Supplementary Online Content

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eTable 1 through eTable 32. Various data reports

eFigure 1. Secondary efficacy variables

eReferences.

This supplementary material has been provided by the authors to give readers additional information about their work.

Supplements

Comparison of Efficacy and Safety between Propranolol and Steroid for Infantile Hemangioma: A Randomized Clinical Trial

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Contents

1. Objectives and Trial Design

1.1. Objective

- To survey the efficacy and safety of propranolol as an initial treatment for infantile hemangioma by randomized controlled trial.

1.2. Trial Design

- Single institution, randomized controlled non-inferiority trial

1.3. Eligibility Criteria

eTable 1. 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

1.4. Sample Size Determination

Patients diagnosed with hemangioma, agreed voluntarily to participate and signed informed consent prior to study entry are the target of the study. Hemangioma volume was measured using magnetic resonance imaging (MRI). In the case where the guardian of a patient refused the use of MRI, we performed an ultrasound examination.

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:

- level of significance = 0.05(α=0.05)
- ratio, experimental group : control group = 1:1(λ=1)
- Type II error (β) is 0.2 to keep the power of the test at 80%.

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)

According to previous studies, propranolol's treatment response (Pt) is assumed to be 85%, and Steroid's treatment response(Pc) is assumed to be 65%.[1-4] 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%.

The sample size's calculation formula and results is as follows:

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

n_c = Adequate sample size

Z_α = Z-score of standard normal distribution for the significance level (type I error) (Significance level 5%: Z_α=1.645)

Z_β = Z-score of standard normal distribution for power (power 80%, one-tailed: Z_β=0.840)

$$\bar{p} = (Pt + Pc)/2$$

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

$q_c = 1\text{-}P_c$

$q_t = 1\text{-}P_t$

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 in total.

1.5 Medication schedule

eTable 2. Medication schedule

Schedule	Baseline	Treatment						
		Visit 1 0-3 days	Visit 2 1±1 week	Visit 3 4±1 weeks	Visit 4 8±1 weeks	Visit 5 12±1 weeks	Visit 6 16±1 weeks	Visit 7 20±1 weeks
		↓	↓	↓	↓	↓	↓	↓
Experimental group (Propranolol)	MRI	Induction					MRI Tapering start	
Control group (Steroid)	MRI						MRI Tapering start	

MRI denotes magnetic resonance imaging.

eTable 3. Drug induction and tapering schedule

A. Induction schedule

Day 1			Day 2			Day 3	
Morning	Noon	Evening	Morning	Noon	Evening	Morning	Noon
Admitted	0.5 mg/kg/day (¼ of dosage)	0.5 mg/kg/day (¼ of dosage)	1.0 mg/kg/day (½ of dosage)	1.0 mg/kg/day (½ of dosage)	2.0 mg/kg/day (Treatment dosage)	2.0 mg/kg/day (Treatment dosage)	Discharged

B. Tapering schedule

Week 16	Week 17	Week 18	Week 19	Week 20
2.0 mg/kg/day (Treatment dosage)	1.5 mg/kg/day (¾ of dosage)	1.0 mg/kg/day (½ of dosage)	0.5 mg/kg/day (¼ of dosage)	0.0 mg/kg/day (Finish)

2. Basic Setting for Statistical Analysis

2.1 General Principle of Result Analysis

The standard level of significance (alpha) was set as 0.05 and a two-tailed test was used in this clinical trial unless otherwise indicated. At each time point, the mean, standard deviation, median, minimum and maximum values were calculated for continuous data and the frequency and percentage was shown for categorical data.

Groups of participants for statistical analysis are as follows.

2.1.1. 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"

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

"Intention to treat population (ITT)" is defined as the group of participants who are randomly assigned. However, if after assignment a participant does not receive a drug injection or if an evaluation is never made after a drug injection, he or she will be excluded from the "intention to treat population".

2.1.3. Safety Population

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

2.1.4. 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.

2.2. Missing Value Adjustment

If primary efficacy was not evaluated due to refusal of MRI scanning or ultrasound examination, missing values are replaced by applying multiple imputation (MI). The MI 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.

2.3. Participation Status and Violation of Trial Protocol

The diagram of participation status, the reasons for withdrawal, and distribution of protocol violation were reported.

2.4. 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.

2.5. Analysis of 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 (area), hemangioma color, ulceration, presence of re-epithelization, proliferative stop point, regression point, and compliance.

eTable 4. Efficacy and safety assessment [5-11]

Primary efficacy variable	
Volume (Treatment Response)	Hemangioma volume measured (mm^3) through MRI scan or ultrasound examination (when patient or guardian refused MRI scan)
Secondary efficacy variables	
Volume (Change in Volume)	Hemangioma volume measured (mm^3) through MRI scan or ultrasound examination (when patient or guardian refused MRI scan)
The surface 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 was determined that an ulceration is present
Re-epithelization	If the surface no longer showed any exudates, it was evaluated as a re-epithelization (evaluated as yes/no)
Exponential Stage Suspension Period	Recorded time of when size (area) did not increase after treatment or decreased by 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 variables	
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

2.5.1. Primary Efficacy Evaluation Variable

The primary efficacy variable is response of treatment using 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 response of treatment 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.

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 -10%, 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.

2.5.2 Secondary Efficacy Evaluation Variable

In this study, the secondary efficacy variable is 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. The variables are evaluated as follow:

- 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.

2.6. 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 by blood sugar test (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.

3. Participants

3.1. Participation Status

The participation status (ITT group, PP group, Safety analysis group) is presented as follows (Figure 1) and reasons for quitting the trial are presented as follows (eTable 5).

A total of 34 patients agreed and registered in this trial. The patients were randomly assigned to either the propranolol group (17 patients) or steroid group (17 patients). Two guardians withdrew consent in the steroid group and one patient in the propranolol did not complete the efficiency test. The efficiency evaluation was conducted in the PP analysis group, which includes 30 target participants (propranolol group: steroid group = 16:14). The safety evaluation was conducted in the ITT analysis group, which had a total of 33 patients (propranolol group: steroid group = 17:16).

eTable 5. Participation status

	Total	Propranolol	Steroid
Registered participants, N	34	17	17
Trial-completed participants, N	32	17	15
Withdrawal, N	2	0	2
1. Violation of inclusion, exclusion criteria	0	0	0
2. Withdrawal of consent	2	0	2
3. Drug adverse reaction	0	0	0
4. Non-compliance	0	0	0
5. Discretion of investigator	0	0	0
6. Others	0	0	0

3.2. 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.

3.2.1. Demographic Analysis

Demographic of the patients are shown in eTable 6. In terms of demographics for the ITT group, the mean age for the 17 participants assigned to the propranolol group was 3.18 months, mean weight was 6.45kg, and mean height was 61.75cm. For the 17 participants assigned to the steroid group, the mean age was 2.65 months, mean weight was 6.02kg, and mean height was 60.51cm. In the propranolol group, 7 of the participants were male (41.18%), and in the steroid group, 8 were male (47.06%). All demographics were not statistically significant at the 5% level, thus it cannot be said that there was any statistical difference between the two groups.

eTable 6. Demographic characteristics

	Propranolol (N=17)	Steroid (N=17)	P-value
Age (month)			
N	17	17	0.4835*
Mean±S.D.	3.18±2.21	2.65±1.97	
Median[Min, Max]	3[0,8]	2[0,8]	
Sex, N(%)			
- Male	7 (41.18)	8 (47.06)	0.7298†
- Female	10 (58.82)	9 (52.94)	
Weight (kg)			
N	17	17	0.4752‡
Mean±S.D.	6.45±1.73	6.02±1.68	
Median[Min, Max]	6.6[3.1,9]	6[3.4,8.3]	
Height (cm)			
N	17	17	0.5491‡
Mean±S.D.	61.75±6.05	60.51±5.96	
Median[Min, Max]	63.1[49.2,69]	61.5[50.1,69]	

Plus-minus values are mean ± SD. There were no significant differences between two groups unless otherwise

indicated. SD denotes standard deviation.

* Wilcoxon Rank Sum test, † Chi-square test, ‡ Independent T-test

eTable 7 describes baseline vital sign of patients. It was found that there was no statistically significant difference in vital signs (SBP, DBP, heart rate, respiratory rate, and body temperature) between the two groups (P-value > 0.05)

eTable 7. Baseline vital sign

	Propranolol (N=17)	Steroid (N=17)	P-value
SBP (mmHG)			
N	17	17	0.3980*
Mean±S.D.	94.24±12.26	91.12±10.04	
Median[Min, Max]	88[80,112]	91[76,108]	
DBP (mmHG)			
N	17	17	0.8367‡
Mean±S.D.	49.82±10.76	50.59±10.69	
Median[Min, Max]	45[35,72]	50[35,68]	
Heart rate (/min)			
N	17	17	0.1119*
Mean±S.D.	131.59±14.27	138.59±13.54	
Median[Min, Max]	128[109,167]	140[118,160]	
Respiratory rate (/min)			
N	17	17	0.8576*
Mean±S.D.	35.76±2.63	36.12±3.77	
Median[Min, Max]	36[30,40]	36[32,44]	
Body temperature (/min)			
N	17	17	0.7960‡
Mean±S.D.	36.89±0.41	36.93±0.38	
Median[Min, Max]	37[36.1,37.5]	36.9[36.3,37.5]	

* Wilcoxon Rank Sum test, ‡ Independent T-test
SBP denotes systolic blood pressure, DBP diastolic blood pressure, SD standard deviation.

3.2.2. Baseline Inspection Result Analysis

Baseline inspection results of two groups are shown in eTable 8 and eTable 9. No abnormalities were found in the chest radiograph image, electrocardiograph, cardiac inspection, and echocardiograph results of any of the subjects, thus there was no statistical difference between the two groups (P-value > 0.05).

eTable 8. Chest X-ray, EKG, cardiac inspection and echocardiogram of patients

Baseline inspection	Propranolol (N=17)	Steroid (N=17)	P-value
Chest X-ray			
Normal	16 (94.12)	16 (94.12)	1.0000§
Abnormal NCS	1 (5.88)	1 (5.88)	
Abnormal CS	0 (0)	0 (0)	
EKG			
Normal	10 (58.82)	8 (47.06)	0.4920†
Abnormal NCS	7 (41.18)	9 (52.94)	
Abnormal CS	0 (0)	0 (0)	
Cardiac inspection and Echocardiogram			
Normal	12 (70.59)	10 (58.82)	0.4729†
Abnormal NCS	5 (29.41)	7 (41.18)	
Abnormal CS	0 (0)	0 (0)	

† Chi-square test, § Fisher's exact test,

NCS denotes not clinically significant, CS clinically significant, EKG electrocardiograph.

In the steroid group, for the blood chemistry categories total bilirubin, alkaline phosphatase and potassium, several subjects had abnormal values: 3 for total bilirubin, 2 for alkaline phosphatase, and 2 for potassium. No subjects showed abnormal values for any of the other inspections.

In the propranolol group, none of the subjects showed abnormal values for any of the test categories.

Excluding alkaline phosphatase, we found no significant difference in blood test or urinalysis results at the 5% level. In the case of alkaline phosphatase, the propranolol group mean was 257.18 IU/L, and the steroid group mean was 315.82 IU/L. Although the steroid group had a higher mean, there was no significant difference.

eTable 9. Complete blood count, blood chemistry and urinalysis of patients

		Propranolol (N=17)	Steroid (N=17)	P-value
Complete Blood Count				
White blood cell ($10^3/\mu\ell$)	N	17	17	0.9451*
	Mean±S.D.	9.38±2.89	9.34±2.9	
	Median[Min, Max]	9.03[5.1,17.72]	8.27[5.76,18.61]	
	Normal	12 (70.59)	12 (70.59)	1.0000†
	Abnormal NCS	5 (29.41)	5 (29.41)	
	Abnormal CS	0 (0)	0 (0)	
Red blood cell ($10^6/\mu\ell$)	N	17	17	0.8052†
	Mean±S.D.	3.94±0.59	3.99±0.47	
	Median[Min, Max]	3.87[2.77,4.79]	4.07[2.95,4.75]	
	Normal	8 (47.06)	8 (47.06)	1.0000†
	Abnormal NCS	9 (52.94)	9 (52.94)	
	Abnormal CS	0 (0)	0 (0)	
Hemoglobin (g/dL)	N	17	17	0.5218‡
	Mean±S.D.	11.2±1.22	11.44±0.88	
	Median[Min, Max]	10.9[9.2,13.2]	11.5[9.7,12.9]	
	Normal	4 (23.53)	0 (0)	0.1026§
	Abnormal NCS	13 (76.47)	17 (100.00)	
	Abnormal CS	0 (0)	0 (0)	
Hematocrit (%)	N	17	17	0.4956‡
	Mean±S.D.	32.79±3.56	33.54±2.69	
	Median[Min, Max]	32.5[26.9,38.4]	33.4[28,37.9]	
	Normal	2 (11.76)	0 (0)	0.4848§
	Abnormal NCS	15 (88.24)	17 (100.00)	
	Abnormal CS	0 (0)	0 (0)	
Platelet ($10^3/\mu\ell$)	N	17	17	0.0636‡
	Mean±S.D.	399.35±128.51	485.47±132.81	
	Median[Min, Max]	369[187,715]	460[295,758]	
	Normal	10 (58.82)	5 (29.41)	0.0842†
	Abnormal NCS	7 (41.18)	12 (70.59)	
	Abnormal CS	0 (0)	0 (0)	
Mean cell volume (fL)	N	17	17	0.9588*
	Mean±S.D.	83.84±6.61	84.66±7.23	
	Median[Min, Max]	81.6[76.2,97.1]	81.8[76.2,98.9]	
	Normal	11 (64.71)	8 (47.06)	0.3001†
	Abnormal NCS	6 (35.29)	9 (52.94)	
	Abnormal CS	0 (0)	0 (0)	

