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Low dose or very low dose phenylephrine and cyclopentolate microdrops for retinopathy of prematurity eye examinations (The Little Eye Drop Study): a randomised controlled non-inferiority trial

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ABSTRACT

Objective To determine if very low dose (VLD, 0.5% phenylephrine, 0.1% cyclopentolate) mydriatic microdrop (approximately 7 µL) administration (up to three doses) is non-inferior to low dose (LD, 1% phenylephrine, 0.2% cyclopentolate) mydriatic microdrop administration for ophthalmologist-determined successful retinopathy of prematurity eye examination (ROPEE).

Design Multicentre, prospective, randomised controlled, non-inferiority clinical trial.

Setting Four neonatal intensive care units in Aotearoa, New Zealand from October 2019 to September 2021.

Patients Infants with a birth weight less than 1250 g or gestational age less than 30+6 weeks and who required a ROPEE.

Interventions The intervention: microdrop (approximately 7 µL) of VLD (0.5% phenylephrine and 0.1% cyclopentolate) to both eyes, or the comparison: microdrop of LD (1% phenylephrine and 0.2% cyclopentolate) to both eyes. Up to three doses could be administered.

Main outcome measures The primary outcome measure was an ophthalmologist-determined successful ROPEE.

Results One hundred and fifty preterm infants (LD mean GA=27.4±1.8 weeks, mean birth weight=1011±290 g, VLD mean GA=27.5±1.9 weeks, mean birth weight=1049±281 g,) were randomised. Non-inferiority for successful ROPEE was demonstrated for the VLD group compared with the LD group (VLD successful ROPEE=100%, LD successful ROPEE=100%, 95% CI no continuity correction −0.05 to 0.05) and for Māori (95% CI no continuity correction −0.02 to 0.19).

Conclusion VLD microdrops enable safe and effective screening for ROPEE in both Māori and non-Māori preterm infants.

Trial registration number ACTRN12619000795190.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Very preterm infants require serial retinal examinations to screen for retinopathy of prematurity (ROP), and with timely diagnosis and treatment permanent blindness can be prevented.

⇒ The evidence base for optimal, lowest-effective-dose, mydriatic eye drop regimens used in ROP eye examinations (ROPEE) is limited, and preterm infants frequently receive mydriatic eye drop doses equivalent to, or higher than, doses administered to adults.

⇒ Drug administration via microdrops (approximately 7 µL) is likely to be associated with fewer adverse effects as the smaller volume will lead to lower systemic absorption, resulting in a reduction in systemic adverse effects.

WHAT THIS STUDY ADDS

⇒ In preterm infants, very low dose (VLD) microdrop administration of phenylephrine (0.5%) and cyclopentolate (0.1%) was non-inferior for successful ROPEE compared with low-dose microdrop administration of phenylephrine (1%) and cyclopentolate (0.2%).

⇒ Successful ROPEE was completed in all infants, and mostly rated as easy by ophthalmologists despite less pupil dilation in infants who received VLD. No significant systemic side effects were identified in either group.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Evidence provided from this research can be used to inform clinical care guidelines, to enable a neonatal specific mydriatic regimen to be used in clinical practice.

⇒ Using a neonatal specific mydriatic regimen will facilitate safer use of mydriatics in preterm infants.

INTRODUCTION

Retinopathy of prematurity (ROP) is a vascular proliferative disorder and, with higher stage disease (stage 3 or 4), represents a leading preventable cause of childhood blindness worldwide.[1] ROP is diagnosed with routine ROP eye examinations (ROPEE) and with timely diagnosis and intervention, blindness can be prevented.[2]

To perform ROPEE, mydriatic eye drops containing phenylephrine with cyclopentolate or tropicamide are used. Throughout neonatal intensive care units (NICUs) in Aotearoa New Zealand

(NZ) and Australia a wide variety of dose regimens are used, with some using doses equivalent to, or exceeding, adult doses.[3] It is estimated that 80% of the mydriatic eye drop volume enters the nasolacrimal duct and is systemically absorbed.[4 5] Systemic absorption of mydriatics in infants can result in adverse effects on the cardiovascular, respiratory and gastrointestinal systems.[6] A systematic review indicated that low dose (LD) mydriatics are likely to be effective for ROPEE with reduced risk of adverse systemic effects.[6] Interventional studies in preterm infants suggest that LD microdrop administration is likely to achieve effective ROPEE and have an improved tolerability profile.[6–8] Whether further dose decrements will achieve successful ROPEE and reduce systemic side effects even further is unknown; thus work is needed to determine lowest effective dose for successful ROPEE. Additionally, among preterm infants the impact of ethnicity (specifically for Māori in NZ), iris pigmentation and stage of ROP on mydriatic response are all factors that remain to be determined and may be an important element for an individualised approach to ROPEE.

