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Literature Review

Efficacy and Safety of Mydriatic Regiments Used in Screening Retinopathy of Prematurity

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ABSTRACT

Background: *ROP screening must be done under pupil dilation to examine the ocular fundus, in order to allow diagnosis and staging of ROP. The objectives of this literature review are to compare the efficacy and safety of topical cyclopentolate, phenylephrine, tropicamide and the combination of these regiments in infants for ROP screening.*

Methods: *The search was conducted through electronic databases providing journal articles with keywords: cyclopentolate, phenylephrine and tropicamide on pupil dilation and systemic side effects in infants on screening Retinopathy of prematurity.The baseline of pupil diameter, frequency of instillation, mean difference amount of dilated pupil size and diameter of the pupil in 30 or 45 minutes and 60 minutes are presented in outcome.*

Results: *The mydriatic agents used in this literature review were phenylephrine, tropicamide, cyclopentolate and the combination of those regiments. Doses of mydriatic agents used in this review are variables. The lowest dose for phenylephrine is 1%, cyclopentolate is 0.2% and tropicamide is 0.5%. The highest dose for phenylephrine is 2.5%, cyclopentolate is 1.0 % and tropicamide is 10 %. The use of mydriatic regiments during newborn ophthalmic examinations has been associated with systemic side effects. Most reports have implicated the sympathomimetic component of the mydriatic solutions as the hypertensive agents.*

Conclusion: *Using only cyclopegic regimens did not produce adequate mydriasis in infants. The combination of low concentration sympathomimetic (phenylephrine 1%) and parasympatholytic (Cyclopentolate 0.2 %) produces adequate pupillary dilation and does not cause an increase in blood pressure and heart rate.*

Retinopathy of prematurity (ROP) is a proliferative retinal vascular disease which appears in premature that affects approximately half of premature infants and able to produce blindness.[1,2] The International Classification of Retinopathy of Prematurity (ICROP) in 1984 published the first classification of ROP.[1,3] In 2005 the classification was revised and the classification was based on the location of retinal involvement by zone (I, II, III), the extent of retinal involvement by clock hour, the stage or severity of retinopathy at the junction of vascularized and avascular retina and the present or absent of dilated and turtous posterior pole vessels (pre plus diseases and plus diseases), aggressive posterior ROP and regression of ROP.[4]

Early Treatment for Retinopathy of Prematurity (ETROP) study observed a group of premature children with birth weight <1251 g. The incidence of ROP reached 68%, and decreased with the increasing birth weight as well as gestational age.[5] Cryotherapy for retinopathy of prematurity (CRYO ROP) study reported the incidence of ROP in premature newborn with birth weight <1251 g was 65,8 %[4,7], in infants with weight between 1000 g and 1251 g occurs in 47%, at birth weight between 750 g and 999 g at birth was 78% and 90% of infants <750 g at birth. The visual loss resulting from ROP occurs in 1300 children/year.[7]

Screening examinations for retinopathy of prematurity are an essential step in protecting preterm infants from blindness. Earlier treatment of ROP could lead to even better visual and retinal structural outcomes. The criteria ROP screening is conditional, based on the situation and facilities of each center or country. Based on *Pokja Nasional* ROP workshop and premature infants 2010, Indonesia has its own recommendation for ROP screening with birth weight ≤1500 g or who were born at ≤ 34 weeks gestational age.[8]

ROP screening must be done under pupil dilation to examine the ocular fundus, in order to allow diagnosis and staging of ROP. The most mydriatic agents used in ROP screening are cyclopentolate, phenylephrine, tropicamide and the combination of these agents. Phenylephrine is a sympathomimetic agent that affects the iris dilator muscle.[9] The topical phenylephrine can cause cardiovascular effects including elevation in blood pressure.[9] Cyclopentolate and tropicamide are anti muscarinic, they abolishes the action of acetylcholine and prevent the sphincter from contraction. Cyclopentolate may cause side effects psychotic reaction, gastrointestinal disturbances and grand mal seizure, although these are rare.[9]

The efficacy and safety of different mydriaticum used in ROP screening vary between studies. Thus, the most effective and safe mydriaticum to dilate the pupil in infants remains questionable.

MATERIALS AND METHODS

The search was conducted through electronic databases providing journal articles that are collected from PubMed, Ophsource and the Cochrane Central database by entering keywords: cyclopentolate, phenylephrine and tropicamide on pupil dilation and systemic side effects in infants on screening Retinopathy of prematurity.

