

The Safety and Efficacy of Propranolol as an Initial Treatment for Infantile Hemangioma: A Randomized Controlled Trial

Protocol outline

Title	The Safety and Efficacy of Propranolol as an Initial Treatment for Infantile Hemangioma: A Randomized Controlled Trial
Purpose	The purpose of this study is to determine the efficacy and safety of propranolol compared to steroid as an initial treatment for infantile hemangioma through randomized controlled clinical trials.
Research Institution	Department of Plastic and Reconstructive Surgery, Seoul National University Hospital
Principal Investigator	Tae Hyun Choi
Subjects	Patients diagnosed with hemangioma in the department of pediatric dermatology and plastic surgery at Seoul National University Children's Hospital who consent to the study.
Research Duration	3 years after Institutional Review Board (IRB) approval
Methods	<ul style="list-style-type: none"> • We will recruit 34 patients with infantile hemangioma • Patients will be randomly assigned to either the control group (steroid group) or the test group (propranolol group) • Baseline inspection will be examined before treatment and subjects will be limited to hemangioma patients who have never been treated and who have a normal heart function. • In the propranolol group, the patients will be admitted and checked for side effects for three days. The effect of treatment of hemangioma will be observed in outpatients • The effect of treatment of hemangioma in steroid group will be observed in outpatients. • While comparing the effect of medication between the two groups, we will monitor the side effects of both drugs.
Estimated Results and Expected Effect	Evidence of using propranolol as the first-line treatment in infantile hemangioma can be suggested.

Contents

1. Title -----	4
2. Research Institution and Address -----	4
3. Principal Investigator and Researchers -----	5
4. Background and Purpose -----	7
5. Target Disease and Subjects -----	8
6. Expected Duration of the Study and Schedules-----	9
7. Eligibility Criteria -----	10
8. Sample Size Determination -----	12
9. Schedule of the Study -----	14
10. Overall Study Design -----	15
11. Trial Design -----	16
Modeling Clinical trial (randomization) -----	16
Baseline Inspection of Participants -----	18
Experimental Group (Propranolol) -----	19
Control Group (Steroid) -----	21
Progress Observations -----	22
Assessment -----	23
Statistical Analysis -----	26
Study discontinuation -----	30
Monitoring and Audit -----	31

Data Management	32
Management of medical supplies	33
12. Counterplan for protecting safety of participants	34
13. Agreement for Compensation	35
14. References	36
15. Principal Investigator	38
16. Informed Consent Form and Participant Information Sheet	42

1. Title

The Safety and Efficacy of Propranolol as an Initial Treatment for Infantile Hemangioma: A Randomized Controlled Trial

2. Research Institution and Address

Research Institute	Department of Plastic and Reconstructive Surgery, Seoul National University Hospital
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4. Background and Purpose

- Hemangioma is a tumor of endothelial cells caused by abnormal proliferation and angiogenesis. This benign tumor is the most common tumor of infants and early children. Although hemangioma small in size do not typically cause problems, it may cause serious problems such as covering eyes, airway obstruction, and digestive diseases.
- Hemangioma often requires treatment due to the occurrence site or associated complications. Historically, steroid is used as the primary treatment for hemangioma, and can be taken as an oral medication or injected to the lesion. However, the use of steroid may lead to various complications, including facial edema, insomnia, nervous reactions, gastroesophageal reflux, acne generation, hirsutism and growth failure. A type of anticancer agent, interferon-alpha, can be used for severe hemangioma in the case where patients do not respond to steroids. However, this anticancer agent also has several possible side effects. Interferon-alpha may cause fever and general weakness, and in severe cases, may cause liver damage, blood toxicity, thyroid hormonal abnormality, as well as neurological and neurodevelopmental toxicity. Thus, many guardians of children patients preferred to wait rather than accept treatment due to concerns over its side effects.
- A study published in 2008 reports that an infant patient with hemangioma showed signs of improvement after taking the hypertension medication propranolol. Subsequently, many centers have conducted small, fragmented clinical trials. For most of the studies, the proliferation of hemangioma stopped within 48 hours for 74% of patients, and within 2 weeks for 97% of patients. This shows better results compared to steroid treatment.
- Many of the trials studying the effect of propranolol are fragmented, one-off case studies that are insufficient to fully comprehend the efficacy and safety of propranolol. This study aims to compare the efficacy and safety of propranolol compared to the standard treatment steroid using a randomized controlled trial.

5. Target disease and Subjects

The target disease is hemangioma, and patients diagnosed with hemangioma in the department of pediatric dermatology and plastic surgery at Seoul National University Children's Hospital are subjects. Only patients who voluntarily consent to participate in the study after the study has been fully explained are subjects of the research.

Volunteer recruitment posters will be released in the hospital and patients who volunteer to participate after fully understanding the study are targets.

Before explaining the study and receiving consent, we will explain to the patient or guardian that magnetic resonance imaging (MRI) scan will be used to measure hemangioma volume. In the case where the guardian of a patient refuses the use of MRI, we will then offer ultrasound examination as an alternative choice and receive consent.