METHODS

This multicentre, prospective, randomised controlled, non-inferiority clinical trial was conducted in four tertiary NICUs in NZ, from October 2019 to September 2021.

Objectives

Primary objective

To determine if very low dose (VLD, 0.5% phenylephrine, 0.1% cyclopentolate) mydriatic microdrop administration (up to three doses) is non-inferior, for efficacy, to LD (1% phenylephrine, 0.2% cyclopentolate) mydriatic microdrop administration for ophthalmologist-determined successful ROPEE.

Secondary objectives

To identify the level of ophthalmologist-rated ease or difficulty of ROPEE, to determine pupil size at the time of ROPEE, and to characterise the impact of VLD or LD microdrop administration on blood pressure, heart rate, respiratory function or feed tolerance following ROPEE.

Exploratory objectives

To determine the efficacy and safety of LD and VLD eye drops in Māori, if light or dark iris pigment, or stage of ROP influences ease of screen, and record treatment-emergent adverse effects.

Participants

Infants were eligible if they had a birth weight less than 1250 g or gestational age less than 30^{+6} weeks and were recruited by the attending clinical team as requiring ROPEE (either first or routine follow-up screening ROPEE) as part of their usual care. Exclusion criteria were ROP greater than stage 2, current eye infection, contraindication to phenylephrine and/or cyclopentolate eye drops. Written informed consent was obtained for all participants. One data set from one ROPEE was collected per participant.

Interventions

Infants were randomised to receive either the intervention: microdrop (approximately 7 μL) of VLD (0.5% phenylephrine and 0.1% cyclopentolate) to both eyes, or the comparison: microdrop of LD (1% phenylephrine and 0.2% cyclopentolate) to both eyes. If the ophthalmologist determined that the pupil was insufficiently dilated with one drop, up to two further microdrops of the same dose were administered to the affected eye(s), 20 min apart.

Outcomes

Primary outcome

Successful ROPEE, defined as the ophthalmologist reporting that the degree of pupil dilation in both eyes did not interfere with the ROPEE following up to three doses of the study eye drops.

Secondary outcomes

The eye examination overall was rated as either easy or difficult (not per eye). Ease of screen was determined by the examining ophthalmologist at the time of ROPEE and defined either as easy or difficult. To determine pupil dilation both eyes were photographed at the time of ROPEE, 30–45 min after microdrop administration.

Mean baseline blood pressure and heart rate measurements were recorded using clinical monitoring equipment in routine use at each trial site. Subsequent measurements were taken 20 min after first eye drop instillation and then immediately before ROPEE. Any clinically significant changes were determined by the clinical team.

Clinical records were reviewed for any change in overall daily level of respiratory support for 24 hours prior, day of and 24 hours after ROPEE.

Feed tolerance was assessed by retrospectively reviewing feed volumes and spills, on the observation chart, for 24 hours prior and 24 hours post ROPEE. Clinical records were reviewed for 7 days post ROPEE for any documentation of necrotising enterocolitis (NEC), as diagnosed by Bell's criteria stage 2 and above.[9]

Baseline characteristics

Ethnicity was determined by asking whānau and/or caregivers to define their infant's ethnicity which was then classified as the priority ethnicity (Ministry of Health, NZ guideline, 2010).[10]

Dark or light iris pigmentation was characterised by the ophthalmologist or when LJK reviewed ocular photographs.

Statistical methods

Sample size

The hypothesis for non-inferiority was the upper 95% CI for the difference in efficacy between the LD and VLD groups (LD – VLD) being less than 15%, with 15% being the predetermined acceptable ROPEE failure rate. The 2005 European Medicines Agency Guideline on the Choice of the Non-Inferiority Margin (EMEA/CPMP/EWP/2158/99) was used to inform the 15% non-inferiority margin.[11] A pilot study was used to determine the treatment effect size. To determine a clinically non-significant difference in efficacy, an expert panel consisting of ophthalmologists working in the field of neonatal retinal screening was consulted. This process determined a 15% non-inferiority margin.

Sample size calculation was performed using simulations with equal treatment group sizes and anticipated success rates based on the prior pilot study, and 95% CI estimations.[7] Allowing for a dropout rate of 3 per group a total of 150 infants was required, with 75 infants per group to obtain an upper 95% CI<15%.