In the initial screening, abstract were reviewed to choose articles that were related to the study purpose based on the keywords. The complete studies related to the abstract were then screened to meet the inclusion and exclusion criteria.

The inclusion criteria were all studies (prospective or retrospective study) that with human subjects, reporting infants who underwent ROP screening examination using mydriatics such as cyclopentolate, phenylephrine and tropicamide or combination of these regiments to dilate the pupil. The size of maximum dilated pupil and side effects was reported in all these articles. Studies were excluded if the full text could not be accessed and if it is not published in English. Restriction of the publication date was not performed.

All studies that met the inclusion criteria were rated according to the level of evidence developed by Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence (Table 1).[10]

Table 1. Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence[10]

Level	Studies
I	Systematic review of randomized trials
II	Randomized trial or observational study with dramatic effect
III	Non-randomized controlled cohort/follow up study
IV	Case-series, case-control studies, or historically controlled studies
V	Mechanism-based reasoning

The baseline of pupil diameter, frequency of instillation, mean difference amount of dilated pupil size and diameter of the pupil in 30 or 45 minutes and 60 minutes are presented in outcome.

RESULTS

The literature search identified 24 articles that were related to the keywords. As many as 10 studies were made with the size of the dilated pupil and systemic side effects as outcomes, while three articles were excluded because the full text could not be access. A total of seventh articles were reviewed in this paper. The articles flow is presented in figure 1.

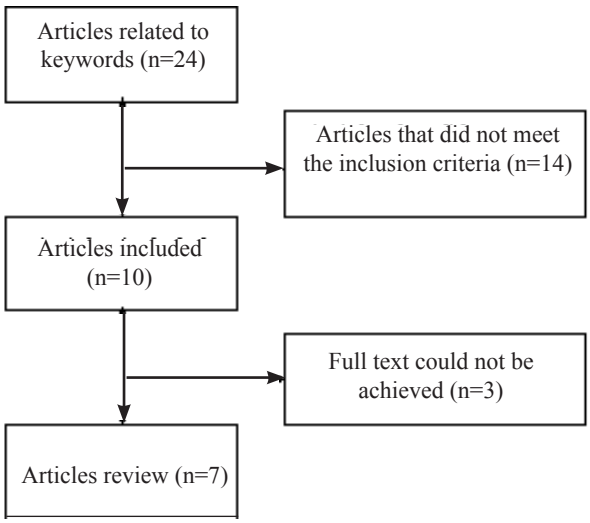

Fig 1. Flowchart of the study selection process

The characteristics data are presented in table 2. There were six studies at level II and one study at level III. All studies were published between 1981-2009. Clinical characteristics of subject among all studies are relatively homogenous. The participants were infants with gestational age at ≤32 weeks and birth weight ≤1600 g. The total subjects in each articles varied from 10-70 infants. The mydriatic agents used in this literature review were phenylephrine, tropicamide, cyclopentolate and the combination of those regiments. Doses of mydriatic agents used inthis review are variables. The lowest dose for phenylephrine is 1%, cyclopentolate is 0.2% and tropicamide is 0.5%. The highest dose for phenylephrine is 2.5%, cyclopentolate is 1.0 % and tropicamide is 1.0%.

Most of the studies were assigned the infants to receive one until three single drops mydriatic solution in each eye with range are 5 until 15 minutes.[12-18] Transcutaneous absorption was minimize by wiping any excess fluid away from peri-ocular area.[14-18] The baseline pupil was measured before instillation of the mydriatic agents and after the instillation the pupil was measured on 30 or 45 and 60 minutes. This data are presented in table 3, 4, and 5.

For optimal evaluation of the peripheral fundus some ophthalmologist recommend a pupillary diameter of at least 6 mm. On table 3, showed phenylephrine 2.5% and its combination achieved dilation of the pupil more than 6 mm. The greatest mean different amount of the pupil diameter at 60 minutes was 4.6±0,8, it is found in Sindel *et al*[14] study.

The result of the combination of phenylephrine and ciclopentolate on size of the pupil more than 6 mm, as shown in table 4. The greatest mean different amount of pupil size was 4.58±0.42 at 60 minutes. It was seen in Punyawattanaporn *et al*[18] study.

Rosales *et al*[12], Isenberg *et al*[13] and Bolt *et al*[15] studies showed dilation of the pupil less than 6 mm and only received cyclopegic agents like cyclopentolate and tropicamide or the combination of this agents. The lowest mean difference of pupil dilation in Rosales *et al*[12] is 3.06 mm as shown in table 5.

