Online Supplemental Material

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Supplemental Method

Participants

Contraindication to phenylephrine and/or cyclopentolate eye drops included, for example, previous significant adverse drug reaction, medical conditions that are contraindicated such as glaucoma. ROP stage 2 or greater are known to have difficult dilation, and therefore could confound the results of this non-inferiority study.

Interventions

A microdrop dose was achieved by attaching a 24-gauge cannula (with needle removed) to the end of a syringe. Repeat dosing of mydriatics, to a maximum of three doses to achieve ROPEE is standard clinical practice.(1, 2)

Outcomes

Secondary outcomes

Easy was rated if fundal examination was not impeded by inadequate pupil dilatation. Difficult was rated if fundal examination was impeded by inadequate pupil dilatation and either further mydriatic drops (up to three doses in total) were required to see the peripheral retina or additional manipulation to overcome inadequate pupil dilatation. A RetCam or Indirect Ophthalmoscope was used to perform ROPEE.

The Metric Graduated Colour Tool (patent 2017904788), with participant number, was placed on a fabric band and then attached to the infants forehead.(3) A red reflex digital photo of each eye was taken at the time of ROPEE. Photos were imported into the GIMP 2.10.22 Image Manipulation Program and the Measure Tool used to measure the pupil diameter.

An increase was indicated if an infant had their respiratory support intensified, e.g., moved from High Flow Oxygen to Continuous Positive Airways Pressure (CPAP). A decrease was indicated if an infant had a reduction in respiratory support, e.g., High Flow to Low Flow Oxygen.

Randomisation

Both LD and VLD microdrops were commercially prepared specifically for this study, of identical appearance and volume, and labelling had drug name (no concentration) and participant name and number. Only the company compounding the eye drops were unmasked to the study. Infant's whānau and/or caregivers and all staff involved with the study, including ophthalmologists involved with assessing ROPEE outcomes were all masked to randomisation.

Statistical Methods

Primary efficacy outcome measures were analysed using interval estimation for the difference between independent proportions. Secondary outcome measures were analysed using Fisher's exact test of independence.

Statistical analysis and sample size calculations were performed using STATA (17, Texas).

References

1. Austin N, Dal S. Consensus statement for Screening for Retinopathy of Prematurity for the Newborn Clinical Network Clinical Reference Group, and the Paediatric Ophthalmology Interest Group. 2015.
2. Ophthalmologists RCo, Health RCoPaC. Guideline for the Screening and Treatment of Retinopathy of Prematurity. 2008.
3. August D, Hitchcock I, Tangney J, Ray RA, Kandasamy Y, New K. Graduated colour tape measure: development and demonstration of this tool in a case series of neonatal skin injuries. J Tissue Viability. 2019;28(3):133-8.

Supplementary Table 1 Primary Outcome Measure in the Modified Intention to Treat Analysis

	Low Dose (n=76)	**Very Low Dose (n=74)**
Successful ROPEE, n (%)		
Yes	76 (100)	74 (100)
No	0	0
95% CI: no continuity correction	-0.05 – 0.05 (p^{LD}-p^{VLD}=0)	
95% CI: continuity correction	-0.06 – 0.06 (p^{LD}-p^{VLD}=0)	

ROPEE = retinopathy of prematurity eye examination, ROP = retinopathy of prematurity, CI = confidence interval.

Supplementary Table 2 Exploratory Outcome Measures for Modified Intention to Treat Analysis

	Easy	**Difficult**	**p-value**
Pupil dilation			
Number of eyes (%)	112 (73)	128 (86)	
5 – 7 mm			
Low dose	98 (98)	2 (2)	
Very low dose	87 (95)	5 (5)	
3 – 4.9 mm			
Low dose	8 (66)	4 (33)	
Very low dose	26 (72)	10 (28)	
Pupil size and ease of screen, OR (95%CI) adjusted for treatment group	0.18 (0.09 – 0.37)		0.000
Iris pigmentation and ease of screen			
Light			
Low dose	48 (94)	3 (6)	
Very low dose	39 (91)	2 (8)	
Dark			

Low dose	39 (91)	4 (9)	
Very low dose	26 (84)	5 (16)	
Iris pigmentation and ease of screen, OR (95%CI) adjusted for treatment group	1.77 (0.53 – 5.93)		>0.05
Stage of ROP following study ROPEE and ease of screen, n (%)			
None			
Low dose	52 (96)	2 (4)	
Very low dose	41 (89)	2 (4)	
Stage 1			
Low dose	9 (90)	1 (10)	
Very low dose	19 (89)	2 (11)	
Stage 2			
Low dose	9 (90)	1 (10)	
Very low dose	7 (89)	2 (89)	
Stage 3			
Low dose	1 (100)	0	
Very low dose	0	0	
Stage of ROP and ease of screen, OR (95%CI) adjusted for treatment group	1.87 (0.92 - 3.80)		>0.05

ROPEE = retinopathy of prematurity eye examination, ROP = retinopathy of prematurity, CI = confidence interval