Randomisation

Infants were randomised to treatment according to computer-generated block randomisation in groups of 10 and stratified by centre. Allocation remained concealed until analysis.

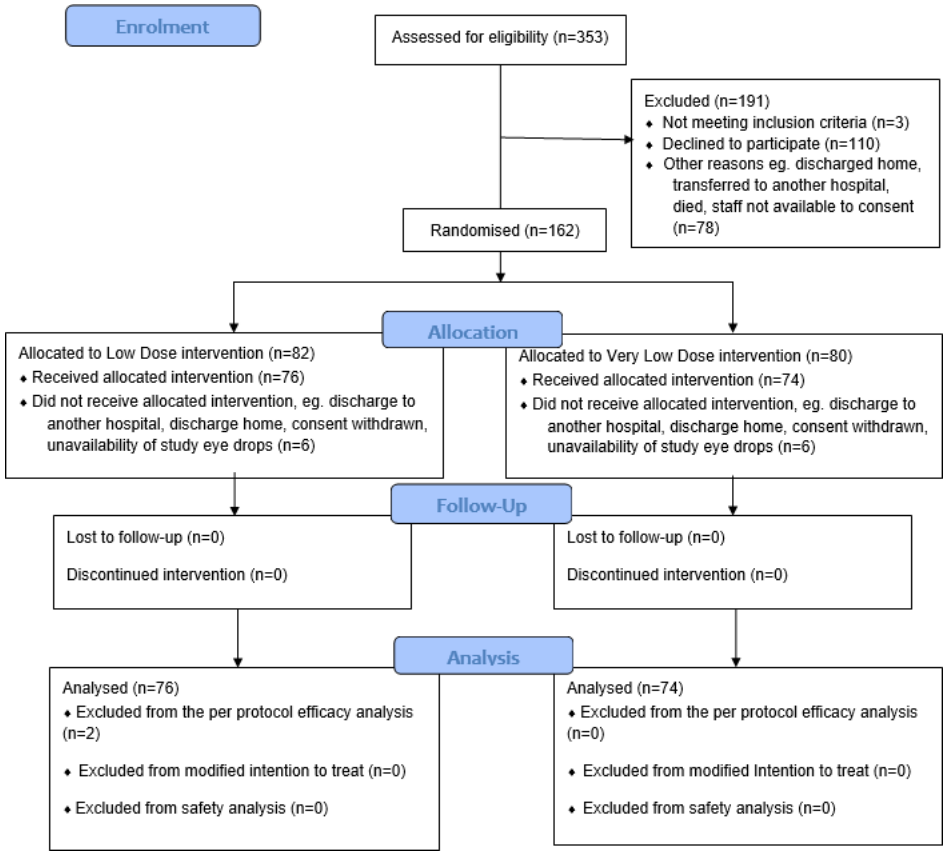

Figure 1 CONSORT flow diagram.

Statistical methods

The primary analysis was per protocol (PP) including all infants with primary outcome efficacy data, and no major protocol deviations (eg, non-study eye drops used). The modified intention-to-treat (mITT) confirmatory analysis included all infants that received study treatment and had outcome observations.

RESULTS

There were 162 infants who met the inclusion criteria and were randomised to receive either LD (n=82) or VLD (n=80) mydriatic eye drops (figure 1). Twelve of these infants (six/group) did not receive the allocated intervention because they were either discharged home, transferred to another hospital, the study eye drops were not available, or consent withdrawn (figure 1). Two infants were recruited into the study but were excluded because ROP was greater than stage 2. The remaining 150 infants underwent ROPEE using the allocated study interventions and are included in the analysis: 76 in the LD group and 74 in the VLD group.

Baseline demographic and clinical characteristics

There were no differences in baseline participant characteristics between those assigned to LD or VLD microdrops (table 1).

Table 1 Baseline demographic and clinical characteristics for all infants

	Low dose (LD) (n=76)	Very low dose (VLD) (n=74)
Gestational age at birth (weeks)	27.4±1.8	27.5±1.9
Gestational age at ROPEE (weeks)	34.9±2.2	35.1±2.5
Birth weight (grams)	1011±290	1049±281
Extremely low birth weight (<1000 g)	42 (54)	32 (3)
Male, n (%)	44 (58)	38 (51)
Ethnicity, n (%)		
Māori	16 (21)	15 (20)
Pacific Peoples	5 (7)	8 (11)
New Zealand European	44 (58)	41 (55)
Asian	10 (13)	9 (12)
Other	1 (1)	1 (1)
Dark iris pigment, n (%)	26 (34)	31 (42)
Stage of ROP, n (%)		
Unknown (first eye examination)	10 (13)	15 (20)
None	50 (66)	41 (55)
Stage 1	8 (11)	14 (19)
Stage 2	5 (7)	3 (4)

Data are mean (SD) or n (%). Missing data for stage of ROP; LD=3, VLD=1.
ROP, retinopathy of prematurity; ROPEE, retinopathy of prematurity eye examination.