Table 2. Characteristic data of review articles

No	Author	Year of published	Level Evidence	Mydriatic agents	Subject (person)	Mean birth weight (grams)	Mean Gestational Age (weeks)
1	Rosales *et al*[12]	1981	III	0,5% T + 2,5% PE	10	<1600	NA
				0,5% T	3		
				0,5% C	3		
				0,5% T +0,5% C	3		
2	Isenberg *et al*[13]	1984	II	0,5% C	10	1198±220	N/A
				0,5% C +0,5% T	10	1227±220	
				1% PE + 0,2% C*	10	1273±251	
3	Sindel *et al*[14]	1986	II	1% T + 2,5% PE*	10	1022±226	28±1,9
				0,5% T + 2,5% PE +0,5% C*	10	1115±281	28,3±1,6
				1% T + 1% PE*	10	1110±317	29,0±2,4
4	Bolt *et al*[15]	1992	II	0,5% T + 2,5% PE*	20	1544	32,3
				0,5% C + 0,5% T*	19	1831	32,6
5	Khoo *et al*[16]	2000	II	0,2% C + 1% PE*	28	1657	NA
				0,5% T + 2,5% PE		1688	
6	Chew *et al*[17]	2005	II	1 %C + 2,5% PE	13	>1000	29,92±2,66
				1% T + 2,5% PE	13		29,23±1,59
				0,2% C + 1% PE*	13		29,44±2,28
7	Punyawattanaporn *et al*[20]	2009	II	0,2% C + 1% PE*	70	1368±438	30.49 + 2.34
				0,2% C + 1% PE*			

PE = Phenylephrine, C = Cyclopentolate, T = Tropicanimde, GA = Gestational age *combination in one bottle

Table 3. Size of dilated pupil using Phenylephrine and Tropicamide

No	Author	Mydriatic Agents	Frequency of Instillation	Pupil Baseline (mm)	30'/45' (mm)	Δ30'/ 45' (mm)	60' (mm)	Δ60' (mm)
1	Rosales *et al*[12]	2.5% PE + 0.5% T	3	2.65	N/A	N/A	6.55	3.9
2	Sindel *et al*[13]	2.5% PE + 0.5% T+ 0.5% C*	2	3.0±0.6	N/A	N/A	7.3±0.4	4.3±0.7
3	Bolt *et al*[15]	2.5% PE + 0.5% T*	2	1.68±0.44	4.0±0.69	2.32±0.56	6.0±0.87	4.32±0.6
				1.65±0.37	3.96±0.62	2.31±0.49	6.1±0.82	4.45±0.5
4	Khoo *et al*[16]	2.5% PE + 0.5% T	3	N/A	N/A	N/A	6.27±0.65	N/A
							6.25±0.66	
5	Sindel *et al*[14]	2.5% PE + 1% T	2	2.8±0.8	N/A	N/A	7.4±0.5	**4.6±0.8**
6	Chew *et al*[17]	2,5% PE + 1% T	2	2.09±0.54^{R}	5.98±0.64^{R}	3.89±0.59^{R}	6.34±0.56^{R}	4.01±0.5^{R}
				2.07±0.44^{L}	6.05±0.7^{L}	3.98±0.6^{L}	6.17±0.56^{L}	3.85±0.5^{L}
7	Sindel *et al*[14]	1% PE + 1% T	2	2.9±0.6	N/A	N/A	7.1±0.6	4.2±1.0

*combination in one bottle

PE = Phenylephrine, C = Cyclopentolate, T = Tropicanimde, R = Right eye, L = Left eye