Mean corpuscular hemoglobin (Pg)	N	17	17	0.9313*
	Mean±S.D.	28.69±2.71	28.89±2.49	
	Median[Min, Max]	27.7[25.2,34]	27.9[26.3,33.5]	
	Normal	11 (64.71)	12 (70.59)	0.7139†
	Abnormal NCS	6 (35.29)	5 (29.41)	
	Abnormal CS	0 (0)	0 (0)	
Mean corpuscular hemoglobin concentration (g/dL)	N	17	17	0.9587*
	Mean±S.D.	34.19±0.99	34.12±0.73	
	Median[Min, Max]	34.2[31.5,36.5]	34.4[32.5,35.1]	
	Normal	15 (88.24)	17 (100.00)	0.4848§
	Abnormal NCS	2 (11.76)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	
Red cell distribution (%)	N	17	17	0.0775‡
	Mean±S.D.	13.38±1.15	14.19±1.43	
	Median[Min, Max]	13.4[11.6,14.9]	14[12.1,17.3]	
	Normal	14 (82.35)	10 (58.82)	0.1322†
	Abnormal NCS	3 (17.65)	7 (41.18)	
	Abnormal CS	0 (0)	0 (0)	
Segmented neutrophil (%)	N	17	17	0.1474‡
	Mean±S.D.	16.29±4.88	19.58±7.72	
	Median[Min, Max]	16.1[7,24.7]	18.3[9,33.5]	
	Normal	0 (0)	0 (0)	-
	Abnormal NCS	17 (100.00)	17 (100.00)	
	Abnormal CS	0 (0)	0 (0)	
Lymphocyte (%)	N	17	17	0.1106‡
	Mean±S.D.	71.95±6.27	67.67±8.73	
	Median[Min, Max]	71[62.4,86]	68.9[49.3,82.7]	
	Normal	0 (0)	0 (0)	-
	Abnormal NCS	17 (100.00)	17 (100.00)	
	Abnormal CS	0 (0)	0 (0)	
Monocyte (%)	N	17	17	0.4364‡
	Mean±S.D.	7.38±2.32	8.16±3.33	
	Median[Min, Max]	7.2[4,13]	8[3,15.5]	
	Normal	14 (82.35)	11 (64.71)	0.4384§
	Abnormal NCS	3 (17.65)	6 (35.29)	
	Abnormal CS	0 (0)	0 (0)	
Eosinophil (%)	N	17	17	0.6205‡
	Mean±S.D.	3.59±1.45	3.91±2.18	

	Median[Min, Max]	3.4[1,6]	3.3[1,8.1]	
	Normal	13 (76.47)	12 (70.59)	-
	Abnormal NCS	4 (23.53)	5 (29.41)	
	Abnormal CS	0 (0)	0 (0)	
Basophil (%)	N	17	17	0.5904*
	Mean±S.D.	0.31±0.29	0.37±0.3	
	Median[Min, Max]	0.3[0,1.1]	0.3[0,1.1]	
	Normal	17 (100.00)	17 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	
Absolute neutrophil count (/㎕)	N	17	17	0.2746‡
	Mean±S.D.	1520.71±647.23	1780.53±713.95	
	Median[Min, Max]	1519[632,3012]	1579[608,2880]	
	Normal	6 (35.29)	7 (41.18)	0.7242†
	Abnormal NCS	11 (64.71)	10 (58.82)	
	Abnormal CS	0 (0)	0 (0)	
Blood Chemistry Test				
Calcium (mg/dL)	N	17	17	0.6589‡
	Mean±S.D.	10.54±0.36	10.6±0.4	
	Median[Min, Max]	10.6[9.8,11]	10.5[10,11.6]	
	Normal	8 (47.06)	10 (58.82)	0.4920†
	Abnormal NCS	9 (52.94)	7 (41.18)	
	Abnormal CS	0 (0)	0 (0)	
Phosphorus (mg/dL)	N	17	17	0.4605‡
	Mean±S.D.	6.4±0.67	6.22±0.75	
	Median[Min, Max]	6.4[5.2,7.6]	6.4[5.1,7.6]	
	Normal	0 (0)	0 (0)	-
	Abnormal NCS	17 (100.00)	17 (100.00)	
	Abnormal CS	0 (0)	0 (0)	
Glucose (mg/dL)	N	17	17	0.4075*
	Mean±S.D.	98.06±10.65	95.53±10.48	
	Median[Min, Max]	94[83,128]	93[82,120]	
	Normal	15 (88.24)	15 (88.24)	1.0000§
	Abnormal NCS	2 (11.76)	2 (11.76)	
	Abnormal CS	0 (0)	0 (0)	
Blood urea nitrogen (mg/dL)	N	17	17	0.5305‡
	Mean±S.D.	7.47±2.74	6.88±2.67	
	Median[Min, Max]	7[2,12]	7[3,12]	

	Normal	3 (17.65)	4 (23.53)	1.0000§
	Abnormal NCS	14 (82.35)	13 (76.47)	
	Abnormal CS	0 (0)	0 (0)	
Uric acid (mg/dL)	N	17	17	0.9725*
	Mean±S.D.	3±0.78	3.02±0.96	
	Median[Min, Max]	2.8[1.9,4.4]	2.9[1.6,5.4]	
	Normal	8 (47.06)	6 (35.29)	0.4858†
	Abnormal NCS	9 (52.94)	11 (64.71)	
	Abnormal CS	0 (0)	0 (0)	
Cholesterol (mg/dL)	N	17	17	0.5632‡
	Mean±S.D.	158.53±28.2	164.35±29.89	
	Median[Min, Max]	155[107,210]	164[114,224]	
	Normal	17 (100.00)	17 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	
Total protein (g/dL)	N	17	17	0.9171‡
	Mean±S.D.	6.27±0.41	6.25±0.56	
	Median[Min, Max]	6.2[5.7,6.9]	6.3[5.2,7.5]	
	Normal	13 (76.47)	12 (70.59)	1.0000§
	Abnormal NCS	4 (23.53)	5 (29.41)	
	Abnormal CS	0 (0)	0 (0)	
Albumin (g/dL)	N	17	17	0.6510*
	Mean±S.D.	4.28±0.25	4.34±0.32	
	Median[Min, Max]	4.3[3.9,4.6]	4.3[3.9,4.9]	
	Normal	17 (100.00)	17 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	
Total bilirubin (mg/dL)	N	17	17	0.0840*
	Mean±S.D.	1.58±3.04	2.93±4.39	
	Median[Min, Max]	0.6[0.1,12]	1[0.3,16.3]	
	Normal	13 (76.47)	12 (70.59)	0.2150§
	Abnormal NCS	4 (23.53)	2 (11.76)	
	Abnormal CS	0 (0)	3 (17.65)[2)]	
Alkaline phosphatase (IU/L)	N	17	17	0.1130*
	Mean±S.D.	257.18±82.36	315.82±104.72	
	Median[Min, Max]	249[163,455]	308[160,516]	
	Normal	14 (82.35)	7 (41.18)	0.0420§
	Abnormal NCS	3 (17.65)	8 (47.06)	
	Abnormal CS	0 (0)	2 (11.76)[3)]	

Aspartate aminotransferase (IU/L)	N	17	17	0.7827*
	Mean±S.D.	44.29±18.93	43.41±15.1	
	Median[Min, Max]	41[22,103]	38[28,75]	
	Normal	8 (47.06)	11 (64.71)	0.3001†
	Abnormal NCS	9 (52.94)	6 (35.29)	
	Abnormal CS	0 (0)	0 (0)	
Alanine aminotransferase (IU/L)	N	17	17	0.6891‡
	Mean±S.D.	30.12±17.4	27.94±13.83	
	Median[Min, Max]	27[0,67]	26[7,58]	
	Normal	13 (76.47)	13 (76.47)	1.0000§
	Abnormal NCS	4 (23.53)	4 (23.53)	
	Abnormal CS	0 (0)	0 (0)	
Creatinine (mg/dL)	N	17	17	0.7572‡
	Mean±S.D.	0.26±0.05	0.26±0.06	
	Median[Min, Max]	0.25[0.21,0.35]	0.25[0.18,0.41]	
	Normal	0 (0)	0 (0)	-
	Abnormal NCS	17 (100.00)	17 (100.00)	
	Abnormal CS	0 (0)	0 (0)	
Natrium (mmol/L)[1)]	N	17	16	0.8742‡
	Mean±S.D.	136.41±1.42	136.5±1.75	
	Median[Min, Max]	136[133,139]	136[134,141]	
	Normal	16 (94.12)	14 (87.50)	0.6012§
	Abnormal NCS	1 (5.88)	2 (12.50)	
	Abnormal CS	0 (0)	0 (0)	
Potassium (mmol/L)[1)]	N	17	16	0.2244‡
	Mean±S.D.	5.02±0.58	5.29±0.67	
	Median[Min, Max]	5.1[4.2,6.6]	5.25[4.1,6.7]	
	Normal	16 (94.12)	11 (68.75)	0.1473§
	Abnormal NCS	1 (5.88)	3 (18.75)	
	Abnormal CS	0 (0)	2 (12.50)[4)]	
Chlorine (mmol/L)[1)]	N	17	16	0.3901‡
	Mean±S.D.	104.12±1.9	104.69±1.85	
	Median[Min, Max]	105[100,107]	104.5[102,108]	
	Normal	17 (100.00)	16 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	
Total carbon dioxide (mmol/L)[1)]	N	17	16	0.1248*
	Mean±S.D.	22.41±2.06	21.56±2.61	

	Median[Min, Max]	23[19,27]	21[19,29]	
	Normal	3 (17.65)	2 (12.50)	1.0000§
	Abnormal NCS	14 (82.35)	14 (87.50)	
	Abnormal CS	0 (0)	0 (0)	
Urinalysis				
Color	Dark yellow	4 (23.53)	6 (35.29)	0.8476§
	Colorless	12 (70.59)	10 (58.82)	
	Yellow	1 (5.88)	1 (5.88)	
	Normal	17 (100.00)	17 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	
Turbidity	Clear	17 (100.00)	17 (100.00)	-
	Normal	17 (100.00)	17 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	
Specific gravity	N	17	17	0.5202*
	Mean±S.D.	1.006±0.003	1.010±0.007	
	Median[Min, Max]	1.005[1.003,1.01]	1.007[1.002,1.02]	
	Normal	13 (76.47)	10 (58.82)	0.2714†
	Abnormal NCS	4 (23.53)	7 (41.18)	
	Abnormal CS	0 (0)	0 (0)	
pH	N	17	17	0.1577*
	Mean±S.D.	6.50±0.79	6.12±0.55	
	Median[Min, Max]	6.5[5.5,7.5]	6[5.5,7]	
	Normal	17 (100.00)	17 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	
Albumin	negative	17 (100.00)	13 (76.47)	0.1026§
	+/-	0 (0)	4 (23.53)	
	Normal	17 (100.00)	13 (76.47)	0.1026§
	Abnormal NCS	0 (0)	4 (23.53)	
	Abnormal CS	0 (0)	0 (0)	
Glucose	negative	17 (100.00)	17 (100.00)	-
	Normal	17 (100.00)	17 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	
Ketone	negative	17 (100.00)	17 (100.00)	-
	Normal	17 (100.00)	17 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	

	Abnormal CS	0 (0)	0 (0)	
Bilirubin	negative	17 (100.00)	17 (100.00)	-
	Normal	17 (100.00)	17 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	
Blood	negative	17 (100.00)	17 (100.00)	-
	Normal	17 (100.00)	17 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	
Urobilinogen	+/-	17 (100.00)	17 (100.00)	-
	Normal	17 (100.00)	17 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	
Nitrate	negative	17 (100.00)	16 (94.12)	1.0000§
	+	0 (0)	1 (5.88)	
	Normal	17 (100.00)	16 (94.12)	1.0000§
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	1 (5.88)[5)]	
White blood cell(s)	negative	11 (64.71)	10 (58.82)	1.0000§
	+/-	1 (5.88)	0 (0)	
	1+	3 (17.65)	3 (17.65)	
	2+	2 (11.76)	3 (17.65)	
	3+	0 (0)	1 (5.88)	
	Normal	11 (64.71)	10 (58.82)	0.7242†
	Abnormal NCS	6 (35.29)	7 (41.18)	
	Abnormal CS	0 (0)	0 (0)	
Red blood cell (/HPF)	<1	13 (76.47)	15 (88.24)	0.6562§
	1~4	4 (23.53)	2 (11.76)	
	Normal	17 (100.00)	17 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	
White blood cell (/HPF)	<1	8 (47.06)	6 (35.29)	0.9185§
	1~4	6 (35.29)	6 (35.29)	
	5~9	2 (11.76)	3 (17.65)	
	10~19	1 (5.88)	2 (11.76)	
	Normal	14 (82.35)	12 (70.59)	0.6880§
	Abnormal NCS	3 (17.65)	5 (29.41)	
	Abnormal CS	0 (0)	0 (0)	
Squamous cell (/HPF)	<1	7 (41.18)	7 (41.18)	1.0000§
	1~4	9 (52.94)	8 (47.06)	

	5~9	1 (5.88)	1 (5.88)	
	10~19	0 (0)	1 (5.88)	
	Normal	16 (94.12)	15 (88.24)	1.0000§
	Abnormal NCS	1 (5.88)	2 (11.76)	
	Abnormal CS	0 (0)	0 (0)	
Transitional cell (/HPF)	0	17 (100.00)	17 (100.00)	-
	Normal	17 (100.00)	17 (100.00)	-
	Abnormal NCS	0 (0)	0 (0)	
	Abnormal CS	0 (0)	0 (0)	

* Wilcoxon Rank Sum test, † Chi-square test, ‡ Independent T-test, § Fisher's exact test
NCS denotes not clinically significant, CS clinically significant, SD standard deviation.
[1)] One patient (S030) did not perform the test.
[2)] Total bilirubin. Abnormal CS: Neonatal jaundice, hepatobiliary disease, or breast milk jaundice is suspected.
[3)] Alkaline phosphatase. Abnormal CS: Neonatal jaundice, hepatobiliary disease, or breast milk jaundice is suspected.
[4)] Potassium Abnormal CS: high level, high level/observation.
[5)] Nitrate Abnormal CS: Urinary tract infection is suspected.