Primary outcome

Using the non-inferiority limit of 15% (0.15), non-inferiority of the VLD regimen, for efficacy, to the LD regimen is demonstrated (95% CI −0.09 to 0.03, which is the difference in proportions

Table 2 Secondary outcome measures for ease of screen, pupil dilation, frequency and grade of ROPEE in the modified intention-to-treat analysis

	Low dose (n=76)	Very low dose (n=74)	P value
Ease of ROPEE, n (%)			
Easy	71 (93)	65 (88)	
Difficult	5 (7)	9 (12)	
RR (95% CI)	0.54 (0.19 to 1.53)		0.27
Number of doses of study drug, n (%)			
One	70 (92)	63 (85)	
Two	4 (5)	11 (15)	
Three	0	0	
Protocol deviation (two study drops, one non-study drop)	2 (3)	0	
RR (95% CI)	0.36 (0.12 to 1.09)		0.10
Pupil dilation			
Number of eyes (%)	112 (73)	128 (86)	
Pupil dilation (mm), mean±SD	5.50±0.70	5.10±0.80	
Difference between means (mm) (95% CI)	0.40 (0.20 to 0.60)		0.01
Pupil dilation range, n (%)			
5–7 mm	100 (90)	92 (72)	
3–4.9 mm	12 (10)	36 (28)	
RR (95% CI)	0.38 (0.21 to 0.70)		0.01
Stage of ROP at EE			
None	54 (71)	46 (62)	
Stage 1	10 (13)	19 (26)	
Stage 2	10 (13)	9 (12)	
Stage 3	2 (3)	0	
RR (95% CI) for none to stage 1 compared with stage 2 or 3	1.30 (0.58 to 2.90)		0.64

Missing data for pupil dilation (LD n=40, VLD n=20).
EE, eye examination; LD, low dose; ROP, retinopathy of prematurity; ROPEE, retinopathy of prematurity eye examination; VLD, very low dose.

(LD=97%, VLD=100%) for the PP (primary) analysis without continuity correction).

Two participants in the LD group had a deviation from the trial protocol (inadvertent administration of the sites' mydriatic regimen (one standard drop size of phenylephrine with tropicamide) rather than trial mydriatic drops at time of ROPEE) and were excluded from the PP analysis (LD n=76, VLD n=74) and included in the mITT analysis (LD n=74, VLD n=74).

Modified intention to treat

The 95% CI for the difference in proportions for the mITT analysis was −0.05 to 0.05 without continuity correction; −0.06 to 0.06 with continuity correction (online supplemental table 1). Thus, using the same non-inferiority limit of 15% (0.15), non-inferiority of the VLD to the LD eye drop regimen was demonstrated.

Secondary outcomes

Ophthalmologist rated ease of screen as easy in most participants (RR 0.54, 95% CI 0.19 to 1.53, p=0.27) (table 2). In most cases, single administration of mydriatic eye drops was given (RR 0.36, 95% CI 0.12 to 1.09, p=0.10). Smaller pupil dilation occurred in the VLD group compared with the LD group (RR 0.38, 95% CI 0.21 to 0.70, p=0.01).

There were 60 (20%) missing data for pupil dilation. Reasons for this were because of the difficulty in obtaining good quality photos of the neonatal eye at the time of ROPEE, specifically; poor lighting, eye averted, pupil only partially visible.

Most participants had ROP diagnosis (in at least one eye) at the time of ROPEE of none or 1 (RR 1.30, 95% CI 0.58 to 2.90, p=0.6395).

Safety

No clinically or statistically significant changes in blood pressure or heart rate occurred after eye drop administration in either the LD or the VLD group (table 3).

No infants had clinically significant respiratory events or change in level of respiratory support following the use of LD or VLD eye drops in the day of, or day following, ROPEE.

Two infants in the LD treatment group required an increase in inspired oxygen concentration without a change of respiratory support modality. One infant in the VLD group required increased inspired oxygen concentration on the day of, and day after, ROPEE.