Table 4. Size of dilated pupil using Phenylephrine and Cyclopentolate

No	Author	Mydriatic Agents	Frequency of Instillation	Pupil Baseline (mm)	30'/45' (mm)	Δ30'/ 45' (mm)	60' (mm)	Δ60' (mm)
1	Isenberg*et al*[15]	1% PE + 0.2% C*	2	N/A	5	N/A	5.6	N/A
2	Khoo*et al*[18]	1% PE + 0.2% C*	3	N/A	N/A	N/A	6.38±0.57 6.34±0.5	N/A
3	Chew*et al*[19]	1% PE + 0.2% C*	2	2.33±0.45^{R} 2.31±0.46^{L}	6.01±0.58^{R} 6.04±0.57^{L}	3.68±0.51^{R} 3.73±0.5^{L}	6.34±0.56^{R} 6.17±0.56^{L}	4.01±0.5^{R} 3.85±0.5^{L}
4	Punyawa ttanapornet *al*[20]	1% PE + 0.2% C*	3	2.19±0.44	6.02±0.56	3.83±0.5	6.77±0.41	4.58±0.42
5	Punyawa ttanapornet *al*[20]	1% PE + 0.2% C*	1	2.18±0.44	5.50±0.80	3.32±0.62	6.13±0.82	3.95±0.63
6	Chew *et al*[19]	2,5% PE + 1% C	2	1.97±0.59^{R} 2.01±0.61^{L}	6.01±0.58^{R} 6.04±0.57^{L}	3.68±0.51^{R} 3.73±0.5^{L}	6.47±0.51^{R} 6.49±0.48^{L}	4.5±0.55^{R} 4.48±0.5^{L}

*combination in one bottle
PE = Phenylephrine, C = Cyclopentolate, T = Tropicanimde, R = Right eye, L = Left eye

Table 5. Size of dilated pupil using Cyclopentolate and Tropicamide

No	Author	Mydriatic Agents	Frequency of Instillation	Pupil Baseline (mm)	30'/45' (mm)	Δ30'/ 45' (mm)	60' (mm)	Δ60' (mm)
1	Rosales*et al*[12]	0.5% T	3	2.44	N/A	N/A	5.5	3.06
2	Rosales*et al*[12]	0.5% C	3	2.44	N/A	N/A	5.5	3.06
3	Isenberg*et al*[13]	0.5% C	2	N/A	4.25	N/A	4.1	N/A
4	Rosales*et al*[12]	0.5% T + 0.5% C	3	2.44	N/A	N/A	5.5	3.06
5	Isenberg*et al*[13]	0.5% T + 0.5% C	2	N/A	4.25	N/A	4.1	N/A
6	Bolt*et al*[15]	0.5% T + 0.5% C*	2	1.95±0.55^{R} 1.95±0.55^{L}	3.9±0.7^{R} 3.8±0.8^{L}	1.95±0.66^{R} 1.92±0.67^{L}	5.42±0.58^{R} 5.4±0.66^{L}	3.47±0.56^{R} 3.45±0.60^{L}

PE = Phenylephrine, C = Cyclopentolate, T = Tropicanimde, R = Right eye, L = Left eye

The use of mydriatic regiments during newborn ophthalmic examinations has been associated with systemic side effects. Most reports have implicated the sympathomimetic component of the mydriatic solutions as the hypertensive agents. This review evaluated the safety of the drugs by examining the changes of blood pressure and heart rate. Vital signs were stable for at least 12 hours prior to the study in all infants. The blood pressure and heart rate was observed four times within 10-15 minutesafter instillations.[12-18] Changes in blood pressure and heart rate are presented in table 6 and 7.

Rosales *et al*[12], Sindel *et al*[13], Bruno *et al*[14] and Boo K *et al*[15] reported phenylephrine 2.5% and its combination achieved the greatest dilation of the pupil, but on table 6 showed blood pressure increased by these agents. The patient who only receive cyclopegic agent (tropicamide and cyclopentolate) showed minimal or none of increasing blood pressure. This reported by Rosales *et al*[12] and Bolt *et al*[15] studies.

The use of phenylephrine 2.5% tends toincrease pulse rate, nearly same with increasing of blood pressure. The other combination of mydriatic agents like phenylephrine 1% and cyclopentolate 0.2% in four studies showed decreasing or stable on blood pressure, in line with the result of the heart rate pulse. Using mono therapy agent like cyclopentolate and tropicamide not even increase the blood pressure, but tend to be ineffective in producing pupillary dilation.

DISCUSSION

In ophthalmology, screening for retinopathy of prematurity is a necessity since the risk loss of vision can be reduced on early treatment. The Multicenter trial of Cryoterapy for Retinopathy of Prematurity (CRYO ROP) achieved a reduction results in threshold retinopathy using cryotherapy.[7] In 2002, The Early treatment for retinopathy of prematurity cooperative group (ETROP) demonstrated better results applying laser treatment in a high risk pre-threshold retinopathy.[19]