3.2.3. Baseline Hemangioma Inspection Result Analysis

The baseline hemangioma inspection results for both groups are as follows (eTable 10). The mean age (calculated by the age at diagnosis) for the propranolol group was 108.76 days and for the steroid group was 89.24 days. For both groups, the face was the most common location of hemangioma (10 cases for propranolol and 13 for steroid). MRI scans (or ultrasound examinations) were conducted for all subjects and the mean hemangioma volume was 14125.35mm^3 for the propranolol group and 9349.54mm^3 for the steroid group. Although the mean volume for the steroid group was higher, there was no significant difference. An image of the lesion region was taken for all groups and the mean area for the propranolol group was 1318.06mm^2 while the mean area for the steroid group was 1093.51mm^2. As with the volume, there was no statistically significant difference between the two groups. In addition, most of the lesions were red in color. One patient from each group had an ulceration and two patients from the propranolol showed re-epithelization.

eTable 10. Results of baseline hemangioma inspection

	Propranolol (N=17)	Steroid (N=17)	P-value
Age at diagnosis (day)[1)]			
N	17	17	0.3652‡
Mean±S.D.	108.76±65	89.24±58.81	
Median[Min, Max]	85[9,247]	73[24,242]	
Location			
- Scalp	1 (5.88)	2 (11.76)[3)]	1.0000§
- Face	10 (58.82)[2)]	13 (76.47)	0.4646§
- Neck	0 (0)	0 (0)	-
- Chest	2 (11.76)[2)]	0 (0)	0.4848§
- Abdomen	1 (5.88)	0 (0)	1.0000§
- Back	1 (5.88)	0 (0)	1.0000§
- Upper extremity	3 (17.65)	2 (11.76)	1.0000§
- Lower extremity	0 (0)	1 (5.88)[3)]	1.0000§
- genitalia	0 (0)	0 (0)	-
- Internal organs (viscera, liver, etc.)	0 (0)	0 (0)	-
MRI			
- No	0 (0)	0 (0)	-
➔ Yes	17 (100.00)	17 (100.00)	
■ size (mm^3)			
Mean±S.D.	14125.35±18246.77	9349.54±16015.69	0.3348*
Median[Min, Max]	6120[370.8,62197]	4048[304,67877.4]	
Medical photo			
- No	0 (0)	0 (0)	-
- Yes	17 (100.00)	17 (100.00)	
Size			
■ Long axis (mm)			
N	17	17	0.7779‡
Mean±S.D.	38.47±24.31	36.18±22.69	
Median[Min, Max]	32[6,101]	30[10,77]	
■ Short axis (mm)			
N	17	17	0.8631*
Mean±S.D.	29.82±23.97	27.88±19.31	
Median[Min, Max]	21[6,92]	22[8,68]	
■ Surface area (mm^2)			
N	17	17	1.0000*
Mean±S.D.	1318.06±1833.07	1093.51±1316.68	

Median[Min, Max]	549.5[28.3,7294.2]	490.6[62.8,3826.9]	
Color			
- Red	11 (64.71)	14 (82.35)	0.4766§
- Purple	2 (11.76)	1 (5.88)	
- Blue	1 (5.88)	0 (0.00)	
- Gray	0 (0.00)	1 (5.88)	
- Apricot	0 (0)	0 (0)	
- Others	3 (17.65)	1 (5.88)	
Pupple / Blue	1	0	
Red / Blue	0	1	
Red to Pupple	1	0	
Red-Pupple	1	0	
Height (mm)			
N	17	17	0.4954‡
Mean±S.D.	4.26±2.22	3.71±2.49	
Median[Min, Max]	5[0.5,10]	3[1,9]	
Ulcer			
- No	16 (94.12)	16 (94.12)	1.0000§
➔ Yes	1 (5.88)	1 (5.88)	
■ Long axis (mm)			
N	1	1	-
Mean±S.D.	12±.	7±.	
Median[Min, Max]	12[12,12]	7[7,7]	
■ Short axis (mm)			
N	1	1	-
Mean±S.D.	4±.	7±.	
Median[Min, Max]	4[4,4]	7[7,7]	
■ Surface area (mm^2)			
N	1	1	-
Mean±S.D.	37.7±.	38.5±.	
Median[Min, Max]	37.7[37.7,37.7]	38.5[38.5,38.5]	
Re-epithelization			
- No	15 (88.24)	17 (100.00)	0.4848§
- Yes	2 (11.76)	0 (0.00)	

* Wilcoxon Rank Sum test, ‡ Independent T-test, § Fisher's exact test
SD denotes standard deviation.
[1)] Age at diagnosis = Date of diagnosis – Date of birth
[2)] Two lesions in one propranolol group (Face, Chest/S026)
[3)] One case overlapped in steroid group (Scalp, Lower extremity/S002)

After hearing each patient's medical history, it was found that the mean age when hemangioma began was 0.68 months for the propranolol group and 0.50 months for the steroid group. The mean period when hemangioma grew the most was 3.12 months for the propranolol group and 2.53 for the steroid group. In the two groups, there was a total of 3 family members who also had hemangioma (propranolol group: patient's mother, steroid group: two female cousins). Furthermore, there was no statistically significant difference in change between the two groups.

eTable 11. History taking of patients

	Propranolol (N=17)	Steroid (N=17)	P-value
History			
■ found at birth			
- Yes	2 (11.76)	4 (23.53)	0.6562§
- No	15 (88.24)	13 (76.47)	
■ Herald sign			
- Yes	0 (0)	3 (17.65)	0.2273§
- No	17 (100.00)	14 (82.35)	
■ Starting time of growth			
N	17	17	0.5267*
Mean±S.D.	0.68±0.79	0.50±0.55	
Median[Min, Max]	0.5[0,3]	0.3[0,2]	
■ The time of biggest size			
N	17	17	0.3901‡
Mean±S.D.	3.12±2.23	2.53±1.66	
Median[Min, Max]	2[0,8]	2[0,6]	
Family History			
- Yes	1 (5.88)	2 (11.76)	1.0000§
- No	16 (94.12)	15 (88.24)	
Risk factor			
■ Genetic factor			
- No	17 (100.00)	16 (94.12)	1.0000§
- Chromosomal abnormality	0 (0)	0 (0)	
- Others	0 (0)	1 (5.88)	
■ Environmental factor[1)]			
- No	7 (41.18)	10 (58.82)	0.3035†
➔ Yes	10 (58.82)	7 (41.18)	
- Maternal Smoking	3	0	
- Maternal alcohol abuse	0	0	
- Maternal drug	0	0	
- Intrauterine physical constriction	1	0	
- Preterm birth	3	3	
- Premature baby	1	2	
- Other	6	5	
Single umbilical artery	1	0	
In vitro fertilization	1	1	
Test-tube baby	0	1	

Asthma of father	0	1	
Artificial fertilization, Placenta previa	1	0	
Myoma during pregnancy	1	0	
Ovarian tumorectomy during pregnancy	0	1	
Threatened abortion	1	0	
Caesarean section	1	0	
Father on thyroid medication during pregnancy	0	1	

* Wilcoxon Rank Sum test, † Chi-square test, ‡ Independent T-test, § Fisher's exact test

SD denotes standard deviation.

[1)] Two environmental factors in one propranolol group,
Three environmental factors in one steroid group
- S002: Preterm birth, premature baby
- S009: Preterm birth, Others (Father on thyroid medication during pregnancy)
- S012: Preterm birth, premature baby
- S021: Intrauterine physical constriction, Preterm birth, premature baby, Others (Artificial fertilization, Placenta previa)
- S028: Maternal Smoking, Others (Single umbilical artery)

3.2.4. Concomitant Drug

eTable 12 shows the concomitant drugs of patients during the duration of the trial. A participant who took regular medication of at least one type of drug is classified as consuming a concomitant drug. During the duration of the trial, 60 people (100%) in the propranolol group and 4 people (44.44%) in the steroid group took a concomitant drug. In the propranolol group, there were 112 cases of concomitant drug consumption by 13 people, and in the steroid group, there were 107 cases by 14 people.

eTable 12. Concomitant drug during the duration of the trial.

	Propranolol (N=17)	Steroid (N=17)	P-value
Concomitant Drug			
- Yes	13 (76.47)	14 (82.35)	1.0000§
- No	4 (23.53)	3 (17.65)	

§ Fisher's exact test

In the propranolol group, the most commonly consumed concomitant drug was Hydrocortisone (D07AA02) (8 cases, 5 people), N02BE01 (Acetaminophen) (8 cases, 6 people), and A07FA01 (Bacillus licheniformis, Ramnos Granule, Medilac-S Powder) (6 cases, 6 people). In the steroid group, the most commonly consumed concomitant drug was R01BA53 (Comy Syrup, Coben Syrup, Colmin-A Syrup) (10 cases/4 people) and A07FA01 (Bacillus licheniformis, Ramnos Granule, Medilac-S Powder) (6 cases, 5 people) according to eTable 13.

eTable 13. Concomitant drug history (unit: number)

			No. of patients		No. of events	
			Propranolol (N=17)	Steroid (N=17)	Propranolol (N=70)	Steroid (N=60)
ATC code		**CM**				
A02	A02BA02	Ranitidine	0 (0)	1 (5.88)	0 (0)	1 (0.93)
A03	A03AA05	Trimebutine maleate	1 (5.88)	0 (0)	1 (0.89)	0 (0)
	A03FA03	Domperidone	2 (11.76)	3 (17.65)	2 (1.79)	4 (3.74)
A07	A07BC05	Dioctahedral smectite	2 (11.76)	1 (5.88)	3 (2.68)	1 (0.93)
	A07DA03	Lopmin Capsule	1 (5.88)	0 (0)	1 (0.89)	0 (0)
	A07FA01	Bacillus licheniformis, Ramnos granule, Medilac-S powder	6 (35.29)	5 (29.41)	6 (5.36)	6 (5.61)
	A07FA02	Olybiol-S capsule, Saccharomyces Boulardii	2 (11.76)	1 (5.88)	2 (1.79)	2 (1.87)
	A07FA5	Bacillus subtilis	0 (0)	1 (5.88)	0 (0)	1 (0.93)
A09	A09AA04	Beta-galactosidase	1 (5.88)	0 (0)	1 (0.89)	0 (0)
D01	D01AC05	Isoconazole Nitrate	1 (5.88)	0 (0)	1 (0.89)	0 (0)
D06	D06AX09	Mupirocin	0 (0)	1 (5.88)	0 (0)	1 (0.93)
D07	D07AA02	Hydrocortisone	5 (29.41)	1 (5.88)	11 (9.82)	1 (0.93)
	D07AA03	Prednisolone valeroacetate	1 (5.88)	2 (11.76)	6 (5.36)	3 (2.8)
	D07AB08	Desonide	1 (5.88)	0 (0)	1 (0.89)	0 (0)
	D07AC18	Prednicarbate	3 (17.65)	0 (0)	3 (2.68)	0 (0)
H02	H02AB04	Methylprednisolone	0 (0)	1 (5.88)	0 (0)	1 (0.93)
	H02AB06	Prednisolone	3 (17.65)	0 (0)	3 (2.68)	0 (0)
J01	J01CA04	Amoxicillin	4 (23.53)	2 (11.76)	5 (4.46)	3 (2.8)
	J01CR02	Moxamentin Duo Syrup, Amocla Duo Syrup, Augmentin Syrup, Crasigen Duo Syrup, Cramoxin Dry Syrup, Maxiclan Duo Syrup, Duonex Dry Syrup	4 (23.53)	4 (23.53)	5 (4.46)	6 (5.61)
	J01DC04	Cefaclor	0 (0)	1 (5.88)	0 (0)	1 (0.93)
	J01DD08	Cefixime	0 (0)	1 (5.88)	0 (0)	1 (0.93)
	J01DD15	Cefdinir	0 (0)	1 (5.88)	0 (0)	2 (1.87)
	J01FA09	Clarithromycin	0 (0)	1 (5.88)	0 (0)	2 (1.87)
	J01FA10	Azithromycin	0 (0)	1 (5.88)	0 (0)	1 (0.93)
J05	J05AX05	Inosiplex	1 (5.88)	0 (0)	1 (0.89)	0 (0)
J07	J07AG51	ActHib	0 (0)	1 (5.88)	0 (0)	1 (0.93)
	J07CA02	Infanrix-IPV	0 (0)	2 (11.76)	0 (0)	2 (1.87)
M01	M01AE01	Ibuprofen	0 (0)	2 (11.76)	0 (0)	2 (1.87)
	M01AE14	Dexibuprofen, Dexpanthenol	5 (29.41)	1 (5.88)	6 (5.36)	1 (0.93)
M09	M09AB	Mucolase Tab, Ceratase Tab, Serronase Tab Duonase Tab, Leodase Tab.	1 (5.88)	4 (23.53)	3 (2.68)	6 (5.61)
N02	N02BE01	Acetaminophen	6 (35.29)	4 (23.53)	8 (7.14)	5 (4.67)

