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Propranolol Oral Treatment for Infantile Hemangioma : A Systematic Review

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Abstract

The most common benign tumor in infants is infantile hemangioma. Propranolol is often used as a treatment in patients with IHs. Efficacy and side effects of oral propranolol are considered important to be systematically reviewed in the management of IH. We searched Google Scholar, Pubmed, Garuda, and Science Direct. The articles matched with the restriction criteria then screened using the PRISMA method. The quality of the articles is tested using GRADE method. Total of 4 of 6289 articles recorded at the identification stage according to the inclusion criteria, 452 patients were treated with oral propranolol. All four articles were randomized clinical trials. Treatment is given at 0.3 month to 15 years of age, the dose given is 1-3 mg/kg/day. The primary end point was performed at week 24. The most common side effect is sleeping disorder (n=85). Serious side effects (Hypotension, bronchospasm, bradycardia, hypoglycemia) were managed by decreasing doses or temporary/permanent discontinuation of oral propranolol. Oral propranolol can be used with good efficacy. Monitor before and during treatment is assessed appropriately to reduce side effect.

Keywords
adrenergic antagonist; propranolol; infantile hemangioma

I. Introduction

Infantile hemangioma, also known as childhood hemangioma (Antony George, 2014), is a benign tumor of the vascular endothelium (Van An Nguyen, 2006). The first characteristic sign of infantile hemangioma is a pale area appearing a few days after birth (Staff, 2021). Infantile hemangiomas have no open lumen and have a high cellular density. This is happen because infantile hemangiomas consist mostly of capillaries that over-proliferate (Mohammed Muneeb Mubashir, 2018). This lesion is more common in women than man and more common in Caucasian children. (Arin K. Greene, 2011) . The neck and head are the most common areas for infantile hemangiomas, accounting for 60% of the incidence recorded in the study, followed by the trunk and extremities. The distribution of these tumors is mostly related to the area of embryological fusion. (Antony George, 2014)

Three-phase evolution of infantile hemangioma is growth, plateau, and involution phase. Rapid growth in the growth phase occurs in the first three months and gradual growth in five to eight months. The lesions remain stable in the plateau phase for 6 to 12 months. The first year to several years of the child's age is the period of the involution phase. The color of an infantile hemangioma that is initially bright red changes to gray or purple and is softer. The skin often changes to excessive fibrofatty or telangiectasia. but often the skin color can return to normal (Amal Chamli, 2019). Most of the threat or serious complications are not found in infants with infantile hemangiomas. Cases that

interfere with normal health and function due to the size or location of the tumor cause treatment of infantile hemangioma to continue (Maguiness SM, 2010). According to Sangy et al (2021) antibodies' ability to induce anti-tumor effects by regulating tumor antigen-specific immune responses has gotten less attention than it deserves. The potential of monoclonal antibodies as immunotherapy vehicles will be examined in this paper. While there are a variety of potential immunomodulatory pathways to explore (e.g., complement activation, interference with inhibitory costimulation)

The use of propranolol after more than 50 years has become widespread. Other studies have found the use of propranolol for noncardiovascular and cardiovascular purposes, such as the use of propranolol for tremor, panic disorder, migraine, and portal hypertension. (Neurol, 2019) Propranolol is the first choice treatment option for infantile hemangioma patients at doses between 2 and 3 mg/kg/day, except in cases where lower doses are required, as defined by clinical practice guidelines. Similar recommendations were made by a review from the AHRQ that the dose of propranolol should be between 2 and 2.5 mg/kg/day. The European expert consensus provides an addition to the initial dose of 1 mg/kg/day and the target dose is the same as recommended by clinical practice guidelines. (Daniel P. Krowchuk, 2019)

Considering the widespread use of propranolol in infantile hemangiomas and uncertainty surrounding this issue, efficacy and side effects of oral propranolol are important to be systematically reviewed in the management of IH.