6. Expected Duration of the Study and Schedules

Research Duration: 3 years after IRB approval

- After clinical trial registration, a research proposal will be submitted to the Food and Drug Administration (FDA).

7. Eligibility Criteria

Patients diagnosed with hemangioma in the department of pediatric dermatology and plastic surgery at Seoul National University Children's Hospital whose guardians voluntarily consent to participate the study after they have been fully explained as well as patients who chose to participate in the study voluntarily after fully reading volunteer recruitment posters are targets. Information about participants is collected to confirm inclusion and exclusion criteria.

Inclusion Criteria

- Hemangioma patient (0-9 months old)
- No prior treatment
- 10-20% volume increase in 2-4 weeks
- Hemangioma that caused organ function
- Hemangioma that will cause an aesthetic problem

(First and second conditions must be met, and at least one of the last 3 conditions must be met)

Exclusion Criteria

- Cardiovascular disease (impossible to use propranolol)
- Drug adverse reaction or allergy history (propranolol, steroid)
- Bradycardia, atrioventricular block, atrial block
- Cardiogenic shock
- Right heart failure (pulmonary hypertension)
- Congestive heart failure
- Hypotension
- Peripheral nerve disease (moderate)
- Angina
- Hormone deficiency patient
- Pulmonary disease (asthma)
- Diabetic ketoacidosis
- Laser treatment history

- Infectious disease
- Herpes, zoster, chickenpox
- Infectious disease, systemic fungal infection without effective antibiotics

8. Sample Size Determination

In this study, the steroid group is set as the control group to evaluate the non-inferiority of the experimental group compared to the control group. The treatment response after 16 weeks of medication is used for the therapeutic index. To calculate the sample size for this study, we used the following assumptions:

- a. level of significance = 0.05($\alpha=0.05$)
- b. ratio, experimental group : control group = 1:1($\lambda=1$)
- c. Type II error (β) is 0.2 to keep the power of the test at 80%.
- d. In this study, the experimental group's primary evaluation variable (Pt) is compared with the control group's primary evaluation variable to test for non-inferiority. Our hypotheses is as follows:
 - H0: 16 weeks after injecting propranolol, the treatment response(Pt) is inferior compared to the treatment response of steroid injection(Pc)
 - H1: 16 weeks after injecting propranolol, the treatment response (Pt) is non-inferior to the treatment response of steroid treatment(Pc)
- e. According to previous studies (Sasaki GH, Pang CY, Wittliff JL. Pathogenesis and treatment of infant skin strawberry hemangiomas: clinical and in vitro studies of hormonal effects. *Plast Reconstr Surg.* 1984;73:359-70, Enjolras O, Riche MC, Merland JJ, Escande JP. Management of alarming hemangiomas in infancy: a review of 25 cases. *Pediatrics* 1990;85:491-8, Bennett ML, Fleischer AB Jr, Chamlin SL, Frieden IJ. Oral corticosteroid use is effective for cutaneous hemangiomas: an evidence-based evaluation. *Arch Dermatol* 2001;137:1208-13, Price CJ, Lattouf C, Baum B, et al. Propranolol vs corticosteroids for infantile hemangiomas: a multicenter retrospective analysis. *Arch Dermatol* 2001;147:1371-6), propranolol's treatment response (Pt) is assumed to be 85%, and Steroid's treatment response (Pc) is assumed to be 65%. In addition, assuming that the propranolol on steroid response rate does not fall by greater than 20%, the non-inferiority margin is selected to be -20%.
- f. The sample size's calculation formula and results is as follows:

$$n_c = \frac{\left(z_\alpha \sqrt{pq} \cdot (\lambda + 1)/\lambda + z_\beta \sqrt{p_c q_c + p_t q_t/\lambda} \right)^2}{(\epsilon - (p_c - p_t))^2}$$

n_c = Adequate sample size

Z_α = Z-score of standard normal distribution for the significance level (type I error) (Significance level 5%:

$$Z_{\alpha}=1.645)$$

Z_{β} = Z-score of standard normal distribution for power (power 80%, one-tailed: $Z_{\beta}=0.840$)

$$\bar{p} = (P_t + P_c)/2$$

$$\bar{q} = 1 - \bar{p}$$

$$q_c = 1 - P_c$$

$$q_t = 1 - P_t$$

Using the above assumptions, the sample size for each group (n) is calculated to be 15 people. Assuming a 10% quit rate, the total target participant number is calculated to be 17 people per group, and 34 people total.

10. Overall Study Design

This study is a single-institution, single-blind, prospective randomized controlled trial of a non-inferiority design. 34 patients with infant hemangioma are randomly assigned to either the steroid group or the propranolol group. Only children who have never been treated and have normal heart function were included. In the propranolol group, patients are admitted and checked for side effects for three days. They then are observed for therapeutic effects as outpatients. In the steroid group, patients are checked as outpatients from the beginning. While comparing the effect of medication between the two groups, the side effects of both drugs are also monitored.