N05	N05BB01	Hydroxyzine, Hydroxyzine HCl	3 (17.65)	0 (0)	4 (3.57)	0 (0)
R01	R01BA02	Pseudoephedrine, Pseudoephedrine HCl	1 (5.88)	1 (5.88)	2 (1.79)	1 (0.93)
	R01BA52	Actifed Syrup	0 (0)	2 (11.76)	0 (0)	2 (1.87)
	R01BA53	Comy Syrup, Coben Syrup, Colmin-A Syrup	5 (29.41)	4 (23.53)	6 (5.36)	10 (9.35)
R03	R03CC	Formoterol fumarate	2 (11.76)	2 (11.76)	2 (1.79)	2 (1.87)
	R03CC11	Tulobuterol	2 (11.76)	1 (5.88)	2 (1.79)	1 (0.93)
	R03DC02	Pranlukast hydrate	1 (5.88)	0 (0)	1 (0.89)	0 (0)
R05	R05CA12	Hederae helix fluid, Ivy leaf dried extract	1 (5.88)	3 (17.65)	1 (0.89)	3 (2.8)
	R05CB01	Acetylcysteine	3 (17.65)	3 (17.65)	4 (3.57)	6 (5.61)
	R05CB03	S-carboxymethylcysteine	2 (11.76)	0 (0)	3 (2.68)	0 (0)
	R05CB10	Ambrocol Tab, Konitop Syrup, ambrocol syrup, ROXOL-C syrup	1 (5.88)	2 (11.76)	1 (0.89)	5 (4.67)
	R05CB15	Erdosteine	0 (0)	1 (5.88)	0 (0)	1 (0.93)
	R05DB21	Privituss Suspension	0 (0)	1 (5.88)	0 (0)	2 (1.87)
	R05FA	Codenal Solution, Codenal Tab, Codaewon Syrup, Cough Syrup	2 (11.76)	4 (23.53)	2 (1.79)	5 (4.67)
R06	R06A	bepotastine calcium dihydrate	0 (0)	1 (5.88)	0 (0)	3 (2.8)
	R06AB04	Chlorpheniramine, Chlorpheniramine Maleate	2 (11.76)	3 (17.65)	5 (4.46)	5 (4.67)
	R06AD07	Mequitazine	1 (5.88)	1 (5.88)	3 (2.68)	1 (0.93)
	R06AE09	Levocetirizine HCl	0 (0)	1 (5.88)	0 (0)	1 (0.93)
	R06AX17	Ketotifen,Ketotifen Fumarate	2 (11.76)	0 (0)	2 (1.79)	0 (0)
	R06CB06	Ambroxol hydrochloride	0 (0)	1 (5.88)	0 (0)	1 (0.93)
R07	R07AX	Skamin Syrup, Umckamin Syrup, Canium Syrup, Pelagon Syrup, Pelarum Syrup	3 (17.65)	2 (11.76)	3 (2.68)	2 (1.87)
S01	S01AA30	Terramycin Eye ointment, Oxytetracycline, Terramycin	2 (11.76)	2 (11.76)	2 (1.79)	2 (1.87)

ATC denotes anatomic therapeutic chemical, CM concomitant medication.

4. Results of Efficacy Evaluation

4.1. Primary Efficacy Evaluation

The primary efficacy variable is the treatment response using hemangioma volume measured by an MRI scan or ultrasound examination (when the patient or guardian refused an MRI scan for a number of reasons).

The response of treatment 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 our analysis, all missing values in the ITT group and ITT group applying MI were replaced with “Reaction” or “Non-reaction” and categorized into two groups: ITT group and PP group. The final research results were results from the ITT analysis group applying MI. MI was used to predict the Reaction/Non-reaction of the secondary efficacy variables size (area), proliferative stop time point, regression time point, color, ulceration size, and presence of re-epithelization.

4.1.1. Missing Value Adjustment by Applying Multiple Imputation

For the ITT analysis group applying MI, the treatment response rate in the propranolol group was 95.65% and that of the steroid group was 91.94%. The difference in response rates between the two groups was 3.71%, and the 95% confidence interval was [-15.43, 22.84]. Because the lower limit of the confidence interval (-15.43%) was greater than -20%, it can be said that propranolol is non-inferior. Also, differences in response rate between the two groups are not significant. (P-value=0.7041)

eTable 14. Treatment response rate (ITT analysis group applying multiple imputation)

	Propranolol (N=17)	Steroid (N=17)	Difference in response rate p_t-p_c [95% C.I.]	P-value
Treatment response rate (applying MI)[1)]				
- Reaction	95.65	91.94	3.71	0.7041†
- Non-reaction	4.35	8.06	[-15.43,22.84]	

† One-sample t-test
ITT denotes intention to treat, MI multiple imputation, CI confidence interval.

[1)] 100 times imputation were applied. Difference in response rate and its confidence interval is the summary of 100 results.[12]

4.1.2. Missing Value Adjustment by Replacement with "Non-reaction"

As a result of the analysis of supplementary validation results for four subjects with missing values (which were replaced with "Non-reaction"), the treatment response rate in the propranolol group was 94.12% and that of the steroid group was 82.35%. The Fisher's Exact test result was that the treatment response rates between the two groups could not be said to be different. The difference in response rates between the two groups was 11.76%, and the 95% confidence interval was [-9.53, 33.06]. Because the lower limit of the confidence interval (-9.53%) was greater than -20%, it can be said that is non-inferior.

eTable 15. Treatment response rate (ITT analysis group replaced with "Non-reaction")

	Propranolol (N=17)	**Steroid (N=17)**	**Difference in response rates p_t-p_c [95% C.I.]**	**P-value**
Treatment response rate ("Non-reaction") – no. of patients (%)				
- Reaction	16 (94.12)	14 (82.35)	11.76	0.6012**
- Non-reaction	1 (5.88)	3 (17.65)	[-9.53,33.06]	

** Fisher's Exact test
ITT denotes intention to treat, CI confidence interval.

4.1.3. Missing Value Adjustment by Replacement with "Reaction"

Analysis of supplementary validation results for four subjects with missing values (also replaced with "reactive") revealed the same results (non-inferior). Since the lower limit of the 95% confidence interval (-18.65, 18.65) is greater than -20%, it is non-inferior.

eTable 16.Treatment response rate (Missing values were replaced with "Reaction")

	Propranolol (N=17)	Steroid (N=17)	Difference in response rates p_t-p_c [95% C.I.]	P-value
Treatment response rate ("Reaction") – no. of patients (%)				
- Reaction	17 (100)	17 (100)	0	-
- Non-reaction	0 (0)	0 (0)	[-18.65,18.65][1)]	

[1)] R software (R for Windows, version 3.1.2/R package – ExactCIdiff)
CI denotes confidence interval.

4.1.4. Primary Efficacy Evaluation (PP population)

In the case of the PP group, the 4 participants with missing values were excluded and the difference in response rate between the two groups was found to be 0%. The 95% confidence interval was [-20.59, 23.16] and because the lower limit is smaller than -20%, we cannot say that it is non-inferior.

eTable 17.Treatment response rate (PP population)

	Propranolol (N=17)	**Steroid (N=17)**	**Difference in response rates p_t-p_c [95% C.I.]**	**P-value**
Treatment response rate (PP population) – no. of patients (%)				
- Reaction	16 (100)	14 (100)	0	-
- Non-reaction	0 (0)	0 (0)	[-20.59,23.16][1)]	

[1)] Calculated by using R software (R for Windows, version 3.1.2/R package – ExactCIdiff)
PP denotes per protocol, CI confidence interval.

4.2. Secondary Efficacy Evaluation

In this study, the secondary efficacy variable was 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 were calculated for continuous data and the frequency and percentage was presented for categorical data.

4.2.1. Size (Volume) of Hemangioma

The rate of change of size (volume) of hemangioma is defined as following;

$$\text{The rate of change of size(volume) of hemangioma(\%)} = \frac{\text{Volume of hemangioma measured in week 16(visit 6)} - \text{Volume of hemangioma measured in baseline(visit 1)}}{\text{Volume of hemangioma measured in baseline(visit 1)}}$$

The mean, standard deviation, and other descriptive statistics used to assess the response of treatment are presented in eTable 18. Independent t-test evaluates the difference between the means of rate of change of volume of hemangioma in the propranolol group and steroid group.

The volume reduction change (%) in the propranolol group was 55.87% and that of the steroid group was 46.52%. The rate of change for the propranolol group was higher than that of the steroid group, but there was no statistically significant difference.

eTable 18. Changes of hemangioma volume

	Propranolol (N=17)	**Steroid (N=17)**	**P-value**
Changes of Volume %)			
N	16	14	0.2684†
Mean±S.D.	-55.87±18.92	-46.52±26.24	
Median[Min, Max]	-62.76[-78.24,-20.49]	-48.17[-80.2,-3.83]	

† Independent T-test
SD denotes standard deviation.

4.2.2. Size (surface area) of Hemangioma

The mean, standard deviation, median, minimum and maximum values of the size of hemangioma for each group, time point, and interaction between group and time points are shown in eTable 19. Generalized estimating equation (GEE) was 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. Differences between groups, time points, and interaction (group * time point) were all not significant (P-value=0.5819, 0.1649, 0.2818 respectively). Thus, it cannot be said that there is a difference between the two groups in the change in hemangioma size. However, although controlling for time did not result in a statistically significant difference (P-value=0.8542, 0.8815, 0.7076), controlling for group did (P-value=0.0148, 0.0077, 0.0405). The average size of hemangioma decreased over time, regardless of the group.

eTable 19. Size (surface area) of hemangioma

		Size of hemangioma		
		Long axis(mm)	**Short axis(mm)**	**Surface area(mm^2)**
Group				
Propranolol	N	119	119	119
	Mean±S.D.	33.91±24.73	24.31±21.6	1050.28±1707.87
	Median[Min, Max]	28[5,110]	16[2,95]	361.1[11,8203.3]
Steroid	N	107	107	107
	Mean±S.D.	31.6±21.37	22.24±15.12	782.29±961.55
	Median[Min, Max]	28[5,77]	17[4,68]	423.9[18.8,3826.9]
Time point				
Visit 1 (Screening)	N	34	34	34
	Mean±S.D.	37.32±23.18	28.85±21.45	1205.79±1575.66
	Median[Min, Max]	31.5[6,101]	21.5[6,92]	520.05[28.3,7294.2]
Visit 2 (Week 1)	N	32	32	32
	Mean±S.D.	34.81±23.61	25.13±19.19	1013.19±1428.78
	Median[Min, Max]	30[6,108]	18.5[4,80]	437.25[18.8,6782.4]
Visit 3 (Week 4)	N	32	32	32
	Mean±S.D.	33.78±24.13	23.72±18.93	959.87±1423.59
	Median[Min, Max]	30[6,110]	17.5[4,80]	412.15[23.6,6908]
Visit 4 (Week 8)	N	32	32	32
	Mean±S.D.	32.5±23.63	22.72±19.77	917.21±1568.63
	Median[Min, Max]	28[5,110]	16[3,95]	380.75[19.6,8203.3]
Visit 5 (Week 12)	N	32	32	32