II. Research Methods

2.1 Strategy of Research, Eligibility Criteria and Outcomes

We included randomised clinical trial evaluating oral propranolol as primary therapy for treating Infantile hemangiomas without a combination of drugs or using other treatments. We excluded preclinical, observational, systematic review and meta-analyses, case studies, letter, editorials, and conference abstract. This research strategies followed the PICO method. That is formed by P of patient or population: infantile Hemangioma; I of intervention or indicator: Oral propranolol; C of comparison or control: placebo or other drugs and O of “outcome”: Efficacy infantile hemangioma and side effects (Akobeng, 2005).

We use Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) for the basis writing this review (David Moher, 2009). We conducted electronic literature search on Google Scholar, Science Direct, Garuda, and Pubmed. The keywords used are “propranolol” AND “hemangioma, capillary” OR “Infantile Hemangioma”. Jailani (2020) stated that emangioma is a benign tumor or hemartoma that occurs due to interference with the development and formation of blood vessels and can occur in all organs such as the liver, spleen, brain, bones, and skin.1 Hemangioma is a benign tumor of blood vessels that can be

Occurs in al organs of the body and occurs most frequently in the head and neck area.2,The languages used are Indonesian and English. Foreign language of journals that don’t provide English or Indonesian translation will be excluded. Place settings taken from all locations in the world without limitation of article search time. The search was carried out until May 2021.

2.2 Study Selection and Data Extraction

Five authors (AN, RP, ZF, AM, and TM) three times independently identified and reviewed the articles obtained. Articles are screened by relevant titles and abstracts, reviewed in full text, and selected or discarded based on inclusion and exclusion criteria.Microsoft Excel was used by five authors tp extract and analyze data. If there is a disagreement regarding the extraction and selection of study data, the five reviewers will resolve it.

2.3 Bias and Quality of Assessment

Articles that have passed selection and extraction are tested for quality using Grading of Recommendations Assessment, Development and Evaluation (GRADE). The quality of assessment were resolved by five reviewer.

III. Results and Discussion

At the data collection stage, 6289 titles were obtained from 4 search engines including Google Scholar (n : 5840), Science Direct (n : 386), Garuda (n : 2) and Pubmed (n : 61).