Arms	Assigned Interventions
Active Comparator: Prednisolone Patients who will receive prednisolone medication (2mg/kg/day) for 16 weeks	Drug: Prednisolone (2mg/kg/day) for 16weeks Other Names: steroid
Experimental: Propranolol Patients who will receive propranolol medication (2 mg/kg/day) for 16 weeks	Drug: Propranolol (2mg/kg/day) for 16weeks Other Names: beta-blocker

11. Trial Design

(1) Modeling Clinical trial

1) Study Objectives

- Primary Objective: To evaluate the non-inferiority of propranolol compared to steroid as the first-line treatment of infantile hemangioma
- Secondary Objective: To test the efficacy and safety of propranolol versus steroid for hemangioma treatment
-

2) Control Group Experimental Group

- It is difficult to compare the effectiveness of propranolol treatment with steroid treatment since the majority of the studies conducted on the off-label drug are fragmented, one-off case studies, not large-scale clinical trials.
- Comparing treatment results between two groups with the same condition is required to verify the effectiveness of treatment.
- Control group- experimental group model is designed to compare steroid and propranolol treatment.

3) Randomized Large Scale Clinical trials

- Research on the possible complications of using propranolol in treating hypertension still continues to be conducted. Accumulated drug use experience for a long time makes it possible to research about safety issues.
- The general condition of hemangioma patients is different from that of hypertensive patients. Also, when using the drug for any purpose, a sufficient study of its safety is required.
- Safety reliability cannot be guaranteed with existing small-scale studies.

- Verification of safety of drug by a randomized large-scale clinical trial is necessary for approval of the drug by the FDA.

4) Randomization

- Researchers confirm exclusion criteria, get informed consent, register participants and randomize patients. Mixed block randomization method will be performed for randomization concealment. The size of the block is 4 or 6 and randomly assigned in a 1:1 ratio to experimental group and control group. Statistical Analysis Software (SAS) is used to produce random numbers and there is no stratification factor in this trial
- Randomization is allocated using a web-based random allocation table made by the Seoul National University Hospital Medical Research Collaborating Center (MRCC). MRCC will be in charge of randomization data management and application. Also, randomization information will be independently managed and access will be limited for researchers and requesters.

(2) Baseline Inspection of Participants (Collecting information to confirm inclusion/exclusion criteria)

1) History taking

- Age when hemangioma began
- Existence of herald sign and color of lesion
- The time when hemangioma first expanded in volume (size)
- The period when hemangioma grew the most
- Family history of hemangioma
- Environmental factors (smoking history of parents, alcohol consumption, drug abuse, intrauterine growth retardation, preterm labor, etc.)

2) Inspection before treatment

- Sex, Date of Birth, Age, Body weight, Height
- Participants should not have any abnormalities in these studies.
 - ✓ Blood test, urinalysis, chest radiography
 - ✓ Heart rate, blood pressure, respiration rate, electrocardiography
 - ✓ Examination and performing echocardiography by pediatric cardiologists.

3) Hemangioma Examination before Treatment

- MRI of hemangioma or ultrasound examination in cases where the patient or guardian refuse MRI scanning for a number of reasons
- Medical photo of lesion
- records of hemangioma size (volume), height, color, ulceration, and re-epithelization

(3) <Experimental Group> Propranolol (After Admitted To Hospital)

- Drug Number 2005009500061, Indenol[®] 10mg, Dosage form : tab, powder (Dongkwang)
- Dosage necessary for treatment is 2 mg/kg/day (3 times per day)
- Children who pass the baseline inspection will be admitted.
- The treatment dosage is gradually reached using the following schedule.

Day 1			Day2			Day3	
Morning	Noon	Evening	Morning	Noon	Evening	Morning	Noon
Admitted	¼ of dosage injected	¼ of dosage injected	½ of dosage injected	½ of dosage injected	Treatment dosage injected	Treatment dosage injected	Discharged

- During admittance, one hour after injection vital signs, glucose levels by blood sugar test (BST) are measured and it should be monitored whether the patients showed any of the following complications.

<ul style="list-style-type: none"> • Decreased heart rate : Heart rate decreased below 70% • Low blood pressure: Systolic blood pressure decreased by more than 25% • Hypoglycemia: glucose reduced to less than 50mg/dl • Difficulty breathing: Wheezing heard through stethoscope

- For patients showing no abnormalities, injections are made 1 week, 4 weeks, 8 weeks, 12 weeks, 16 weeks, and 20 weeks after initial injection for a total of 6 outpatient observations and 16 weeks of injections. After 16 weeks, drug dosage will be adjusted as follows: (Unit: mg/kg/day)

Week 16	Week 17	Week 18	Week 19	Week 20
2.0	1.5	1.0	0.5	0

- Even in the case where hemangioma is 100% resolved by Week 16, the above protocol will be followed to adjust drug dosage and the result will be observed only.
- In the case where after 16 weeks the child's guardian requests treatment or treatment is required due to

remaining hemangioma, the above protocol will not be followed and the researcher can adjust drug dosage at his discretion.