		Mean±S.D.	31.44±23.35	21.72±17.58	832.28±1354.75
		Median[Min, Max]	26[5,110]	15.5[3,80]	337.55[19.6,6908]
Visit 6 (Week 16)		N	32	32	32
		Mean±S.D.	30.22±22.79	20.88±17.5	781.45±1311.87
		Median[Min, Max]	26[5,105]	15[3,80]	318.3[19.6,6594]
Visit 7 (Week 20)		N	32	32	32
		Mean±S.D.	29.34±22.73	19.97±16.87	736.37±1226.45
		Median[Min, Max]	25[5,102]	15[2,75]	311.65[11,6005.3]
Group*Time point					
Visit 1 (Screening)	**Propranolol**	N	17	17	17
		Mean±S.D.	38.47±24.31	29.82±23.97	1318.06±1833.07
		Median[Min, Max]	32[6,101]	21[6,92]	549.5[28.3,7294.2]
	Steroid	N	17	17	17
		Mean±S.D.	36.18±22.69	27.88±19.31	1093.51±1316.68
		Median[Min, Max]	30[10,77]	22[8,68]	490.6[62.8,3826.9]
Visit 2 (Week 1)	**Propranolol**	N	17	17	17
		Mean±S.D.	36.76±25.66	27.18±22.09	1189.75±1738
		Median[Min, Max]	30[6,108]	20[6,80]	447.5[28.3,6782.4]
	Steroid	N	15	15	15
		Mean±S.D.	32.6±21.73	22.8±15.7	813.1±993.64
		Median[Min, Max]	30[6,77]	17[4,55]	427[18.8,3324.5]
Visit 3 (Week 4)	**Propranolol**	N	17	17	17
		Mean±S.D.	35.76±26.49	25.59±22.38	1145.69±1765.08
		Median[Min, Max]	25[8,110]	20[4,80]	361.1[31.4,6908]
	Steroid	N	15	15	15
		Mean±S.D.	31.53±21.83	21.6±14.55	749.27±915.14
		Median[Min, Max]	30[6,75]	17[5,55]	423.9[23.6,3238.1]
Visit 4 (Week 8)	**Propranolol**	N	17	17	17
		Mean±S.D.	33.88±25.7	24.41±23.92	1094.68±1996.15
		Median[Min, Max]	28[6,110]	17[3,95]	361.1[23.6,8203.3]
	Steroid	N	15	15	15
		Mean±S.D.	30.93±21.83	20.8±14.29	716.07±901.68
		Median[Min, Max]	28[5,75]	15[4,55]	423.9[19.6,3238.1]
Visit 5 (Week 12)	**Propranolol**	N	17	17	17
		Mean±S.D.	32.59±25.33	22.53±20.63	951.75±1693.61
		Median[Min, Max]	25[5,110]	16[3,80]	345.4[19.6,6908]
	Steroid	N	15	15	15
		Mean±S.D.	30.13±21.68	20.8±14.01	696.88±865.42

		Median[Min, Max]	27[5,73]	15[4,54]	329.7[19.6,3094.5]
Visit 6 (Week 16)	**Propranolol**	N	17	17	17
		Mean±S.D.	30.59±24.47	21.12±20.52	866.09±1635.07
		Median[Min, Max]	25[5,105]	15[3,80]	294.4[19.6,6594]
	Steroid	N	15	15	15
		Mean±S.D.	29.8±21.56	20.6±14.02	685.52±858.42
		Median[Min, Max]	27[5,73]	15[4,54]	329.7[19.6,3094.5]
Visit 7 (Week 20)	**Propranolol**	N	17	17	17
		Mean±S.D.	29.29±24.27	19.53±19.41	785.94±1503.22
		Median[Min, Max]	25[5,102]	15[2,75]	294.4[11,6005.3]
	Steroid	N	15	15	15
		Mean±S.D.	29.4±21.71	20.47±14.12	680.19±861.29
		Median[Min, Max]	27[5,73]	15[4,54]	329.7[18.8,3094.5]
	Group	**P-value[1)]**	0.8542	0.8815	0.7076
	Time of visit	**P-value[2)]**	0.0148	0.0077	0.0405

SD denotes standard deviation. [1)] GEE; effect of treatment [2)] GEE; effect of time point

4.2.3. Color of Hemangioma

Frequency and percentage of color of hemangioma by group, time and group*time effects are shown in eTable 20. Most hemangiomas were either red or blue in color and never apricot. Results from generalized estimating equation (GEE) showed that group, time, group*time effects were all nonsignificant.

eTable 20. Color of hemangioma

		Color								P-value
		Red	Red /Purple	Purple	Red /Blue	Purple /Blue	Blue	Gray	Pink	
Group										
Propranolol		94 (78.99)	5 (4.20)	5 (4.20)	0 (0)	2 (1.68)	12 (10.08)	0 (0)	1 (0.84)	0.6072[1)]
Steroid		92 (85.98)	0 (0)	3 (2.80)	2 (1.87)	0 (0)	3 (2.80)	7 (6.54)	0 (0)	
Time point										
Visit 1 (Screening)		25 (73.53)	2 (5.88)	3 (8.82)	1 (2.94)	1 (2.94)	1 (2.94)	1 (2.94)	0 (0)	0.1114[2)]
Visit 2 (Week 1)		25 (78.13)	0 (0)	3 (9.38)	1 (3.13)	1 (3.13)	1 (3.13)	1 (3.13)	0 (0)	
Visit 3 (Week 4)		27 (84.38)	0 (0)	1 (3.13)	0 (0)	0 (0)	2 (6.25)	1 (3.13)	1 (3.13)	
Visit 4 (Week 8)		26 (81.25)	1 (3.13)	1 (3.13)	0 (0)	0 (0)	3 (9.38)	1 (3.13)	0 (0)	
Visit 5 (Week 12)		27 (84.38)	1 (3.13)	0 (0)	0 (0)	0 (0)	3 (9.38)	1 (3.13)	0 (0)	
Visit 6 (Week 16)		27 (84.38)	1 (3.13)	0 (0)	0 (0)	0 (0)	3 (9.38)	1 (3.13)	0 (0)	
Visit 7 (Week 20)		29 (90.63)	0 (0)	0 (0)	0 (0)	0 (0)	2 (6.25)	1 (3.13)	0 (0)	
Group*Time point										
Visit 1 (Screening)	**Propranolol**	11 (64.71)	2 (11.76)	2(11.76)	0 (0)	1 (5.88)	1 (5.88)	0(0)	0(0)	
	Steroid	14 (82.35)	0 (0)	1 (5.88)	1 (5.88)	0 (0)	0 (0)	1 (5.88)	0 (0)	
Visit 2 (Week 1)	**Propranolol**	13 (76.47)	0 (0)	2(11.76)	0 (0)	1 (5.88)	1 (5.88)	0 (0)	0 (0)	
	Steroid	12 (80.00)	0 (0)	1 (6.67)	1 (6.67)	0 (0)	0 (0)	1 (6.67)	0 (0)	
Visit 3 (Week 4)	**Propranolol**	14 (82.35)	0 (0)	0 (0)	0 (0)	0 (0)	2 (11.76)	0 (0.00)	1 (5.88)	
	Steroid	13 (86.67)	0 (0)	1 (6.67)	0 (0)	0 (0)	0 (0)	1 (6.67)	0 (0)	
Visit 4 (Week 8)	**Propranolol**	13 (76.47)	1 (5.88)	1 (5.88)	0 (0)	0 (0)	2 (11.76)	0 (0.00)	0 (0)	
	Steroid	13 (86.67)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6.67)	1 (6.67)	0 (0)	
Visit 5 (Week 12)	**Propranolol**	14 (82.35)	1 (5.88)	0 (0)	0 (0)	0 (0)	2 (11.76)	0 (0.00)	0 (0)	
	Steroid	13 (86.67)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6.67)	1 (6.67)	0 (0)	
Visit 6 (Week 16)	**Propranolol**	14 (82.35)	1 (5.88)	0 (0)	0 (0)	0 (0)	2 (11.76)	0 (0.00)	0 (0)	
	Steroid	13 (86.67)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6.67)	1 (6.67)	0 (0)	
Visit 7 (Week 20)	**Propranolol**	15 (88.24)	0 (0)	0 (0)	0 (0)	0 (0)	2 (11.76)	0 (0.00)	0 (0)	
	Steroid	14 (93.33)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (6.67)	0 (0)	

[1)] GEE; effect of treatment
[2)] GEE; effect of time point

4.2.4. Re-epithelization

The frequency and percentage of re-epithelization by group, time and group by time interaction are shown in eTable 21. There were 8 cases of re-epithelization in the propranolol group and 4 cases in the steroid group during the entire research period. Of the 34 total participants, re-epithelization occurred for 2 people (both in the propranolol group) during Visit 1 (screening). For Visits 1 (screening) and 2 (week 1), re-epithelization only occurred for participants in the propranolol group. Re-epithelization cases were observed in both groups for Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12). In Visit 6 (Week 16), only the steroid group saw a case of re-epithelization. No cases of re-epithelization were observed in Visit 7 (Week 20).

Penalized maximum likelihood method was used to evaluate significance instead of GEE (generalized estimating equation) because using zero as the number of re-epithelization can cause inaccurate estimation.[13] The interaction (Group*Time point) effect was not significant (P-value=0.8633) in evaluating the difference in the incidence of re-epithelization over time between the two groups. Furthermore, group (P-value=0.3169) and time point (P-value=0.9003) effects were all nonsignificant.

eTable 21. Re-epithelization

		Re-epithelization		P-value
		Yes	No	
Group				
Propranolol		8 (6.72)	111 (93.28)	0.3169[1)a)]
Steroid		4 (3.74)	103 (96.26)	
Time point				
Visit 1 (Screening)		2 (5.88)	32 (94.12)	0.9003[2)a)]
Visit 2 (Week 1)		2 (6.25)	30 (93.75)	
Visit 3 (Week 4)		3 (9.38)	29 (90.63)	
Visit 4 (Week 8)		2 (6.25)	30 (93.75)	
Visit 5 (Week 12)		2 (6.25)	30 (93.75)	
Visit 6 (Week 16)		1 (3.13)	31 (96.88)	
Visit 7 (Week 20)		0 (0.00)	32 (100.00)	
Group*Time point				
Visit 1 (Screening)	**Propranolol**	2 (11.76)	15 (88.24)	
	Steroid	0 (0.00)	17 (100.00)	
Visit 2 (Week 1)	**Propranolol**	2 (11.76)	15 (88.24)	
	Steroid	0 (0.00)	15 (100.00)	
Visit 3 (Week 4)	**Propranolol**	2 (11.76)	15 (88.24)	
	Steroid	1 (6.67)	14 (93.33)	
Visit 4 (Week 8)	**Propranolol**	1 (5.88)	16 (94.12)	
	Steroid	1 (6.67)	14 (93.33)	
Visit 5 (Week 12)	**Propranolol**	1 (5.88)	16 (94.12)	
	Steroid	1 (6.67)	14 (93.33)	
Visit 6 (Week 16)	**Propranolol**	0 (0.00)	17 (100.00)	
	Steroid	1 (6.67)	14 (93.33)	
Visit 7 (Week 20)	**Propranolol**	0 (0.00)	17 (100.00)	
	Steroid	0 (0.00)	15 (100.00)	

[1)] Logistic Regression; effect of treatment
[2)] Logistic Regression; effect of time
a: penalized likelihood was used to solve the separation problem(P-value and odds ratio can be inaccurately estimated because frequency is none or too low)

4.2.5 Ulceration

4.1.5.1. Ulceration

eTable 22 shows the frequency and percentage of ulceration presentation in patients according to group and time. During the entire duration of the clinical trial, there was one case of ulceration in the propranolol group and 2 cases in the steroid group. In Visit 1 (screening), ulceration was found in 2 out of 34 people, one per group. In Visit 2 (Week 1), there was one case from the steroid group. From Visit 3 (Week 3), no ulceration cases were observed. Results from penalized maximum likelihood method showed that interaction (Group*Time point)(P-value=0.9987), group and time point effects were all non-significant.

eTable 22. Ulceration

		Ulceration		P-value
		Yes	No	
Group				
Propranolol		1 (0.84)	118 (99.16)	0.4868[1)a)]
Steroid		2 (1.87)	105 (98.13)	
Time point				
Visit 1 (Screening)		2 (5.88)	32 (94.12)	0.7770[2)a)]
Visit 2 (Week 1)		1 (3.13)	31 (96.88)	
Visit 3 (Week 4)		0 (0.00)	32 (100.00)	
Visit 4 (Week 8)		0 (0.00)	32 (100.00)	
Visit 5 (Week 12)		0 (0.00)	32 (100.00)	
Visit 6 (Week 16)		0 (0.00)	32 (100.00)	
Visit 7 (Week 20)		0 (0.00)	32 (100.00)	
Group*Time point				
Visit 1 (Screening)	**Propranolol**	1 (5.88)	16 (94.12)	
	Steroid	1 (5.88)	16 (94.12)	
Visit 2 (Week 1)	**Propranolol**	0 (0.00)	17 (100.00)	
	Steroid	1 (6.67)	14 (93.33)	
Visit 3 (Week 4)	**Propranolol**	0 (0.00)	17 (100.00)	
	Steroid	0 (0.00)	15 (100.00)	
Visit 4 (Week 8)	**Propranolol**	0 (0.00)	17 (100.00)	
	Steroid	0 (0.00)	15 (100.00)	
Visit 5 (Week 12)	**Propranolol**	0 (0.00)	17 (100.00)	
	Steroid	0 (0.00)	15 (100.00)	
Visit 6 (Week 16)	**Propranolol**	0 (0.00)	17 (100.00)	
	Steroid	0 (0.00)	15 (100.00)	
Visit 7 (Week 20)	**Propranolol**	0 (0.00)	17 (100.00)	
	Steroid	0 (0.00)	15 (100.00)	

[1)] Logistic Regression; effect of treatment
[2)] Logistic Regression; effect of time
a: penalized likelihood was used to solve the separation problem(P-value and odds ratio can be inaccurately estimated because frequency is none or too low)

4.2.5.2. Size of Ulceration

The mean, standard deviation and other descriptive statistics of the ulceration size for each group, time point, and group by time interaction are presented in eTable 23. If no ulceration was found, the size was recorded as “0”. From Visit 3 (Week 4), no ulceration cases were observed and the size was recorded as “0”.

The group by time interaction was not significant (P-value=0.5710, 0.3666, 0.5709), thus it cannot be said that there is a difference between the two groups in the change in ulceration size.