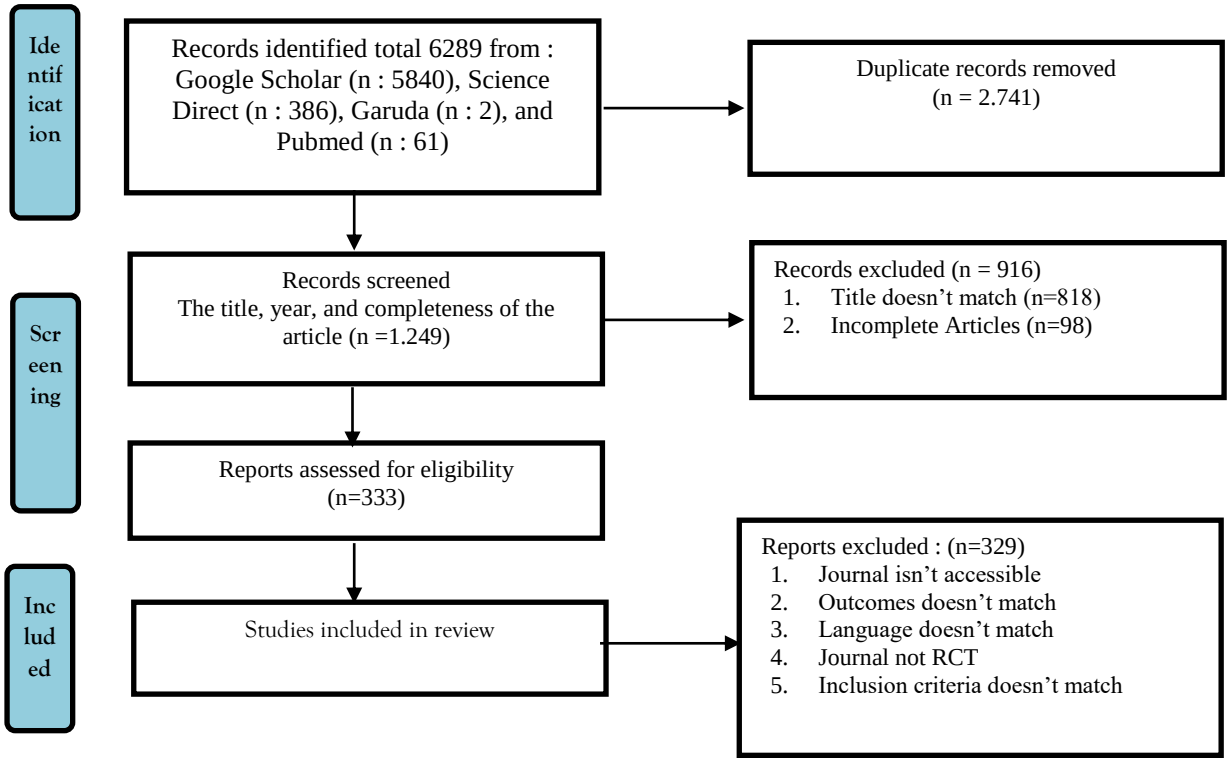

Figure 1. *Prisma Diagram*

Delete duplicate data from each database by extracting manually on the microsoft excel application (n : 2741) continued with title and abstract screening (n : 1249). Reports assessed for eligibility (n : 333) there is no exclusion of eligibility because all journals are uploaded to a valid database. Journals were excluded because they didn't meet inclusion criteria, could not access data, didn't have Indonesian or English translation, and were not RCT. At the full text screening, the final results were 4 articles (figure 1).

Table 1. General characteristics and initial grade

First Author (Year of Publication)	Country	Subject	Population	Comparison	Title	Method	Initial Grade
Marcia Hogeling, et al (2011)	Australia	Between the ages 9 weeks to 5 years	40 Children	Placebo	A Randomized Controlled Trial of Propranolol for Infantile Hemangioma	RCT	High
C. Léauté-Labrèze, et al (2015)	France, Germany, Spain, Australia, Mexico, Czech Republic, Peru, Poland, California, United State of America, England, New Zealand, Lithuania, Hungary, Canada, and Illinois	Mean age 103.8 days	460 Children	Placebo	A Randomized, Controlled Trial of Oral Propranolol in Infantile Hemangioma	RCT	High
Aziz Eghbali, et al (2017)	Iran	Mean age 39.6 month	37 Children	Observation	A 24-Week Treatment of Pediatric Hemangioma with Oral Propranolol	Randomized, Open Label, Crossover Trial	High
Kyu Han Kim , et al (2017)	Korea	Mean age 3,3 month	34 Children	Steroid	Comparison of Efficacy and Safety Between Propranolol and Steroid for Infantile Hemangioma	RCT	High

Table 2. Final GRADE method

First Author (Year of Publication)	Limitations	Incosistency of Result	Indirectness of Evidence	Imprecision of Results	Publication Bias	Large Impact	Plausible Confounding Factors	Dose Response Gradient	Final Grade
Marcia Hogeling, et al (2011)	-	-	-	-	-	-	-	-	High
C. Léauté-Labrèze, et al (2015)	-	-	-	-	-	-	-	-	High
Aziz Eghbali, et al (2017)	-	-	-	-	-	-	-	-	High
Kyu Han Kim, et al (2017)	-	-	-	-	-	-	-	-	High

The two studies were comparative randomized control trial of propranolol vs placebo, a comparative study of propranolol vs steroids, and a journal randomized open label crossover trial comparative propranolol vs receivedno treatment of 32 patients taking propranolol. The majority of genders in the journals identified were female (71 %) (Table 4). Propranolol treatment was started at the youngest age was 0.3 months and the oldest was 15 years (Table 3). The oral dose of propranolol given is in the range of 1-3 mg/kg/day. C. Léauté-Labrèze et al. (2015) gave doses of 1 mg/kg/day for three and six months, also the dose 3 mg/kg/day for three and six months separately. The duration of treatment with propranolol was 16-24 weeks (Table 3). Two of the five selected studies described the type of infantile hemangioma. The most common type of hemangioma was localized (n=358). All studies provide information regarding the location of Infantile Hemangiomas. The most common locations are on facials (Table 3).