- In the case where a complication symptom is observed, treatment from a pediatrician will be sought immediately.

(4) <Control Group> Steroid

- Drug Code 2015014400690, PRD suspension[®] 1mg/mL Dosage form: syrup (Hanlim)
- Dosage necessary for treatment is 2 mg/kg/day (1 time per day)
- Outpatient observations and injections are made for children who passed baseline inspections.
- In outpatient observations, one hour after the first injection vital signs, glucose level (BST) is measured, and signs for abnormalities are monitored.
- For patients with no abnormalities, outpatient observations and injections are made 1 week, 4 weeks, 8 weeks, 12 weeks, 16 weeks, and 20 weeks after initial injection for a total of 6 outpatient observations and 16 weeks of injections.
- After 16 weeks, drug dosage will be adjusted as follows: (Unit: mg/kg/day)

Week 16	Week 17	Week 18	Week 19	Week 20
2.0	1.5	1.0	0.5	0

- Even in the case where hemangioma is 100% resolved by Week 16, the above protocol will be followed to adjust drug dosage and the result will be observed only.
- In the case where after 16 weeks the child's guardian requests treatment or treatment is required due to remaining hemangioma, the above protocol will not be followed and the researcher can adjust drug dosage at his discretion. Therapy will be tapered off over the last month and patients will be observed for signs of relapse in follow-up inspections.
- In the case where a complication symptom is observed, treatment from a pediatrician will be sought immediately.

(5) Progress Observations (Outpatient Visit)

- Patients showing no special signs are observed 1 week after, 4 weeks after, 8 weeks after, 12 weeks after, and 20 weeks after initial injection, for a total of 6 outpatient progress observations.
- During every visit, weight, height, vital signs, and glucose level (BST) are measured. After 1 week from the initial injection, an electrocardiogram examination is performed. After 4 weeks, blood test, urinalysis, and another electrocardiogram examination will be given. After 8 weeks and 16 weeks, two turns of growth factors and cytokine examinations will be conducted in addition to monitoring for any of the associated complications mentioned above.

Schedule	Baseline	Treatment						
		0~3days	1±1	4±1	8±1	12±1	16±1	20±1
Visit(week)								
Informed consent	O							
History taking	O							
Height, body weight	O		O	O	O	O	O	O
Chest X-ray	O							
EKG	O		O				O	
echocardiography	O							
Vital sign	O	O	O	O	O	O	O	O
Physical examination	O	O	O	O	O	O	O	O
BST		O	O	O	O	O	O	O
Blood test	O			O				
Urinalysis	O			O				
Inclusion criteria/ Exclusion criteria	O							
Randomization	O							
Hemangioma inspection (Efficacy assessment)	O		O	O	O	O	O	O
Safety assessment (including adverse reaction)		O	O	O	O	O	O	O
MRI or ultrasonography	O						O	
Medical photography	O		O	O	O	O	O	O

EKG denotes electrocardiography, BST blood sugar test, MRI magnetic resonance imaging.

(6) Assessment (Outpatient Visit)

- The researchers or coordinator checks the following during each outpatient visit. Hemangioma is assessed at Week 16 and compared to the pre-treatment status by performing a MRI scan or ultrasound evaluation (when the patient or guardian refused an MRI scan).
- If an MRI scan is conducted by the rules during screening, an MRI exam is performed and hemangioma volume is measured during week 16. Likewise, an ultrasound examination is made and hemangioma volume is measured during week 16 for patients who receive an ultrasound exam instead of an MRI. However, an exception is made in the case where the patient or guardian request a change of examination, thus the examination method may differ. (A radiology professor answered during consultation that even if the examination method differs between screening and week 16, it is possible to evaluate hemangioma volume.)
- One radiology specialist conducts the MRI scans and ultrasound examinations (when a MRI scan is refused by the patient or guardian). As the study is patient-assessor blind, the radiology specialist measures hemangioma volume without any patient information. Once a week, the patient's guardian measures and records hemangioma size (area) and ulceration size (independent, centralized, blinded evaluations of standardized photographs).
- Prior to the study, the coordinator should be educated about recording hemangioma size, ulceration size, color, and existence of re-epithelization with medical photos from hemangioma cases not included in the study.
- The coordinator will be tested for ability to record hemangioma size, ulceration size, color, and existence of re-epithelization with medical photos of cases not included in the study and not used in education
- Guardians of patient measure hemangioma size (surface area) and ulceration size using a ruler once a week.
- The response is classified as follows:
 - ✓ Reaction is defined as proliferative stop or regression
 - ✓ Proliferative stop is defined as no further increase in the size (by volume) after treatment began or a size reduction of less than 25%.
 - ✓ Regression is defined as a size reduction of more than 25% compared to original size after treatment began.
 - ✓ Non-reaction means increase of the lesion.