However, although controlling for time did not result in a statistically significant difference (P-value=0.9137, 0.5534, 0.7552), controlling for group did (P-value=0.5730, 0.3692, 0.7365). The average size of ulceration decreased over time, regardless of the group.

eTable 23. Size of Ulceration

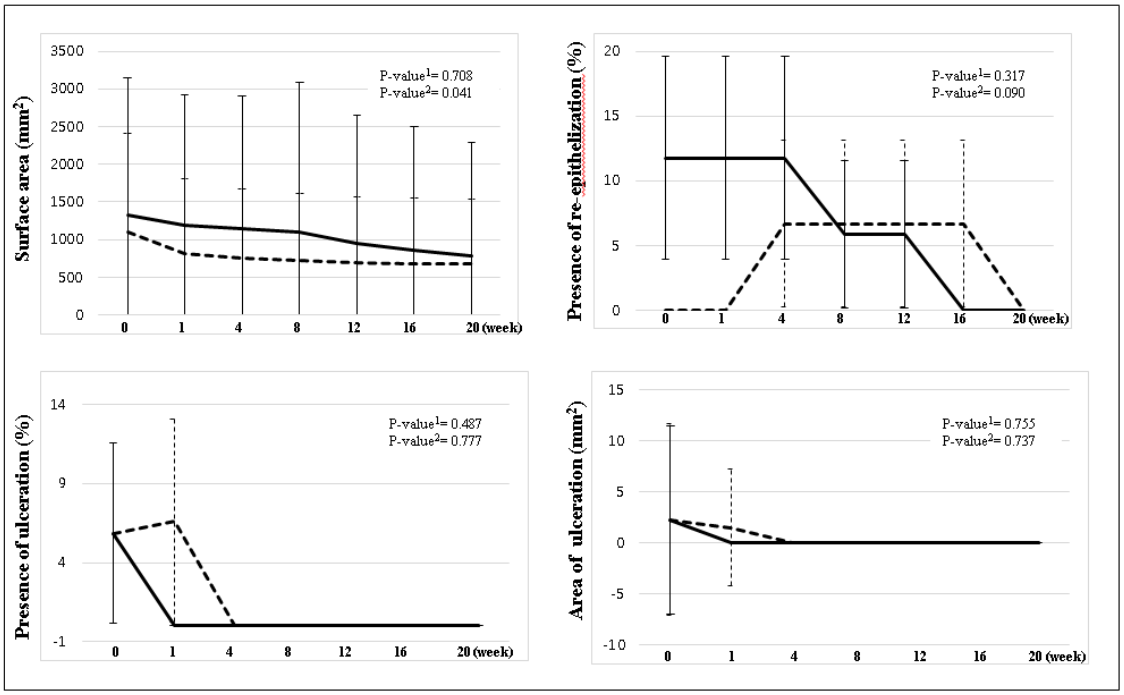
			Ulceration		
			Long axis(mm)	Short axis(mm)	Surface area (mm^2)
Group					
Propranolol		N	119	119	119
		Mean±S.D.	0.10±1.1	0.03±0.37	0.32±3.46
		Median[Min, Max]	0[0,12]	0[0,4]	0[0,37.7]
Steroid		N	107	107	107
		Mean±S.D.	0.13±0.95	0.10±0.78	0.57±4.27
		Median[Min, Max]	0[0,7]	0[0,7]	0[0,38.5]
Time point					
Visit 1 (Screening)		N	34	34	34
		Mean±S.D.	0.56±2.35	0.32±1.36	2.24±9.1
		Median[Min, Max]	0[0,12]	0[0,7]	0[0,38.5]
Visit 2 (Week 1)		N	32	32	32
		Mean±S.D.	0.22±1.24	0.13±0.71	0.69±3.89
		Median[Min, Max]	0[0,7]	0[0,4]	0[0,22]
Visit 3 (Week 4)		N	32	32	32
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
Visit 4 (Week 8)		N	32	32	32
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
Visit 5 (Week 12)		N	32	32	32
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
Visit 6 (Week 16)		N	32	32	32
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
Visit 7 (Week 20)		N	32	32	32
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
Group*Time point					
Visit 1 (Screening)	**Propranolol**	N	17	17	17
		Mean±S.D.	0.71±2.91	0.24±0.97	2.22±9.14
		Median[Min, Max]	0[0,12]	0[0,4]	0[0,37.7]
	Steroid	N	17	17	17
		Mean±S.D.	0.41±1.7	0.41±1.7	2.26±9.34

		Median[Min, Max]	0[0,7]	0[0,7]	0[0,38.5]
Visit 2 (Week 1)	**Propranolol**	N	17	17	17
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
	Steroid	N	15	15	15
		Mean±S.D.	0.47±1.81	0.27±1.03	1.47±5.68
		Median[Min, Max]	0[0,7]	0[0,4]	0[0,22]
Visit 3 (Week 4)	**Propranolol**	N	17	17	17
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
	Steroid	N	15	15	15
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
Visit 4 (Week 8)	**Propranolol**	N	17	17	17
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
	Steroid	N	15	15	15
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
Visit 5 (Week 12)	**Propranolol**	N	17	17	17
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
	Steroid	N	15	15	15
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
Visit 6 (Week 16)	**Propranolol**	N	17	17	17
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
	Steroid	N	15	15	15
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
Visit 7 (Week 20)	**Propranolol**	N	17	17	17
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
	Steroid	N	15	15	15
		Mean±S.D.	0±0	0±0	0±0
		Median[Min, Max]	0[0,0]	0[0,0]	0[0,0]
	Group	**P-value[1)]**	0.9137	0.5534	0.7552
	Time point	**P-value[2)]**	0.5730	0.3692	0.7365

SD denotes standard deviation.

[1)] P-value according to GEE; effect of treatment
[2)] P-value according to GEE; effect of time point

eFigure 1. Secondary efficacy variables. There was no significant difference between the treatment groups and time in other secondary efficacy evaluations such as hemangioma color, the presence of re-epithelization, the presence of ulceration, the size of ulceration, and medication administration (P>0.05)



4.2.6. The Time of Reaching Proliferative Stop and Regression

The median time and range of the time for reaching proliferative stop or regression after steroid or propranolol medication is presented in eTable 24. In addition, the frequency and percentage of subjects who experienced a proliferative stop or regression were calculated. The log rank test was conducted to determine the significance of the difference in time point for showing proliferative stop or regression between the steroid group and propranolol group. The time of reaching proliferative stop or regression is defined as the difference between the day at proliferative stop or regression and the day of random assignment. The difference between the day of withdrawal and the day of random assignment was used in the case of withdrawn participants.

In the case of the propranolol group, in all 17 subjects proliferation stopped or a regression occurred. The median time it took to reach proliferative stop or regression was 12 days after random assignment. For the steroid group, 15 subjects out of 17 showed proliferative stop or regression, and the median time was 11 days after random assignment. Results from a log rank test showed that there was no difference between the two groups.

eTable 24. The time of reaching proliferative stop or regression

	Propranolol (N=17)	**Steroid (N=17)**	**P-value***
Event(proliferative stop or regression)	17	15	0.3424
Censored	0	2	
- Median time(day)	12	11	
- 95% CI	[11,15]	[10,14]	

* Log-rank test
CI denotes confidence interval.

When defining regression to be a decrease of at least 25% compared to Visit 1, 13 out of 17 subjects in the propranolol group experienced regression and the median time was 62 days after random assignment. For the steroid group, regression occurred for 9 out of 17 subjects and the median time was 120 days. Conducting a log rank test resulted in no difference between the two groups.

eTable 25. The time of regression

	Propranolol (N=17)	**Steroid (N=17)**	**P-value***
Event(regression)	13	9	0.5325
Censored	4	8	
- Median time(day)	62	120	
- 95% CI	[25,155]	[15,-][1)]	

* Log-rank test
CI denotes confidence interval.
[1)] Upper bound was not estimated because of discontinuance of trial.

4.2.7. Compliance

eTable 26 shows descriptive statistics including the mean and standard deviation of medication duration and outpatient visits. Medication duration is defined as the period between the day of visit and the day of next visit if patient answered “Yes” to “Administrating medication as scheduled” questionnaire. If “No” was the answer, medication duration is defined as the period between the day of visit and the day patient stopped the medication and the sum of the periods was used in statistical analysis. The number of outpatient visits counts outpatient visits out of 7 scheduled visits.

In terms of medication administration, in Visit 2 (Week 1) all subjects from both groups were administered medication, but in Visit 3 (Week 4) four subjects from the propranolol group and one from the steroid group did not take medication. For the remaining visits, there was a subject who did not take medication. Furthermore, excluding Visit 2 (Week 1), for each visit the number of subjects who took medication was higher for the steroid group than the propranolol group. When time point was controlled for, there was no statistically significant difference at the 5% level between the two groups in terms of medical administration (P-value=0.0566). In addition, there was also no difference in terms of total medication duration and outpatient visits (P-value=0.4375, 0.1633).

eTable 26. Compliance

		Propranolol (N=17)	Steroid (N=17)	P-value
Medication				
Visit 2 (Week 1)	Yes	17 (100.00)	15 (100.00)	0.0566[2)]
	No	0 (0)	0 (0)	
Visit 3 (Week 4)	Yes	13 (76.47)	14 (93.33)	
	No	4 (23.53)	1 (6.67)	
Visit 4 (Week 8)	Yes	10 (58.82)	11 (73.33)	
	No	7 (41.18)	4 (26.67)	
Visit 5 (Week 12)	Yes	10 (58.82)	11 (73.33)	
	No	7 (41.18)	4 (26.67)	
Visit 6 (Week 16)	Yes	8 (47.06)	9 (60.00)	
	No	9 (52.94)	6 (40.00)	
Visit 7 (Week 20)	Yes	9 (52.94)	10 (66.67)	
	No	8 (47.06)	5 (33.33)	
Medication duration				
	N	17	15	0.4375††
	Mean±S.D.	120.29±24.99	128.53±25.86	
	Median[Min, Max]	123[64,154]	147[82,151]	
Number of outpatient visits				
	N	17	17	0.1633††
	Mean±S.D.	7.00±0.00	6.29±1.99	
	Median[Min, Max]	7[7,7]	7[1,7]	

† Independent T-test, †† Wilcoxon Rank Sum test
SD denotes standard deviation.
[1)] Excluded from analysis if patient did not take the medication or did not remember the day of stop.
[2)] As there is no case for "administration medication in schedule =No" at Visit 2 (Week 1), logistic regression was used considering that all data are independent. (Interaction (Group * Time point) was not significant but time effect was significant when group was controlled for (P-value=0.0226)).

5. Results of Safety Evaluation

In the steroid group, after random assignment there was one subject (S025) who did not have at least one safety assessment completed. Safety analysis was conducted for the remaining 33 people (safety population).

During the duration of the clinical test, the number and percentage of participants who experienced at least one adverse reaction was recorded for each adverse reaction and separated by group. Information regarding the extent of adverse reaction, result, causality, and related measures was also arranged by group. In addition, for each group the side effect category and rate of incidence was 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.

5.1. Complications

Results from observing complications after drug injection for both groups showed that the frequency for hypertension was highest for most visits. In Visit 2 (Week 1), there were 0 cases of other complications for the propranolol group and 5 cases for the steroid group. With a P-value of 0.0149, the incidence rate difference between the two groups was statistically significant. In Visit 4 (Week 8), there were 0 cases of facial edema for the propranolol group and 5 cases for the steroid group. Thus, the P-value (0.0149) also indicated a statistically significant difference between the two groups. In Visit 6 (Week 16), the number of cases for all complications was 5 for the propranolol group and 10 for the steroid group. The difference was statistically significant.

eTable 27. Complications

	Propranolol (N=17)[2]		Steroid (N=16)[2]		P-value
	Yes	No	Yes	No	
Duration of admission[3]					
Decreased heart rate	0 (0)	17 (100.00)	-	-	-
Low blood pressure	1 (5.88)	16 (94.12)	-	-	-
Hypoglycemia	0 (0)	17 (100.00)	-	-	-
Trouble breathing	0 (0)	17 (100.00)	-	-	-
Facial edema	0 (0)	17 (100.00)	-	-	-
Gastroesophageal reflux	0 (0)	17 (100.00)	-	-	-
Hypertension	6 (35.29)	11 (64.71)	-	-	-
Growth disability	0 (0)	17 (100.00)	-	-	-
Others[1]	6 (35.29)	11 (64.71)	-	-	-
None	6 (35.29)	11 (64.71)	-	-	-
Visit 2 (Week 1)					
Decreased heart rate	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Low blood pressure	1 (5.88)	16 (94.12)	0 (0)	15 (100.00)	1.0000**
Hypoglycemia	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Trouble breathing	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Facial edema	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Gastroesophageal reflux	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Hypertension	1 (5.88)	16 (94.12)	1 (6.67)	14 (93.33)	1.0000**
Growth disability	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Others[1]	0 (0.00)	17 (100.00)	5 (33.33)	10 (66.67)	0.0149**
None	15 (88.24)	2 (11.76)	10 (66.67)	5 (33.33)	0.2095**
Visit 3 (Week 4)					
Decreased heart rate	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Low blood pressure	1 (5.88)	16 (94.12)	0 (0)	15 (100.00)	1.0000**
Hypoglycemia	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Trouble breathing	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Facial edema	0 (0)	17 (100.00)	1 (6.67)	14 (93.33)	0.4688**
Gastroesophageal reflux	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Hypertension	2 (11.76)	15 (88.24)	3 (20.00)	12 (80.00)	0.6454**
Growth disability	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Others[1]	9 (52.94)	8 (47.06)	8 (53.33)	7 (46.67)	0.9823*
None	7 (41.18)	10 (58.82)	3 (20.00)	12 (80.00)	0.2654**
Visit 4 (Week 8)					
Decreased heart rate	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Low blood pressure	1 (5.88)	16 (94.12)	0 (0)	15 (100.00)	1.0000**