No infants developed clinically significant gastrointestinal complications, including NEC, following administration of LD or VLD mydriatic microdrops on the 7 days following the ROPEE.

No infants developed treatment-emergent adverse effects following the use of LD or VLD eye drops.

Exploratory outcomes

Pupil dilation impacted ease of screen at ROPEE (adj OR 0.18, 95% CI 0.09 to 0.97, p=0.01), with difficulty increasing in the VLD group with pupil dilation between 3 mm and 4.9 mm (online supplemental table 2).

Neither iris pigmentation (adj OR 1.77, 95% CI 0.53 to 5.93, p>0.05) nor presence of ROP impacted ease of ROPEE (adj OR 1.8, 95% CI 0.92 to 3.80, p>0.05). All infants who had stage 2 or 3 ROP diagnosed (LD n=11, VLD n=9), had successful eye examinations, with most rated as easy (LD: ROP2 90%, VLD: ROP2 89%).

Exploratory Māori subgroup PP efficacy analysis

The proportion of Māori infants recruited was 20% (n=31), with no protocol deviations in either group. All infants had a successful ROPEE (95% CI −0.02 to 0.19) (online supplemental table 3).

There were no statistically significant differences between groups for number of administrations, ease of screen, eye colour or ROP. There was a statistically significant difference between pupil dilation means of LD and VLD groups (0.6 mm, 95% CI 0.2 to 0.9 mm, p=0.003) (online supplemental table 3).

There was a statistically significant increase in blood pressure from baseline in the LD group, but this was transient and did not require clinical intervention (online supplemental table 4).

No Māori infants in either group had an increase in respiratory support or emergence of gastrointestinal symptoms, including NEC, during data collection compared with non-Māori infants.

DISCUSSION

In this randomised controlled trial, we have demonstrated that VLD mydriatic microdrops are non-inferior to LD mydriatic microdrops for successful completion of ROPEE in preterm infants. Successful ROPEE was completed in all infants, most had single administration of the mydriatics, and most of the eye examinations were rated as easy by ophthalmologists, although

Table 3 Secondary outcome measure per protocol analysis for blood pressure (BP) and heart rate

	Low dose (n=76)	Very low dose (n=74)	P value
BP			
Baseline			
Number of BP measurements (%)	76 (100)	74 (100)	
BP (mm Hg) mean±SD	54±12	55±11	
(95% CI)	(51 to 57)	(52 to 57)	
20 min			
Number of BP measurements (%)	76 (100)	71 (96)	
BP (mm Hg) mean±SD (95% CI)	52±9	53±10	
	(50 to 54)	(51 to 55)	
Change in BP from baseline to 20 min			
Mean change in BP (mm Hg)±SD	1.80±12.60	0.70±1.20	0.57
(95% CI)	(–1.10 to 4.70)	(–1.70 to 3.10)	
Prior to ROPEE			
Number of BP measurements (%)	73 (96)	71 (96)	
Mean BP (mm Hg)±SD	55±9	53±10	
(95% CI)	(53 to 57)	(51 to 55)	
Change in BP from baseline to ROPEE			
Mean change in BP (mm Hg)±SD	–0.30±11.90	0.90±9.40	0.47
(95% CI)	(–3.20 to 2.50)	(–1.30 to 3.20)	
Heart rate			
Baseline			
Number of heart rate measurements (%)	75 (99)	72 (97)	
Mean heart rate (beats/min) ± SD	160±14	160±16	
(95% CI)	(157 to 163)	(156 to 164)	
20 min			
Number of heart rate measurements (%)	76 (100)	72 (97)	
Mean heart rate (beats/min) ± SD	156±15	158±14	
(95% CI)	(153 to 159)	(155 to 161)	
Change in heart rate from baseline to 20 min			
Mean change in heart rate (beats/min) ± SD	2.80±23.30	0.70±13.70	0.5
(95% CI)	(–2.50 to 8.20)	(–2.60 to 3.90)	
Prior to ROPEE			
Number of heart rate measurements (%)	73 (96)	71 (91)	
Mean heart rate (beats/min) ± SD	154±15	156±16	
(95% CI)	(150 to 158)	(152 to 160)	
Change in heart rate from baseline to ROPEE			
Mean change in heart rate (beats/min) ± SD	6.40±16.80	2.5±14.4	0.15
(95% CI)	(2.40 to 10.4)	(–0.9 to 6.0)	

ROPEE, retinopathy of prematurity eye examination.

difficulty did increase in the VLD group with pupil dilation below 4.9 mm.