✓ Increase is defined as the size (by volume) at primary efficacy evaluation point being greater than the size measured when treatment started.

- In the case where a patient does not react to steroid or propranolol drug therapy and hemangioma rapidly grows so that symptoms worsen, or an associated complication arise, another drug therapy will be considered or other departments such as the plastic surgery, general surgery, otorhinolaryngology, or pediatric department will be consulted for surgical treatment

Primary Appraisal Categories	
Size (Volume) (Treatment response)	Hemangioma volume measured(mm ³) through MRI scan or ultrasound examination (when patient or guardian refuse MRI scan)
Secondary Appraisal Categories	
Size (Volume) (Change in volume)	Hemangioma volume measured (mm ³) through MRI scan or ultrasound examination (when patient or guardian refused MRI scan)
Size (Area)	Hemangioma's major and minor axes measured in mm
Color	Hemangioma's color categorized as red/purple/blue/gray/apricot (Evaluated as 1, 2, 3, 4, 5 points respectively)
Ulceration size	Ulceration's major and minor axes measured in mm to check whether surface integrity is maintained. In the case of a bleeding history, it is determined that an ulceration is present
Re-epithelization	If the surface no longer showed any exudates, it is evaluated as a re-epithelization (evaluated as yes/no)
Progression stop period	Recorded no further increase in the size (by volume) after treatment began or a size reduction of less than 25%.
Regression period	Recorded time of when size (area) decreased by more than 25% after treatment started
Compliance	Length of medication or number of outpatient visits
Safety Evaluation Categories (Drug Side Effects)	

Decreased heart rate	If heart rate is below 70% of normal heart rate or if symptoms of decreased heart rate is observed
Low blood pressure	If systolic blood pressure decreased by more than 25% of initial blood pressure
Hypoglycemia	If blood sugar is decreased to less than 50mg/dl, if fatigue or other symptoms of hypoglycemia are observed
Trouble breathing	If symptoms of bronchoconstriction are observed or wheezing is heard through stethoscope
Facial edema	If temporal region and cheeks expand and a double chin appears
Gastroesophageal reflux	If patient vomits more than 4 times a day
Hypertension	If blood pressure increases by more than 25% compared to initial blood pressure
Growth disability	If weight and height falls below 5 percentile or no growth is observed during four-month observation period
Adverse reaction	If an adverse reaction such as secondary reaction, interaction, immunologic drug reaction, intolerance, specific reaction, allergies, etc. are observed.

(7) Statistical Analysis

1) Efficacy Variables

The primary efficacy variable is hemangioma volume measured by a MRI scan or ultrasound examination (when the patient or guardian refused a MRI scan for a number of reasons). The secondary efficacy variable is hemangioma size (volume, area), hemangioma color, ulceration, presence of re-epithelization, proliferative stop point, regression point, and compliance.

2) Defined Analysis Groups

a. Per Protocol Population (Per Protocol Set, PP Population)

“Per protocol population” is defined as the group of participants who adhere to the protocol and complete the trial. However, those whose efficacy variables cannot be measured will be excluded from the “per protocol population”

b. Intention to Treat Population (Full Analysis Set, Intent-to-Treatment Population)

“Intention to treat population” is defined as the group of participants who are randomly assigned.

c. Safety Population

“Safety population” refers to all participants who have at least one safety assessment performed after assignment.

d. Subject of Analysis for Efficacy and Safety

For efficacy evaluation, the intention to treat population (ITT population) is the main subject of analysis for the primary efficacy variable and the per-protocol population (PP population) is the secondary subject of analysis. For safety evaluation, the safety population is the subject of analysis.

3) Statistical analysis method

a. Demographic Analysis and Baseline Inspection Results Analysis

To evaluate for differences in demographics, baseline inspections (age, sex, weight, height, etc.), and baseline hemangioma inspection results between the two groups, the t-test or Wilcoxon rank sum test (depending on normality test results) is conducted for continuous data and the Chi-square test or Fisher's exact test (depending on frequency distribution) is used for binary data.

b. Primary Efficacy Evaluation Method

The primary efficacy variable is hemangioma volume measured by a MRI scan or ultrasound examination (when the patient or guardian refused a MRI scan for a number of reasons). We classified cases where size did not increase (proliferative stop) or size decreased below the initial size before treatment as a reactive treatment response. To show that the experimental group's treatment response rate is non-inferior to the control group's treatment response rate, we obtained a 95% confidence interval for $P_t - P_c$ (experimental group's treatment response rate – control group's treatment response rate). If the lower limit of the confidence interval is greater than -20%, it can be said that the experimental group's treatment response is non-inferior. In addition, differences in treatment response rate between the two groups are checked using the Chi-square test and Fisher's exact test.