Table 3. List of Studies Identified and Selected Through Database Searches

First Author, Year of Publication	Study Type	Patients Treated with Propranolol, n	Gender		Age	Type IH, n	Localization IH, n
			Male	Female			
Marcia Hogeling, 2011	RCT, Prozpanolol vs Placebo	19	5	14	11 weeks – 4 years	Focal (16) Segmental (3) Multiple (5)	Lip (4) Facial (7) Torso (1) Orbital (3) Nasal (3) Limb (1)
C. Léauté-Labrèze, 2015	RCT, Propranolol vs Placebo	401	114	287	35-150 days	Segmental (23) Localized (358) Indeterminate (20)	Facial (278) Non Facial (123)
Aziz Eghbali, 2017	Randomized, Open Label, Crossover Trial	32	10	22	1 month - 15 years	No multiple	Head and neck (18) Trunk (10) Extremite (4)
Kyu Han Kim, 2017	RCT, Propranolol vs Steroid	17	7	10	0.3 - 8.2 months	-	Scalp (1) Face (10) Chest (2) Abdomen (1) Back (1) Upper extremities (3)

One of the journal, four patients were treated with oral propranolol had received systemic corticosteroid treatment. There is no clearer explanation about the reasons for the previous treatment being discontinued (Hogeling et al, 2011). During the study, none of the patients were treated with steroids.

Table 4. Patient Information

	n	%
Female	333	71
Male	136	29
Prior Treatment	10	0.79
Propranolol	4	0.85
Placebo	6	1.28

Efficacy of propranolol measured the IH color, size, and elevation by the blinded investigator. C. Leaute et al. (Christine Léauté-Labrèze, 2015) reported after 24 weeks 61 of 101 patients (60%) used propranolol regimen. Two of 55 patients (4%) used placebo had successful treatment (P<0.001). Aziz Eghbali et al. (Aziz Eghbali, 2017) reported a significant decrease was present in hemangioma size after a month (30 cm2 vs 16 cm2, P<0.01). Marcia Hogeling et al. (Marcia Hogeling, 2011) reported that in patients given propranolol, color and volume changes occurred earlier, at 4 to 8 weeks. The vascular tumor didn't show replaced by fibrofatty tissue during IH involution in older patient population. However, propranolol was not completely to be excellent responders. Similar to Marcia Hogeling et al. (2011), Kyu Han Kim et al. (Kyu Han Kim, et al., 2017) reported that the volume reduction in patients with propranolol (55.87%) was better than using steroids (46.52%), but was not significantly different (P=0.27). The surface area of IH in both groups was significantly reduced (P=0.2), here was no significant difference between the two groups (P=0.92) (Table 5).

Table 5. Propranolol Treatment Parameters

First Author	Dose of Propranolol	Planned Initiation Dose	Duration End of Treatments	Efficacy Analysis
Marcia Hogeling	2 mg/kg/d	A week 1 mg/kg/d divided three times daily for, then increased to 2 mg/kg/d divided three times daily from second until 24 weeks.	24 weeks	Color and volume changes occurred earlier.
C. Léauté-Labrèze	1 mg/kg/d 3 mg/kg/d	Propranolol doses divided into two daily, three or six months.	24 weeks	60% patients assigned to the selected propranolol had succesfull treatment at week 24, propranolol group was greater than placebo group.
Aziz Eghbali	2 mg/kg/d	Propranolol doses divided into twice daily, 6 months.	24 weeks	Significan decrease of size was present after a month (30 cm^2 vs 16 cm^2).
Kyu Han Kim	2 mg/kg/d	Propranolol divided into three times daily.	16 weeks	There was no significant difference between groups, propranolol group was greater than steroid group.