Our study, alongside other published literature, suggests that the use of microdrops produces adequate pupil dilation for a successful ROPEE.[7 8 12] A surprising finding was that ophthalmologists were able to perform a ROPEE with pupil dilation as low as 3 mm, although there were 20% missing pupil dilation data, so results should be interpreted with caution. Ophthalmologists were more likely to rate the screen as easy when the pupil was dilated between 5 mm and 7 mm. This is supported by Vicente *et al* who recommend a pupil dilation >5 mm to adequately view the retina.[13] Pupil dilation requirements for adequacy of view may differ between clinicians and by having a multicentre trial we can be confident that the findings reflect this. Although there was not a statistically significant difference for the ease of screen between the two groups, there was a statistically significant difference in pupil dilation; however this did not influence the success of the ROPEE.

Previous studies have suggested that infants with dark iris pigmentation may require higher mydriatic doses,[14–16] however we found that iris pigment did not have an impact on ease of screen or ROPEE success rate.

Mydriatic eye drops are associated with adverse effects and therefore efforts to reduce drug exposure during ROPEE are ongoing. In addition to cardiovascular and respiratory effects, case reports and studies have documented NEC, seizures, anticholinergic syndrome, periorbital pallor and renal failure associated with ROPEE examinations and medications.[12 17–27] None of these complications were observed during our study. There is conflicting evidence in literature about clinically significant changes in blood pressure and respiratory rates in preterm infants following mydriatic use.[6 28] In Māori infants, we found a small but statistically significant elevation in blood pressure in infants in the LD group, although the clinical implication of this finding is limited due to the small sample size. Others have reported on elevated blood concentrations of mydriatics

associated with altered oxygen saturations, suggesting a tiered approach to mydriatic dosing for infants who require respiratory support.[29] If the risk of systemic absorption was minimised by using microdrops, then a tiered approach to dosing would likely not be required, and this is supported in our study with no changes in respiratory support needed in either group of infants.

Māori infants in NZ are less likely to experience the same level of advantage and systemic privilege for equitable health outcomes; therefore, to contribute to achieving health equity for Māori, recruitment and participation inclusion in clinical trials are needed.[30 31] Our study had a high recruitment rate of Māori infants (20%), and analysis included a focus on these infants given their indigenous status and priority of equity within NZ. Safety and efficacy outcomes for this group were not significantly different than NZ European infants, including iris pigment. Subgroup analysis of Māori infants within this study is a strength, to ensure equity is considered in the analysis.[32] Overall, LD microdrops are an option to reduce the risk of adverse effects.

Limitations

Results should not be extrapolated to infants born at more than 30 weeks gestational age or to older children as mydriatic responsivity outside of our target population may differ. Although there were two protocol deviations, it is not anticipated that this influenced the overall outcomes. Blood pressure and heart rate data only reflect the influence of one administration of the study eye drops. If one eye was determined to be difficult, the entire eye exam was coded as difficult. If an additional dose was required, the entire eye exam was coded as both eyes needing two or three drops. It is also thought that infants with ROP grade 2 or 3 may have pupils more resistant to dilation and may require higher mydriatic doses; however there were insufficient participant numbers in this study to allow analysis for this potential influence on mydriasis. Further investigation is required.

The exploratory Māori analysis suggests trends for this group, and an adequately powered study to allow equal explanatory power for Māori in the future is required given high rates of prematurity for Māori infants.[32]

CONCLUSION

VLD microdrops enable safe, effective screening for ROPEE in all preterm infants. Both LD and VLD microdrop eye drop regimens were effective at providing sufficient pupil dilation for ROPEE.

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Contributors Study concept: RB. Study design: LJK, RB, DMR, NM and MJS. Data acquisition: LJK, LE, NCA, MJB, JMA and site research nurses. Data analysis: LJK, DMR, NM. Data interpretation: LJK, NM, LE, MJS, JMA, DMR. Drafting of the report: LJK. Overall content guarantor: LJK

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Competing interests None declared.

Patient consent for publication Consent obtained from parent(s)/guardian(s).

Ethics approval This study involves human participants and was approved by Central Health and Disability Ethics Committee, Southern Aotearoa, New Zealand (19/STH/114, 20/06/2019). Locality approval was given by each site. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. The data that support the findings of this study will be made available by LJK via Figshare, but restrictions apply to the availability of the deidentified data and are not publicly available.

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