c. Secondary Efficacy Evaluation Method

In this study, the secondary efficacy variable is hemangioma size (volume), hemangioma size (area), hemangioma color, presence of ulceration and ulceration size, presence of re-epithelization, proliferative stop point, regression point, and compliance. At each time point, the mean, standard deviation, median, minimum and maximum values are calculated for continuous data and frequency and percentage is presented for categorical data. Each variable is evaluated as follows:

- Hemangioma size (volume): The rate of change between the hemangioma size (volume) during Baseline (Visit 1) and Week 16 (Visit 6) was calculated, and an independent t-test or Wilcoxon's rank sum test was used to evaluate for differences between the two groups.
 - ※ Rate of change (%) of hemangioma size (volume) = $[(\text{hemangioma volume measured at Week 16 (Visit 6)} - \text{hemangioma volume measured at Baseline (Visit 1)}) / (\text{hemangioma volume measured at Baseline (Visit 1)})]$
- Hemangioma size (area), ulceration size: A mixed model or generalized estimating equation (GEE) is used to determine if there are any differences in hemangioma size (area) and ulceration size depending on time

point, or differences between groups, or group patterns across different time points.

- Hemangioma color: A model using GEE is used to evaluate changes over time in the incidence of hemangioma by color or differences between groups.
- Presence of ulceration and ulceration size, Presence of re-epithelization ulceration: A model using GEE is used to evaluate changes over time in the incidence of ulceration and re-epithelization or differences between groups.
- Proliferative stop point, regression point: The Kaplan-Meier method is used to estimate survival time and a log-rank test is used to analyze differences in survival functions. After steroid or propranolol is injected, the median value and range of proliferative stop or regression time point is presented and the frequency and percentage is calculated for the participant who stopped proliferating or experienced regression. In addition, the log-rank test is used to compare the two groups.
- Compliance: Using descriptive statistics such as means and standard deviations for each visit, the independent t-test or Wilcoxon's rank sum test is used to determine any differences in compliance between the two groups.

d. Safety Analysis

- The safety population is the subject of analysis.
- During the duration of the clinical test, the number of participants who experienced at least one adverse reaction and percentage is recorded for each adverse reaction and separated by group. Information regarding extent of adverse reaction, result, causality, and related measures is also arranged by group. Statistical methods such as Fisher's exact test were used to for comparative analysis between groups. In addition, for each group the side effect category and rate of incidence is calculated. In the case of vital signs, glucose level (BST), and safety evaluation categories (decreased heart rate, low blood sugar, low blood pressure, etc.), which were measured one hour after injection, descriptive statistics were used to summarize the data. For continuous data, the t-test or Wilcoxon rank sum test is conducted depending on normality test results. For binary data, depending on frequency distribution the Chi-square test or Fisher's exact test is used to evaluate differences between injection groups. To evaluate for differences in demographics, baseline inspections (age, sex, weight, height, etc.) and baseline hemangioma inspection results between the two groups, the t-test or Wilcoxon rank sum test (depending on normality test results) is conducted for continuous data and the Chi-square test or Fisher's exact test (depending on frequency

distribution) is used for binary data.

e. Missing value

- If primary efficacy was not evaluated due to refusal of MRI scanning or ultrasound examination, missing values are replaced by applying multiple imputation. The multiple imputation method was used to predict the “Reaction” or “Non-reaction” using some of secondary efficacy variables such as size (area), proliferative stop time point, regression time point, color, ulceration size, and presence of re-epithelization.
- In addition, data with replaced missing values in primary efficacy is analyzed to assess the effect of missing value.
- Missing values for secondary efficacy variables has not been replaced.

(8) Study discontinuation

- Violation of inclusion criteria or exclusion criteria
- Withdrawal of consent
- Complication or Adverse reaction of drug
- Low compliance
- Investigators or care providers may discontinue in his discretion.

(9) Monitoring and Audit

- Monitors other than assistants designated by the investigator should protect the rights and welfare of participants and ensure that the study is conducted in accordance with the protocol and Good Clinical Practice. Patient data should be continuously monitored to make sure the information in the electronic Case Report Form (eCRF) is accurate.
- After the first participant registration, researchers request 1st Patient Monitoring Service of Quality Improvement (QI) in clinical study center of Seoul National University Hospital to make early detection and correction of error possible.
- Principal investigator inspects all the records at the beginning and the end of the study by requesting Medical Research Collaborating Center (MRCC) to assure the reliability of collected data. This inspection is irrelevant to monitoring and quality assurance.
- The investigator is responsible for the confirmation of the previously announced content and procedure of inspection, cooperation in providing relevant documents, records, and amendments, and keeping data.

(10) Data Entry and Data Management/Storage, Methods for Protection of Personal Information of Participants and Research Data

- Collected data for the study is kept in files with passwords and in the laboratory with locks.
- Data entry is limited to authorized staff members
- Unnecessary personal information would be sealed especially for patient names, resident registration number, patient number and other identifiable data. Identification codes connected to personal information are separately managed.
- All records obtained from the research are kept for 10 years after completion of the study.
- Data entry uses e-CRF(www.phactax.org) established after request to MRCC and MRCC is in charge of data management
- When publishing the results of the study, any publication cannot contain any personal identification.