Hypoglycemia	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Trouble breathing	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Facial edema	0 (0)	17 (100.00)	5 (33.33)	10 (66.67)	0.0149**
Gastroesophageal reflux	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Hypertension	0 (0)	17 (100.00)	2 (13.33)	13 (86.67)	0.2117**
Growth disability	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Others[1)]	8 (47.06)	9 (52.94)	7 (46.67)	8 (53.33)	0.9823*
None	9 (52.94)	8 (47.06)	4 (26.67)	11 (73.33)	0.1310*
Visit 5 (Week 12)					
Decreased heart rate	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Low blood pressure	1 (5.88)	16 (94.12)	0 (0)	15 (100.00)	1.0000**
Hypoglycemia	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Trouble breathing	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Facial edema	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Gastroesophageal reflux	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Hypertension	1 (5.88)	16 (94.12)	3 (20.00)	12 (80.00)	0.3192**
Growth disability	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Others[1)]	8 (47.06)	9 (52.94)	7 (46.67)	8 (53.33)	0.9823*
None	8 (47.06)	9 (52.94)	7 (46.67)	8 (53.33)	0.9823*
Visit 6 (Week 16)					
Decreased heart rate	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Low blood pressure	0 (0)	17 (100.00)	1 (6.67)	14 (93.33)	0.4688**
Hypoglycemia	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Trouble breathing	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Facial edema	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Gastroesophageal reflux	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Hypertension	2 (11.76)	15 (88.24)	4 (26.67)	11 (73.33)	0.3828**
Growth disability	0 (0.00)	17 (100.00)	1 (6.67)	14 (93.33)	0.4688**
Others[1)]	4 (23.53)	13 (76.47)	7 (46.67)	8 (53.33)	0.1691*
None	12 (70.59)	5 (29.41)	5 (33.33)	10 (66.67)	0.0351*
Visit 7 (Week 20)					
Decreased heart rate	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Low blood pressure	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Hypoglycemia	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Trouble breathing	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Facial edema	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Gastroesophageal reflux	0 (0)	17 (100.00)	0 (0)	15 (100.00)	-
Hypertension	0 (0)	17 (100.00)	3 (20.00)	12 (80.00)	0.0917**

Growth disability	0 (0)	17 (100.00)	1 (6.67)	14 (93.33)	0.4688**
Others[1)]	11 (64.71)	6 (35.29)	5 (33.33)	10 (66.67)	0.0765*
None	6 (35.29)	11 (64.71)	8 (53.33)	7 (46.67)	0.3047*

* Chi-square test, ** Fisher's Exact test
[1)] Details were presented for adverse reaction.
[2)] Overwriting available.
[3)] Only patients in the propranolol group were admitted.

5.2. Adverse Reactions

The number of subjects who had at least one adverse reaction was 31 (16 from experimental group, 15 from control group) out of a total of 33. In terms of cases by group, in the experimental group there was 70 cases across 16 patients and in the control group there was 60 cases across 15 patients. No serious adverse events occurred. The adverse events that occurred mostly had little to no relevance to the drug administered, and most have recovered or are in the process of recovering.

eTable 28. Summary of adverse reaction reported during the duration of the trial

	Propranolol (N=17)	Steroid (N=16)	P-value
Adverse Reaction			
The number of subjects who had at least one adverse reaction	16 (94.12)	15 (93.75)	1.0000**
The number of adverse reactions	70	60	
Serious Adverse Reaction			
The number of subjects who had at least one serious adverse reaction	0 (0)	0 (0)	-
The number of serious adverse reactions	0	0	
Causality			
1= Certain	0 (0)	0 (0)	
2= Probable/likely	0 (0)	0 (0)	
3= Possible	10 (14.29)	24 (40.00)	
4= Unlikely	56 (80.00)	35 (58.33)	
5= Probably not related	4 (5.71)	1 (1.67)	
6= Unassessable/unclassifiable	0 (0)	0 (0)	
Action after adverse reaction			
1=None	22 (31.43)	29 (48.33)	
2=Dose reduction	0 (0)	0 (0)	
3=Addition medication for adverse reaction	48 (68.57)	27 (45.00)	
4=non-pharmaceutical treatment	0 (0)	2 (3.33)	
5=Stop applying medication	0 (0)	2 (3.33)	
6=Not applicable	0 (0)	0 (0)	
Results			
1= Recovered	54 (77.14)	46 (76.67)	
2= Not recovered	0 (0)	2 (3.33)	
3= Recovering	16 (22.86)	11 (18.33)	
4= Death	0 (0)	0 (0)	
5=Lost to follow up	0 (0)	0 (0)	
6=Unknown	0 (0)	1 (1.67)	

* Chi-square test, ** Fisher's Exact test

The eTable 29 is the chart for adverse reactions during the duration of trials for the two groups. The most common adverse event for both the propranolol group and the steroid group was nasopharyngitis, which occurred in 13 patients (21 cases) in the propranolol group and in 8 patients (14 cases) in the steroid group. In terms of number of subjects, the Dermatitis atopic (total 10 patients, 7 in propranolol and 3 in steroid) and Diarrhea (total 10 patients, 6 in propranolol and 4 in steroid) were the next most common adverse reactions.

eTable 29. Chart of adverse reactions during the duration of trials

Adverse reaction		Number of subject		Number	
		Propranolol (N=17)	Steroid (N=16)	Propranolol (N=70)	Steroid (N=60)
System Organ Class	**Preferred Term**				
Eye disorders	Eye discharge	2 (11.76)	0 (0)	2 (2.86)	0 (0)
Gastrointestinal disorders	Constipation	1 (5.88)	3 (18.75)	1 (1.43)	3 (5.00)
	Diarrhea	6 (35.29)	4 (25.00)	8 (11.43)	6 (10.00)
	Dyspepsia	0 (0)	1 (6.25)	0 (0)	1 (1.67)
	Vomiting	4 (23.53)	6 (37.5)	4 (5.71)	6 (10.00)
General disorders and administration site conditions	Fatigue	1 (5.88)	0 (0)	1 (1.43)	0 (0)
	Pyrexia	4 (23.53)	2 (12.5)	6 (8.57)	2 (3.33)
Infections and infestations	Abscess limb	1 (5.88)	0 (0)	1 (1.43)	0 (0)
	Abscess oral	0 (0)	1 (6.25)	0 (0)	1 (1.67)
	Bronchiolitis	1 (5.88)	0 (0)	1 (1.43)	0 (0)
	Hand-foot-and-mouth disease	1 (5.88)	0 (0)	1 (1.43)	0 (0)
	Intertrigo candida	1 (5.88)	0 (0)	1 (1.43)	0 (0)
	Nasopharyngitis	13 (76.47)	8 (50)	21 (30)	14 (23.33)
	Otitis media	1 (5.88)	2 (12.5)	1 (1.43)	2 (3.33)
	Pharyngitis	1 (5.88)	0 (0)	1 (1.43)	0 (0)
	Pneumonia	0 (0)	1 (6.25)	0 (0)	1 (1.67)
	Urinary tract infection	1 (5.88)	1 (6.25)	1 (1.43)	1 (1.67)
Injury, poisoning and procedural complications	Excoriation	1 (5.88)	1 (6.25)	1 (1.43)	1 (1.67)
Metabolism and nutrition disorders	Hyperglycemia	0 (0)	1 (6.25)	0 (0)	1 (1.67)
	Hypophagia	1 (5.88)	0 (0)	1 (1.43)	0 (0)
Nervous system disorders	Burning sensation	0 (0)	1 (6.25)	0 (0)	1 (1.67)
Psychiatric disorders	Agitation neonatal	0 (0)	4 (25)	0 (0)	4 (6.67)
	Bulimia nervosa	0 (0)	1 (6.25)	0 (0)	1 (1.67)
	Insomnia	1 (5.88)	4 (25)	1 (1.43)	5 (8.33)
Respiratory, thoracic and mediastinal disorders	Epistaxis	1 (5.88)	0 (0)	1 (1.43)	0 (0)
	Rhinorrhea	0 (0)	1 (6.25)	0 (0)	1 (1.67)
Skin and subcutaneous tissue disorders	Acne infantile	1 (5.88)	0 (0)	1 (1.43)	0 (0)
	Alopecia	0 (0)	1 (6.25)	0 (0)	1 (1.67)
	Dermatitis allergic	0 (0)	1 (6.25)	0 (0)	1 (1.67)
	Dermatitis atopic	7 (41.18)	3 (18.75)	7 (10.00)	3 (5.00)
	Dermatitis diaper	0 (0)	1 (6.25)	0 (0)	1 (1.67)
	Eczema	1 (5.88)	0 (0)	1 (1.43)	0 (0)
	Heat rash	1 (5.88)	0 (0)	1 (1.43)	0 (0)

	Intertrigo	1 (5.88)	0 (0)	1 (1.43)	0 (0)
	Milia	1 (5.88)	0 (0)	1 (1.43)	0 (0)
	Papule	2 (11.76)	0 (0)	2 (2.86)	0 (0)
	Rash	1 (5.88)	2 (12.5)	1 (1.43)	2 (3.33)
	Urticaria	1 (5.88)	1 (6.25)	1 (1.43)	1 (1.67)

5.3. Vital Signs and Glucose level (Blood sugar test)

Vital signs and glucose level (BST) at one hour after injection in test group are shown in eTable 30.

eTable 30. Vital signs and glucose level – Test group

			N	Propranolol (N=17)
Systolic blood pressure (mmHG)				
Day 1	**Midday**	Mean±S.D. Median[Min, Max]	17	97.59±16.5 100[71,130]
	Evening	Mean±S.D. Median[Min, Max]	17	94.59±14.22 94[70,126]
Day 2	**Morning**	Mean±S.D. Median[Min, Max]	17	97.65±15.05 97[76,128]
	Midday	Mean±S.D. Median[Min, Max]	17	93.94±14.35 88[67,121]
	Evening	Mean±S.D. Median[Min, Max]	17	89.12±14.73 86[68,119]
Day 3	**Morning**	Mean±S.D. Median[Min, Max]	17	93.82±9.83 91[81,114]
Diastolic blood pressure (mmHG)				
Day 1	**Midday**	Mean±S.D. Median[Min, Max]	17	47.12±8.12 48[31,60]
	Evening	Mean±S.D. Median[Min, Max]	17	45.88±12.14 44[24,72]
Day 2	**Morning**	Mean±S.D. Median[Min, Max]	17	49.94±10.28 47[26,66]
	Midday	Mean±S.D. Median[Min, Max]	17	46.18±11.04 45[34,72]
	Evening	Mean±S.D. Median[Min, Max]	17	44.41±9.35 43[34,74]
Day 3	**Morning**	Mean±S.D. Median[Min, Max]	17	44.35±6.94 43[30,57]
Heart rate (/min)				
Day 1	**Midday**	Mean±S.D. Median[Min, Max]	17	131.88±9.45 130[117,158]
	Evening	Mean±S.D. Median[Min, Max]	17	126.41±15.54 128[97,150]
Day 2	**Morning**	Mean±S.D. Median[Min, Max]	17	128.06±11.04 126[117,155]

	Midday	Mean±S.D. Median[Min, Max]	17	122.88±11.19 125[102,138]
	Evening	Mean±S.D. Median[Min, Max]	17	122.47±17.39 118[100,163]
Day 3	**Morning**	Mean±S.D. Median[Min, Max]	17	123.47±12.49 120[102,154]
Respiratory rate (/min)				
Day 1	**Midday**	Mean±S.D. Median[Min, Max]	17	35.29±5.24 36[24,44]
	Evening	Mean±S.D. Median[Min, Max]	17	35.65±5.8 36[26,48]
Day 2	**Morning**	Mean±S.D. Median[Min, Max]	17	38.59±7.51 38[30,60]
	Midday	Mean±S.D. Median[Min, Max]	17	37.06±7.49 36[28,58]
	Evening	Mean±S.D. Median[Min, Max]	17	38.71±7.58 40[30,52]
Day 3	**Morning**	Mean±S.D. Median[Min, Max]	17	36.35±6.09 36[26,48]
Body temperature (℃)				
Day 1	**Midday**	Mean±S.D. Median[Min, Max]	17	36.66±0.43 36.7[36,37.4]
	Evening	Mean±S.D. Median[Min, Max]	17	36.81±0.37 36.8[36,37.7]
Day 2	**Morning**	Mean±S.D. Median[Min, Max]	17	36.69±0.31 36.7[36,37.4]
	Midday	Mean±S.D. Median[Min, Max]	17	36.75±0.42 36.8[36.1,37.5]
	Evening	Mean±S.D. Median[Min, Max]	17	36.62±0.26 36.6[36.2,37]
Day 3	**Morning**	Mean±S.D. Median[Min, Max]	17	36.86±0.39 36.7[36.3,37.7]
Blood sugar test (mg/dL)				
Day 1	**Midday**	Mean±S.D. Median[Min, Max]	17	103±13.44 102[86,142]
	Evening	Mean±S.D. Median[Min, Max]	17	101.76±12.59 102[71,123]
Day 2	**Morning**	Mean±S.D. Median[Min, Max]	17	108.06±16.03 104[87,146]
	Midday	Mean±S.D.	17	102.18±11.6

		Median[Min, Max]		102[82,133]
	Evening	Mean±S.D. Median[Min, Max]	17	98.82±12.52 102[79,123]
Day 3	**Morning**	Mean±S.D. Median[Min, Max]	17	104.12±9.28 103[86,119]

SD denotes standard deviation.