Table 6. Blood pressure effects of mydriatics agents

No	Authors Mydriatic Agents	Rosales *et al*[12]	Isenberg *et al*[13]	Sindel *et al*[14]	Bolt *et al*[15]	Khoo *et al*[16]	Chew *et al*[17]	Punyawattanaporn *et al*[18]
1	2.5% PE + 1.0% T	-	-	Decreased 17.1±10.4%	-	-	Elevated 12.2%	-
2	2.5% PE + 0.5% T	Elevated >20%[#]	-	-	Elevated 3.1%	Elevated	-	-
3	2.5% PE + 1.0% C	-	-	-	-	-	Elevated 14.06%	-
4	1% PE + 0.2% C	-	Decreased 5.8±14%	-	-	Decreased	Elevated 10.1%	Stable in single and triple dose
5	1.0% PE + 1.0% T	-	-	Elevated 7.7±9.3%	-	-	-	-
6	2.5% PE + 0.5% T + 0.5% C	-	-	Elevated 22.8±17.4%	-	-	-	-
7	0.5% T	Stable	-	-	-	-	-	-
8	0.5% C	-	Decreased 10±12%	-	-	-	-	-
9	0.5% C + 0.5% T	Stable	Decreased 10±12%	-	Elevated 10%	-	-	-

Table 7. Pulse rate effects of mydriatic agents

No	Authors Mydriatic Agents	Rosales *et al*[12]	Isenberg *et al*[13]	Sindel *et al*[14]	Bolt *et al*[15]	Khoo *et al*[16]	Chew *et al*[17]	Punyawa ttanaporn *et al*[18]
1	2.5% PE + 1.0% T	-	-	Elevated 6.0±6.1%	-	-	Elevated <10 beats/ minutes	-
2	2.5% PE + 0.5% T	Stable	-	-	Decreased 0.9%	Decreased 8.86 beats/ minutes	-	-
3	2.5% PE + 1.0% C	-	-	-	-	-	Elevated <10 beats/ minutes	-
4	1% PE + 0.2% C	-	Decreased 1.7±11%	-	-	Decreased 9.64 beats/ minutes	Elevated <10 beats/ minutes	N/A
5	1.0% PE + 1.0% T	-	-	Elevated 4.4±5.2%	-	-	-	-
6	2.5% PE + 0.5% T + 0.5% C	-	-	Elevated 10±10.6%	-	-	-	-
7	0.5% T	Stable	-	-	-	-	-	-
8	0.5% C	-	Elevated 7.5±18%	-	-	-	-	-
9	0.5% C + 0.5% T*	Stable	Elevated 7.5±18%	-	Elevated 4.9%	-	-	-

PE = Phenylephrine, C = Cyclopentolate, T = Tropicanimde, R = Right eye, L = Left eye

In order to perform an ROP examination, the ophthalmologist views the retina with an indirect ophthalmoscope and the infant's eye is dilated with mydriaticum. Maximum mydriasis is required for an adequate indirect ophthalmoscopy in premature infants to allow diagnosis and grading of ROP. Dilation of the pupil or mydriasis is the result of an imbalance of dilator action. It can be caused by increased activity of the sympathetic pathway; decreased activity along the parasympathetic pathway and direct stimulation or inhibition of the effector smooth muscles. Furthermore, the dilator pupillary muscle is innervated by long ciliary nerves that carrying the postganglionic fibers of the sympathetic nervous system and synapse in the superior cervical ganglion. The dilator muscle of the iris contains fibers that extend radially through the iris of the eye.[22] Two classes of drugs that produce a mydriasis effect when instilled into the eye is sympathomimetic or adrenergic agents, including phenylephrine, hydroxyamphetamine, adrenaline and the parasympatholytic agents or anticholinergic including anti-muscarinic drugs (atropine, tropicamide, and cyclopentolate).[9] Anti-muscarinic drugs abolished the action of acetylcholine cause paralysis of the iris spinchter and paralyze the ciliary muscle. Anti muscarinic can cause dose related toxicity such as flushing, fever, tachycardia and even seizure.[9] Buyukcam A *et al*[22] reported a case of myoclonic seizure due to 1% cyclopentolate eye drop in preterm infant.

CONCLUSION

Phenylephrine 2.5% with Tropicamide 1.0% reach the greatest dilated pupil compared with the other mydriatic regimens. Size of the pupil more than 7mm, but these regimens can cause increase blood pressure and minimal heart rate increase. Using only cyclopegic regimens did not produce adequate mydriasis in infants. The combination of low concentration sympathomimetic (phenylephrine 1%) and parasympatholytic (Cyclopentolate 0.2%) produces adequate pupillary dilation and does not cause an increase in blood pressure and heart rate.

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