(11) Management of medical supplies for clinical trials

- Pharmacist in Clinical Trials Center Pharmacy, Biomedical Research Institute, Seoul National University Hospital: Hong Won Jang (T. 82-2-2072-1688)

12. Counterplan for protecting safety of participants

The research is based on the recently revised Helsinki declaration (2008, 59th WMA General Assembly, Seoul) and considers the rights and welfare of patients. The principal investigator and all researchers have thorough knowledge of the protocol of the study and respond actively to the problems of subjects. Information about the study, benefits and safety issues will be explained to guardian and researchers will receive informed consent prior to the study.

For the privacy of participants, encrypted specimen which is not able to discriminate personal information and security systemized software for personal information related to specimen will be used. Principal investigator and Co-principal investigators are in charge of the privacy of participants. Specimen can be collected when blood is gathered for diagnostic or therapeutic purpose.

13. Agreement for Compensation

If participants become damaged even though the principal investigator followed all related rules and regulations and conducted research in strict conformity with references to protocol, recommendations, and suggestions, participants are able to receive compensation under the agreement for compensation.

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15. Principal Investigator

1) Identification

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2) Scholarship

Year	Name of School	Major	Degree
1991. 3 - 1997. 2	Keimyung University College of Medicine	Medicine	Doctor of Medicine
1998.3 – 2000.2	Keimyung University College of Medicine	Plastic surgery	Master's
2000. 3 - 2002. 2	Keimyung University College of Medicine	Plastic surgery	Ph.D.

GCP Training: Online training course for Good Clinical Practice by SNUH Human Research Protection Program Center, 24 Feb 2014

3) Research

1. Han KW, Choi TH, Son DG. Skin Color of Koreans: Statistical Evaluation of Affecting Factors. Skin Research and Technology 2006;12;170-177

2. Kim JS, Han KH, Choi TH, Kim NG, Lee KS, Son DG, Kim JH. Correction of the Nasal Tip and Columella in Koreans by a Complete Septal Extension Graft Using an Extensive Harvesting Technique. *Journal of Plastic, Reconstructive and Aesthetic Surgery* 2007;60;163-170 (**Corresponding author**)

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with Free Flap: Anatomical and Clinical Study. *Microsurgery* 2010;30;32-36

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16. Informed Consent Form and Participant Information Sheet

Informed Consent Form and Participant Information Sheet

1. Title of Research Project: The Safety and Efficacy of Propranolol as an Initial Treatment for Infantile Hemangioma: A Randomized Controlled Trial

2. Name of Principal Investigator: Tae Hyun Choi, Associate Professor of Department of Plastic and Reconstructive Surgery, Seoul National University College of Medicine

3. Introduction

The purpose of this clinical trial is to survey the efficacy and safety of propranolol as an initial treatment for infantile hemangioma through a randomized controlled trial. You are invited to be part of this research as your child has been diagnosed with infantile hemangioma. This research is only for patients who voluntarily agree to participate. Prior to participation, it is important to understand the purpose of this study.

4. Purpose of the Research

Several studies show that propranolol is effective in treating infantile hemangioma but do not prove its use as a first-line treatment. Since no study has been conducted to compare propranolol and steroid, clinicians do not know which more treatment is more effective. This clinical trial will evaluate the efficacy and safety of propranolol as the primary treatment for infantile hemangioma.

5. Information on the Trial Drug

- Propranolol (drug code 2005009500061, Indenol[®] 10mg, dosage form: tab, powder)

- Prednisolone (drug code 2015014400690, PRD 1mg/ mL, dosage form: syrup)

6. Alternatives to Participating

The control group will be treated with steroid, which is currently used as standard treatment for hemangioma.

7. Description of Study

a. Procedures and Protocol

We will make inspections before treatment (sex, date of birth, age, weight, height), take an MRI scan or ultrasonography (if the patient or parent refuses to take MRI scan), medical photography of the lesion, and will record the surface area of hemangioma, color, ulceration and re-epithelization. In addition, we will perform a blood test, urinalysis, chest radiography, heart rate, blood pressure, and electrocardiography. A pediatric cardiologist will examine and perform the echocardiography. Participants will be randomly assigned in a 1:1 ratio to either the test group or control group. We will observe 1 week, 4 weeks, 8 weeks, 12 weeks, 16 weeks, and 20 weeks after initial oral medication for a total of 6 outpatient observations and 16 weeks of inpatient or outpatient-based medications.

b. Duration and Number of Subjects

The research will take place over 5 months in total and 34 people will participate

c. Exclusion Criteria and Duty of Participation

Patients with cardiovascular disease, respiratory disease (asthma etc.) and steroid/laser treatment history cannot be included. Also, patients with infectious disease without effective antibiotics, systemic fungal infection, herpes, zoster, chickenpox and patients who received live attenuated vaccines are excluded.