Vital signs and glucose level (BST) measured at 1 hour after injection for outpatients in the control group are shown in eTable 31.

eTable 31. Vital signs and glucose level (BST)- Control group

		N	**Steroid (N=16)**
SBP (mmHG)			
Initial	Mean±S.D. Median[Min, Max]	16	90.19±8.22 89.5[80,103]
DBP (mmHG)			
Initial	Mean±S.D. Median[Min, Max]	16	50.25±9.46 47.5[40,67]
HR (/min)			
Initial	Mean±S.D. Median[Min, Max]	16	147.63±14.02 148[124,171]
RR (/min)			
Initial	Mean±S.D. Median[Min, Max]	16	35.88±2.87 36[30,40]
BT (℃)			
Initial	Mean±S.D. Median[Min, Max]	16	36.96±0.35 37[36,37.4]
BST (mg/dL)			
Initial	Mean±S.D. Median[Min, Max]	15	121±18.7 120[87,149]

SBP denotes systolic blood pressure, SD standard deviation, DBP diastolic blood pressure, HR heart rate, RR respiratory rate, BT body temperature, BST blood sugar test.

eTable 32. Vital signs and blood glucose level

	level	Propranolol	Steroid	p_value
SBP	N	17	16	0.113*
	Mean±SD	97.59±16.5	90.19±8.22	
	Median[Min, Max]	100[71,130]	89.5[80,103]	
DBP	N	17	16	0.588*
	Mean±SD	47.12±8.12	50.25±9.46	
	Median[Min, Max]	48[31,60]	47.5[40,67]	
HR	N	17	16	0.003*
	Mean±SD	131.88±9.45	147.63±14.02	
	Median[Min, Max]	130[117,158]	148[124,171]	
RR	N	17	16	0.8548*
	Mean±SD	35.29±5.24	35.88±2.87	
	Median[Min, Max]	36[24,44]	36[30,40]	
BT	N	17	16	0.036*
	Mean±SD	36.66±0.43	36.96±0.35	
	Median[Min, Max]	36.7[36,37.4]	37[36,37.4]	
BST	N	17	15	0.0023*
	Mean±SD	103±13.44	121±18.7	
	Median[Min, Max]	102[86,142]	120[87,149]	

* Wilcoxon Rank Sum test

SBP denotes systolic blood pressure, SD standard deviation, DBP diastolic blood pressure, HR heart rate, RR respiratory rate, BT body temperature, BST blood sugar test.

6. Conclusion

A total of 34 patients agreed and registered in this trial. The patients were randomly assigned to either the propranolol group (17 patients) or steroid group (17 patients). Trials were finished without any severe violation of protocol. The efficiency evaluation was conducted in the PP analysis group, which includes 30 target participants (propranolol group: steroid group = 16:14). The safety evaluation was conducted in safety population, which had a total of 33 patients (propranolol group: steroid group = 17:16).

In terms of demographics for the ITT group, the mean age for the 17 participants assigned to the propranolol group was 3.18 months, mean weight was 6.45kg, and mean height was 61.75cm. For the 17 participants assigned to the steroid group, the mean age was 2.65 months, mean weight was 6.02kg, and mean height was 60.51cm. In the propranolol group, 7 of the participants were male (41.18%), and in the steroid group, 8 were male (47.06%). All demographics were not statistically significant at the 5% level ($P<0.05$), thus it cannot be said that there was any statistical difference between the two groups.

It was found that there was no statistically significant difference in vital signs (systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature) between the two groups. In addition, no abnormalities were found in the chest radiograph image, electrocardiograph, cardiac, and echocardiograph results of any of the patients, thus there was no statistical difference between the two groups.

In the steroid group, for the blood chemistry categories total bilirubin, alkaline phosphatase, and potassium, several patients had abnormal values: 3 for total bilirubin, 2 for alkaline phosphatase, and 2 for potassium. One patient showed an abnormal value of positive for the urinalysis category NIR. No patient showed abnormal values for any of the other inspections.

In the propranolol group, none of the patients showed abnormal values for any of the test categories. Excluding alkaline phosphatase, we found no significant difference in blood test or urinalysis results at the 5% level. In the case of alkaline phosphatase, the propranolol group mean was 257.18 IU/L, and the steroid group mean was 315.82 IU/L. Although the steroid group had a higher mean, there was no significant difference.

The baseline hemangioma inspection results for both groups are as follows. The mean age (calculated by the age at diagnosis) for the propranolol group was 108.76 days and for the steroid group was 89.24 days. For both groups, the face was the most common location of hemangioma (10 cases for propranolol and 13 for steroid). MRI scans (or ultrasound examinations) were conducted for all patients and the mean hemangioma volume was 14125.35mm^3 for the propranolol group and 9349.54mm^3 for the steroid group. Although the mean

volume for the steroid group was smaller, there was no significant difference (P=0.33). An image of the lesion region was taken for all groups and the mean area for the propranolol group was 1318.06mm^2 while the mean area for the steroid group was 1093.51mm^2. As with the volume, there was no statistically significant difference between the two groups (P=1.00). In addition, most of the lesions were red in color. One patient from each group had an ulceration and two patients from the propranolol showed re-epithelization.

After hearing each patient's medical history, 2 people of propranolol group and 4 people of steroid group had hemangioma when they were born. None of propranolol group and 3 people of steroid group have herald sign. It was found that the mean age when hemangioma began was 0.68 months for the propranolol group and 0.50 months for the steroid group (P=0.53). The mean period when hemangioma grew the most was 3.12 months for the propranolol group and 2.53 for the steroid group (P=3.91). 3 people (mother in propranolol group, 2 cousins in steroid group) have family history of hemangioma. Furthermore, there was no statistically significant variable between two groups.

During the duration of the trial, 60 people (100%) in the propranolol group and 4 people (44.44%) in the steroid group took a concomitant drug. In the propranolol group, there were 112 cases of concomitant drug consumption by 13 people, and in the steroid group, there were 107 cases by 14 people.

In the propranolol group, the most commonly consumed concomitant drug was Hydrocortisone (D07AA02) (8 cases, 5 people), N02BE01(Acetaminophen) (8 cases, 6 people), and A07FA01(Bacillus licheniformis, Ramnos Granule, Medilac-S Powder) (6 cases, 6 people). In the steroid group, the most commonly consumed concomitant drug was R01BA53 (Comy Syrup, Coben Syrup, Colmin-A Syrup) (10 cases/4 people) and A07FA01 (Bacillus licheniformis, Ramnos Granule, Medilac-S Powder) (6 cases, 5 people).

6.1. Efficacy Evaluation

6.1.1. Primary Efficacy Evaluation

In our analysis, all missing values in the ITT group and ITT group applying multiple imputation were replaced with “Reaction” or “Non-reaction” and categorized into two groups: ITT group and PP group. The final research results were results from the ITT analysis group applying MI. Multiple imputation was used to predict the Reaction/Non-reaction of the secondary efficacy variables size (area), proliferative stop time point, regression time point, color, ulceration size, and presence of re-epithelization.

For the ITT analysis group applying MI, the treatment response rate in the propranolol group was 95.65% and that of the steroid group was 91.94%. The difference in response rates between the two groups was 3.71%, and the 95% confidence interval was [-15.43, 22.84]. Because the lower limit of the confidence interval (-15.43%) was greater than -20%, it can be said that propranolol is non-inferior.

As a result of the analysis of supplementary validation results for four subjects with missing values (which were replaced with “Non-reaction”), the treatment response rate in the propranolol group was 94.12% and that of the steroid group was 82.35%. The Fisher’s Exact test result was that the treatment response rates between the two groups could not be said to be different. The difference in response rates between the two groups was 11.76%, and the 95% confidence interval was [-9.53, 33.06]. Because the lower limit of the confidence interval (-9.53%) was greater than -20%, it can be said that is non-inferior.

Another analysis of supplementary validation results for four subjects with missing values (also replaced with “Reaction”) revealed the same results (non-inferior). Since the lower limit of the 95% confidence interval (-18.65, 18.65) is greater than -20%, it is non-inferior.

In the case of the PP group, the 4 participants with missing values were excluded and the difference in response rate between the two groups was found to be 0%. The 95% confidence interval was [-20.59, 23.16] and because the lower limit is smaller than -20%, we cannot say that it is non-inferior.

6.1.2. Secondary Efficacy Evaluation

The volume reduction changes (%) were 55.87% and 46.52% in the propranolol group and steroid group, respectively. The rate of changes in propranolol was higher, but there was no significant statistically differences (P=0.27).

The average size of hemangioma decreased over time, regardless of the group. In addition, the interaction (Group * Time Point) was not significant, thus it cannot be said that there is a difference between the two groups in the change in hemangioma size. However, although controlling for time did not result in a statistically significant difference, controlling for group did.

After checking the frequency and percentage of color by group and time, we found that most hemangioma were either red or blue in color. In the case where the color was apricot, the color was gone by the 7^{th} visit. Results from generalized estimating equation (GEE) showed that group, time, group*time effects were all nonsignificant.

There were 8 cases of re-epithelization in the propranolol group and 4 cases in the steroid group during the entire research period. Out of the 34 participants, re-epithelization occurred for 2 people (both in the propranolol group) during Visit 1 (screening). For Visits 1 (screening) and 2 (week 1), re-epithelization only occurred for participants in the propranolol group. Re-epithelization cases were observed in both groups for Visit 3 (Week 4), Visit 4 (Week 8), and Visit 5 (Week 12). In Visit 6 (Week 16), only the steroid group saw a case of re-epithelization. No cases of re-epithelization were observed in Visit 7 (Week 20). Furthermore, results of logistic regression show that group, time point, group * time point effects were all nonsignificant.

During the entire duration of the clinical trial, there was one case of ulceration in the propranolol group and 2 cases in the steroid group. In Visit 1 (screening), ulceration was found in 2 out of 34 people, one per group. In Visit 2 (Week 1), there was one case from the steroid group. From Visit 3 (Week 3), no ulceration cases were observed. The ulceration found in 2 people during Visit 1 (screening) was $37.7mm^2$ (propranolol group) and $38.5mm^2$ (steroid group), and the ulceration found in Visit 2 (Week 1) was $22mm^2$ from the steroid group. If no ulceration was found, the size was recorded as “0”. From Visit 3 (Week 2), the descriptive statistics quantity was all “0”. Results from logistic regression showed that group, time point, group*time point effects were all nonsignificant. Moreover, using generalized estimating equation (GEE) also resulted in nonsignificant group, time point, and group*time point effects.

In the case of the propranolol group, in all 17 subjects proliferation stopped or a regression occurred.

The median time it took to reach proliferative stop or regression was 12 days after random assignment. For the steroid group, 15 subjects out of 17 showed proliferative stop or regression, and the median time was 11 days after random assignment. Results from a log rank test showed that there was no difference between the two groups.

When considering regression to be a decrease of at least 25% compared to Visit 1, 13 out of 17 subjects in the propranolol group experienced regression and the median time was 62 days after random assignment. For the steroid group, regression occurred for 9 out of 17 subjects and the median time was 120 days. Conducting a log rank test resulted in no difference between the two groups.

In terms of medication administration, in Visit 2 (Week 1) all subjects from both groups were administered medication, but in Visit 3 (Week 4) four subjects from the propranolol group and one from the steroid group did not take medication. For the remaining visits, there was a subject who did not take medication. Furthermore, excluding Visit 2 (Week 1), for each visit the number of subjects who took medication was higher for the steroid group than the propranolol group. When time point was controlled for, there was no statistically significant difference at the 5% level between the two groups in terms of medical administration (P-value=0.0566). In addition, there was also no difference in terms of total medication duration and outpatient visits (P-value=0.4375, 0.1633).

6.2. Safety Evaluation

In the steroid group, after random assignment there was one patient (S025) who did not have at least one safety assessment completed. Safety analysis was conducted for the remaining 33 patients (safety population).

Results from observing complications after drug for both groups showed that the frequency for hypertension was highest for most visits. Other complications in steroid group (n=5) were statistically significantly more than in the propranolol group (n=0) in Visit 2 (week 1) (P= 0.01). The facial edema in steroid group (n=5) was statistically significantly more than in the propranolol group (n=0) in Visit 4 (week 8) (P= 0.01). The number of cases for all complications in the steroid group (n=10) was statistically significant higher than that of the propranolol group (n=5) in Visit 6 (week 16) (P=0.04).

The number of patients who had at least one adverse reaction was 31 (16 from propranolol group, 15 from steroid group) out of a total of 33. In the experimental group there was 70 cases across 16 patients and in the control group there was 60 cases across 15 patients (P=1.00). No serious adverse reaction occurred. The adverse reactions that occurred mostly had little to no relevance to the drug administered, and most have recovered. The most common adverse reaction for both the propranolol group and the steroid group was nasopharyngitis, which occurred in 13 patients (21 cases) in the propranolol group and in 8 patients (14 cases) in the steroid group. In terms of number of patients, the dermatitis atopic (total 10 patients, 7 in propranolol and 3 in steroid) and diarrhea (total 10 patients, 6 in propranolol and 4 in steroid) were the next most common adverse reactions.

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