Supplementary Table 3 Exploratory Outcome Measure Analysis for Māori

	Low Dose (n = 16)	**Very Low Dose (n = 15)**	**p-value**
Successful ROPEE, n (%)			
Yes	16 (100)	15 (100)	
No	0	0	
95% CI: no continuity correction	-0.20 – 0.19		
95% CI: continuity correction	-0.25 – 0.24		
Number of doses of study drug, n (%)			
One	15 (94)	15 (100)	
Two	1 (6)	0	
RR (95% CI)	2 (1.40 - 2.86)		>0.05
Ease of screen, n (%)			
Easy	15 (94)	13 (87)	
Difficult	1 (6)	2 (13)	
RR (95% CI)	0.62 (0.12 - 3.20)		>0.05
Pupil dilation			
Number of eyes (%)	28 (88)	29 (97)	
Pupil dilation (mm), mean ± SD	5.5 ± 0.6	5 ± 0.8	
Difference between means (mm) (95% CI)	0.6 (0.2 – 0.9)		0.003
Pupil dilation range (mm)			
5 – 7 mm	27 (96)	19 (66)	
3 – 4.9 mm	1 (4)	10 (34)	

	Low Dose (n = 16)	**Very Low Dose (n = 15)**	**p-value**
Iris pigmentation and ease of screen, n (%)	**Easy**	**Difficult**	
Light			
Low dose	9 (100)	0	
Very low dose	8 (100)	0	
Dark			
Low dose	6 (86)	1 (14)	
Very low dose	5 (71)	2 (29)	
Iris pigmentation and ease of screen, OR (95%CI) adjusted for treatment group	1 (95%CI not calculable)		
Stage of ROP following study ROPEE and ease of screen, n (%)			
None			
Low dose	10 (100)	0	
Very low dose	9 (90)	1 (10)	
Stage 1			
Low dose	3 (100)	0	
Very low dose	4 (80)	1 (20)	
Stage 2			
Low dose	2 (66)	1 (33)	
Very low dose	0	0	
Stage of ROP and ease of screen, OR (95%CI) adjusted for treatment group	5.59 (0.60 - 51.97)		>0.05

ROPEE = retinopathy of prematurity eye examination, ROP = retinopathy of prematurity, EE = eye examination, CI = confidence interval.

Supplementary Table 4 Exploratory Outcome Measure Analysis for Blood Pressure and Heart Rate responses in Māori

	Low Dose (n = 16)	**Very Low Dose (n = 15)**	**p-value**
Mean blood pressure			
Baseline			
Number of BP measurements (%)	16 (100)	14 (93)	
Mean BP (mmHg) ± SD (95% CI)	48 ± 7.5 (44 – 52)	60 ± 15 (51 – 69)	
20 min			
Number of BP measurements (%)	16 (100)	13 (93)	
Mean BP (mmHg) ± SD (95% CI)	51 ± 12 (45 – 57)	53 ± 10 (47 – 59)	
Change in blood pressure from baseline to 20 min			
Mean change in BP (mmHg) ± SD (95% CI)	-2.7 ± 11.2 (-8.7 – 3.3)	5.8 ± 2.5 (0.3 – 11.2)	0.037
Prior to ROPEE			
Number of BP measurements (%)	15 (94)	13 (93)	
Mean BP (mmHg) ± SD	52 ± 8	55 ± 11	

(95% CI)	(42 – 62)	(48 – 62)	
Change in blood pressure from baseline to ROPEE			
Mean change in BP (mmHg) ± SD (95% CI)	-1.3 ± 16 (-9.8 – 7.2)	4.0 ± 10.9 (-2.5 – 10.7)	>0.05
Heart Rate			
Baseline			
Number of HR measurements (%)	16 (100)	14 (93)	
Mean HR (beats/min) ± SD (95% CI)	157 ± 13 (150 – 164)	165 ± 21 (153 – 177)	
20 min			
Number of HR measurements (%)	16 (100)	13 (93)	
Mean HR (beats/min) ± SD (95% CI)	151 ± 8.8 (146 – 156)	158 ± 14 (150 – 166)	
Change in heart rate from baseline to 20 min			
Mean change in HR (beats/min) ± SD (95% CI)	6.6 ± 12.6 (-0.1 – 13.3)	4.8 ± 15.7 (-4.6 – 14.3)	>0.05
Prior to ROPEE			
Number of HR measurements (%)	16 (100)	13 (93)	
Mean HR (beats/min) ± SD (95% CI)	149 ± 12 (143 – 155)	158 ± 13 (150 – 166)	
Change in heart rate from baseline to ROPEE			
Mean change in HR (beats/min) ± SD (95% CI)	8.3 ± 16.3 (-0.4 – 17.0)	4.0 ± 10.9 (-2.5 – 10.7)	>0.05

BP = blood pressure, SD = standard deviation, ROPEE = retinopathy of prematurity eye examination, min = minute, HR = heart rate, CI = confidence interval.