d. Schedule of the Study

Children assigned to the propranolol group will receive treatment as an inpatient. They will be administered twice on the first day (1/4 of dosage, total 0.33mg/kg/day), and 3 times on the second day (1/2 of dosage for twice, treatment dosage for once, total 1.33mg/kg/day). During admittance, we will monitor whether the patient shows any complications. A treatment dosage of 2mg/kg/day will be used on the third day of admittance and will be continued until 16 weeks. After 16 weeks, drug dosage will be tapered off and treatment will be stopped (Week 17: 1.5mg/kg/day, Week 18: 1.0mg/kg/day, Week 19: 0.5mg/kg/day. Week 20: 0mg/kg/day). In the case

where after 16 weeks the child's guardian requests treatment or treatment is required due to remaining hemangioma, the above protocol will not be followed and the researcher will adjust drug dosage at his discretion. We will follow up with patients at 1 week, 4 weeks, 8 weeks, 12 weeks, 16 weeks, and 20 weeks after initial oral medication and assess hemangioma lesion and patient condition at Week 16.

Children assigned to the steroid group will be take 2 mg/kg/day (1 time per day) of syrup for 16 weeks. After 16 weeks, drug dosage will be tapered off and treatment will be stopped (Week 17: 1.5mg/kg/day, Week 18: 1.0mg/kg/day, Week 19: 0.5mg/kg/day. Week 20: 0mg/kg/day). In the case where after 16 weeks the child's guardian requests treatment or treatment is required due to remaining hemangioma, the above protocol will not be followed and the researcher will adjust drug dosage at his discretion. We will follow up with patients at 1 week, 4 weeks, 8 weeks, 12 weeks, 16 weeks, and 20 weeks after initial oral medication and assess hemangioma lesion using MRI of ultrasonography (if patients or parents refuse to take MRI scan for several reasons) at Week 16.

8. Expected side effects, risks and discomforts

Propranolol medication can cause the heart rate to decrease below 70% of the initial heart rate and symptoms may follow decreased heart rate. Low blood pressure, hypoglycemia (glucose reduced to less than 50mg/dl), and difficulty breathing (wheezing heard through stethoscope) can be possible.

Steroid medication can cause facial edema, vomiting (over 4 times per day), and high systolic blood pressure. On rare occasions, growth disability can be induced. A child is considered to have growth disability if he or she has a height and body weight below the 5th percentile of the same age and growth of height and body weight is retarded during the observation period.

Adverse reactions (toxicity, immunologic drug reaction, intolerance, allergic reaction etc.) and unexpected risks can be observed in both propranolol medication and steroid medication. Patients should be admitted for 3 days when they are treated with propranolol as the drug can cause discomfort.

9. Benefits

If your child participates in this research, medical benefits will be guaranteed and knowledge obtained from the study will help treat other patients with similar diseases.

10. Providing Significant New Findings to Subjects

Significant new findings that may be related to the subject's willingness to continue participation will be reported immediately to patients and guardians.

11. Reimbursements

Expenses incurred as a result of participation in the research will be reimbursed, but no financial rewards will be given for participation.

12. Compensation for Complication

In the case where a complication symptom is observed, the principal investigator has the responsibility for compensation and treatment from specialists will be sought immediately.

13. Confidentiality

The information we collect from this research project will be kept confidential. Researchers are only able to see collected information without personal information. The signature of the participant or representative of the participant on the consent form makes sharing information available. Confidential information will not be shared in cases of publication.

14. Voluntary participation

Your participation in this research is entirely voluntary. You may choose not to participate in this research project or stop participating at any time. If you choose not to participate, your decision will be respected and your child's treatment will continue without being affected.

15. Right to Refuse or Withdraw

This study will be stopped if a patient violates excluding criteria or declines to participate. Complications, adverse reactions, and low compliance can also lead to discontinued participation of a patient in the study at any time. Investigators or care providers may also discontinue at his discretion

16. Chief investigator and contact number

- Tae Hyun Choi, 02-2072-1978

- Jae Hoon Jeong 010-9130-8974

- Hyunjung Lee research nurse 02-2072-1765

- Seoul National University Hospital Institutional Review Board (IRB) 02-2072-0694,
e-mail snuhirb@gmail.com

Informed Consent Form

1. I have been explained information verbally, accurately read the information sheet, and discussed with the researchers.

2. The risks and benefits have been explained and my questions have been answered to my satisfaction.

3. I consent voluntarily to participate as a participant in this research.

4. I may refuse to participate or choose to stop participating in the research at any time without my treatment being affected. I acknowledge that my decision will never harm me.

5. I consent that my personal information will be collected and assessed for medical research within the law after signing the Informed Consent Form and Participant Information Sheet.

6. A copy of this Informed Consent Form will be provided to the participant.

Print name of Participant

Print name of Guardian Relation Signature of witness Date (Day/month/year)

Print Name of Researcher Signature of Researcher Date (Day/month/year)