Kyu Han Kim et al. (2017) reported a significantly lower oral administration of propranolol than in the steroid group based on a safety analysis.. The heart rate (131.88 vs 147.63 bpm, P=0.003), temperature (36.66°C vs 36.96°C, P=0.04), level of blood glucuse (103 vs 121mg/dl, P=0.002). Side effects were observed 16 patients from propranolol and 15 patients from steroid (P=0.90). There were 70 adverse events, no serious side effects occurred. According to study of Marcia Hogeling et al. (2011), the most serious side effects of propranolol were bradycardia and hypotension. In this study it was noted that a child experienced cold extremities and improved for several weeks. Two of four children received inhaled fluticasone propionate because the patient had bronchiolitis during the trial. In another case, an upper respiratory tract infection forced a patient on propranolol to discontinue the study, even without wheezing. Propranolol suspension containing artificial sweeteners causes other patients to suffer from dental caries in the molars. An increase in redness or volume was noted upon discontinuation of propranolol in the majority of children under one year of age. C.Leaute et al. (2015) had bronchospasm as a side effect of propranolol in 2 patients which led to temporary discontinuation of treatment with propranolol (one received a placebo). However, Aziz Eghbali et al. (2017) studies reported that during one year treatment there is none side effects in two groups related to propranolol therapy (Table 6).

Table 6. Side Effect Patients

Side Effect	16 weeks	24 weeks					Total, n
	2 mg/kg/d	1 mg/kg/d		2 mg/kg/d	3 mg/kg/d		
		3 mo	6 mo		3 mo	6 mo	
Serious Side Effects							
Hypotension	5	2	1		3		11
Hypoglycemia			1			1	2
Bradycardia			1		1		2
Hipertention	7						7
Bronchospasm					2	1	3
Other							
Bronchiolitis		6	7	4	6	10	33
Bronchitis		5	8		11	17	41
Vomiting		16	13		10	13	52
Sleep disorder		28	14	2	19	22	85
Cold hands/feet		8	10	1	1	10	30
Agitation		12	18		8	7	45
Constipation		9	6		9	4	28
Decreased appetite		5	3		5	1	14
Somnolence		6	4		1	1	12
Streptococcal infection				1			1
Viral gastroenteritis				1			1
Respiratory infection				1			1
Elevated alkaline phosphatase				1			1
Dental caries				1			1
Diarrhea		16	14		17	28	75
Ulceration of IH				1			1
Any adverse event	16						16

Discussion

Our systematic review included various treatment doses, dosage initiation plans, efficacy, and side effects. Sources taken from this systematic review are reliable sources with high quality so that research results and data can be accounted for. Collecting data from the discussion of various studies presents its own challenges for us. Apart from these limitations, the subjects selected in this systematic review have relatively uniform results, making it easier for the author to takes conclusions.

In the article the authors found that there was discontinuation of systemic corticosteroid use prior to treatment with oral propranolol. The reasons for discontinuing treatment before starting and starting propranolol are not discussed in detail in all articles, but are largely due to inappropriate or insufficient response to this treatment. The main indications for treatment are sites that may impair function or cause aesthetic impairment, delay corticosteroid therapy, or fail to respond to corticosteroid therapy. The location of the infantile hemangioma does not seem to affect the rate of response to treatment with oral propranolol.

Propranolol oral treatment was noted to be more effective and comfortable to use when young than in their teens. This is in line with the theoretical basis which states that in the growth phase of infantile hemangiomas tend to experience rapid development in the first three months of birth so that early treatment can slow or even stop the process of infantile hemangioma development. The initiation of oral administration of propranolol and when to stop the drug were not described in detail in the articles we encountered, but there were mentions when severe side effects such as hypotension, hypoglycemia, bradycardia, hypertension, and bronchospasm occurred, the treatment was better discontinued. Back ulceration occurred in an eleven year old child who had a large focal infantile hemangioma, took two months to heal. An article report that oral propranolol have no significant efficacy for infantile hemangioma. It is unclear why some Ihs don't respond good treatment as well as others, whether this is related to factors such as tumor blood supply or expression of beta-adrenergic receptors.The article also states, if within the targeted period the appearance of the infantile hemangioma does not improve or even enlarges, then discontinuing oral propranolol use or switching to other treatments should be considered.

IV. Conclusion

Oral propranolol can be used with good efficacy. Monitor before and during treatment is assessed appropriately to reduce side effect.

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