized estimating equation (GEE) will be used for analysis of "Faces Pain Scale – Revised (FPS-R)". P-value will be presented. (Table 4, 5)

3.8.7.8.3 Secondary Outcome Analysis

- Postoperative adverse effects will be presented as "n and percentages" in terms of "postoperative bleeding" or "other postoperative adverse effects" on "immediate period (within 24 hr)" or "delayed period (after 24 hr)". (Table 6)

3.8.8 Contamination & co-intervention

- Contamination may happen in case of hardware problems e.g. unavailable sterile instruments, malfunction of vessel sealing system machine. Standard CKT will be used instead of VSST and intention-to-treat will be used for analysis in this setting.
- Intraoperative blood loss (IBL) and operative time (OT) will be obtained at the time of intervention. If co-intervention (e.g. concomitant medications) occurs, it will affect both sides of tonsillectomy equally.
- Consistent, standardized protocol of preoperative, intraoperative and postoperative care including every medication will be used to minimize co-intervention.
- Other medications (e.g. analgesia) or procedures (e.g. hemostasis) that the patients may receive will be recorded in "Adverse Effects" report form.

- Every effort will be used to make the patients understand the protocol and the patients will get needed information and help promptly

3.8.9 Compliance

- Intraoperative blood loss (IBL) and operative time (OT) will be obtained at the time of intervention, so compliance is good
- Good F/U (telephone and visit) is needed for 14 days.
- Evaluations of "Faces Pain Scale – Revised (FPS-R)" and "Adverse Effects" need patients' co-operation & understanding, so every effort will be used to make the patients understand and follow the protocol correctly and the patients will get needed information or help promptly.
- The 2nd research assistant will call every patient to gather data and fill in "Faces Pain Scale – Revised (FPS-R)" & "Adverse Effects" report form.

3.8.10 Expected benefits

- The information of efficacy and adverse effects of vessel sealing system tonsillectomy from this study may provide information to choose better choice for tonsillectomy in order to reduce operative time, intraoperative blood loss, postoperative pain, postoperative bleeding and adverse effects.

3.8.11 Limitations

- Amount of blood loss is defined by amount of fluid in milliliters including blood and saliva measured from container and gauze. The saliva in the fluid is too difficult to be separated from blood. In this study, amount of total fluid collected from each tonsillectomy is assumed to be amount of blood loss.
- Operative time of either technique may be skewed by the biased surgeon. The surgeon involving in the study (the principal investigator) has to understand the protocol and try to perform both techniques without bias.
- Operative time of bilateral CKT will be less than 2 times of unilateral CKT duration. During packing for homeostasis on one side of tonsil, ENT surgeons usually do the other side CKT until the second tonsil is removed, then go back to stop bleeding on the first side.

- Postoperative pain is the subjective symptom and the outcome measurement is the Faces Pain Scale – Revised (FPS-R), so the patients may feel uncertain to evaluate. Missing data in Faces Pain Scale – Revised (FPS-R) might be similar in both sides because that data will be obtained at the same time. Therefore, overall pain scores from both sides are comparable.
- Vessel sealing system tonsillectomy is a new technique, and there is always a learning curve in all new techniques, whereas cold knife tonsillectomy, as described previously, has been the gold standard technique in our department for the last 15 years. Undeniably, our senior surgeon (the principal investigator) is at least as practiced and familiar with cold knife tonsillectomy.
- Dropout rate from loss of follow up may occur.

3.8.12 Ethical considerations

- The research was approved Ethics Committee of Faculty of Medicine, Chulalongkorn University.
- The research was conducted and followed the guidelines from the Declaration of Helsinki
- The information about the details of the interventions, potential postoperative adverse effects and its treatment will be explained to the patients or patient's parents (in young patients) before signing the consent (or assent) forms.
- The patients have right to decide to withdraw from the protocol at any time without interfering their medical care.
- Vessel sealing system was registered and approved by US F.D.A. The VSS equipment in this study conforms to IEC (International Electrotechnical Commission) standard for RF electrosurgical generator: IEC 60601-1 both general and particular standards.
- Patients will get an appropriate standard care if there are any complications during the study.
- The research assistants and investigator will keep the confidentiality on the patients' information.

3.8.13 Disclosure

- A grant for conducting the trial was supported by Ratchadapiseksompotch research fund, Faculty of Medicine, Chulalongkorn University.