

Retinopathy of prematurity: systemic complications associated with different anaesthetic techniques at treatment

Paul M Haigh, Malcolm L Chiswick, Eamonn P O'Donoghue

Abstract

Background—Treatment of retinopathy of prematurity (ROP) in the UK is subject to considerable regional variation in terms of anaesthetic support. Change in practice at St Mary's neonatal medical unit from topical to general anaesthesia and, subsequently, to sedation/analgesia allowed comparison of the impact of these three modalities on infants' early postoperative course in a consecutive, non-randomised, observational study.

Methods—The study population consisted of 30 babies undergoing treatment of threshold ROP. Twelve were treated using topical anaesthesia alone (group A), six using general anaesthesia (group B), and 12 using sedation/analgesia combined with elective intubation and artificial ventilation (group C). Daily measurements of infant health were recorded starting 4 days preoperatively and continuing for 7 days postoperatively to facilitate the formulation of a cardiorespiratory stability index as follows: (0) improvement from baseline, (1) no change from baseline, (2) mild instability, (3) marked instability, and (4) life threatening event.

Results—Within the first 48 hours postoperatively in group A 5/12 showed mild instability and 4/12 showed marked instability (including three babies suffering life threatening events requiring emergency resuscitation). In group B within the first 48 hours postoperatively 1/6 showed mild and 1/6 showed marked instability, and in group C 5/12 babies showed mild instability alone. There was a significant difference for cardiorespiratory stability scores between the three groups overall for the 7 days postoperatively (repeated measures ANOVA, $p = 0.018$).

Conclusions—Premature infants undergoing cryotherapy for ROP who were treated using topical anaesthesia alone had more severe and protracted cardiorespiratory complications.

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more, the oculocardiac reflex is well developed in infants,⁸ and this, together with their increased cardiorespiratory instability, makes preterm infants especially vulnerable when undergoing treatment for retinopathy of prematurity (ROP). Significant systemic complications occurring during and after ROP treatment have been reported⁹⁻¹¹ but, to date, little has been published to indicate which anaesthetic technique provides optimum conditions for these high risk babies.

In the UK there is wide variation in the type of anaesthesia used for the treatment of ROP. A recent nationwide study,¹² which targeted 118 neonatal units, found that 23% of units are using topical anaesthesia alone, 57% are using general anaesthesia, and 20% are using a combination of modalities.

At Manchester Royal Eye and St Mary's hospitals there had been a change in practice, prompted by concern regarding infant stress and risk of systemic complications, from using topical anaesthesia alone to using general anaesthesia and subsequently sedation/analgesia. This allowed a consecutive, non-randomised, observational study comparing the impact of these different anaesthetic techniques on the systemic stability of babies receiving treatment for ROP.

Methods

All babies undergoing retinal ablative treatment of threshold ROP over a 2 year 8 month period to 1994 (when laser superseded cryotherapy) were included in the study. The total study population could be divided into three groups (A, B, or C) according to the modality of anaesthesia used for treatment. Group A consisted of babies treated using topical anaesthesia alone, group B babies treated using full inhalational general anaesthesia, and group C babies treated using sedation/analgesia. The details of the anaesthetic techniques used for the three groups are given in Table 1. All babies underwent cryotherapy without conjunctival incision using a Schulenburg cryoprobe, all treatments were carried out by the same surgeon (EO'D), and all babies received steroid/antibiotic drops (for 2 weeks) and cycloplegic drops (for 1 week) to the treated eyes. The Cryo-ROP study criteria for threshold disease were fulfilled by all subjects, all of whom had zone 2 involvement. Data were collected from the neonatal medical unit (NMU) records and prospectively evaluated using standard proforma.

Manchester Royal Eye Hospital

P M Haigh
E P O'Donoghue

Regional Neonatal Medical Unit, St Mary's Hospital, Whitworth Park, Manchester
M L Chiswick

Correspondence to:
Mr E P O'Donoghue,
Manchester Royal Eye Hospital, Oxford Road, Manchester M13 9WH.

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It is now well recognised that neonates and infants perceive pain^{1,2} and that they mount a substantial stress response to painful stimuli.³⁻⁵ Premature infants tend to be more unstable systemically than full term infants of the same postnatal age, and are more susceptible to episodes of apnoea and bradycardia.^{6,7} Further-

Table 1 Study population (n = 30)

Group	Anaesthetic technique	Treatment site and doctor responsible for giving anaesthetic
A (n = 12)	Topical amethocaine	Operating theatre, paediatric anaesthetist
B (n = 6)	N ₂ O/O ₂ , halothane, muscle relaxation, and intubation	Operating theatre, paediatric anaesthetist
C (n = 12)	Fentanyl continuous intravenous infusion, pancuronium, and intubation	Neonatal medical unit, neonatologist

Table 2 Cardiorespiratory stability scoring

Score	Designation	Criteria
0	Improved from baseline	Decreased oxygen requirement (>20% relative change in F _{IO₂})
1	No change from baseline	
2	Mild instability	Increased oxygen requirement (20–50% relative change in F _{IO₂}), more apnoeas and/or bradycardias responding to gentle stimulation (100% increase or 5 if none before)
3	Marked instability	Increased oxygen requirement (>50% relative change in F _{IO₂}), more apnoeas and/or bradycardias responding to vigorous stimulation (100% increase or 5 if none before), higher ventilation requirement
4	Life threatening event	Requiring emergency resuscitation (for example, intubation, suction/bag and mask oxygen, cardiac massage)

F_{IO₂} = fractional inspired oxygen concentration.

Table 3 Median values (ranges) for gestational age, birth weight, postmenstrual age at treatment, weight at treatment, and duration of treatment

	Group A	Group B	Group C
Gestational age ¹ (weeks)	25 (24–28)	26 (25–30)	25 (23–27)
Birth weight ² (g)	800 (620–990)	780 (660–1134)	660 (500–1055)
Postmenstrual age at treatment ³ (weeks)	35.5 (34–40)	37 (34–44)	36 (34–39)
Weight at treatment ⁴ (g)	1390 (1097–1730)	1616 (1266–2700)	1445 (1200–1957)
Duration of treatment ⁵ (minutes)	48 (30–65)	50 (40–70)	50 (30–65)

No significant difference between groups. ¹p = 0.12, ²p = 0.12, ³p = 0.19, ⁴p = 0.06, ⁵p = 0.47, Kruskal–Wallis one way ANOVA.

Table 4 Incidence of bronchopulmonary dysplasia (incidence BPD), ventilatory support at the time of treatment (vent support at Rx), duration of artificial ventilation from birth (dura IPPV), and treatment with surfactant (surfactant Rx) and systemic steroid (steroid Rx)

Patient No	Group	Incid BPD	Vent support at Rx	Dura IPPV (days)	Surfactant Rx	Steroid Rx
1	A	+	HB	33	Yes	Yes
2	A	+	HB	19	Yes	No
3	A	+	HB	64	Yes	No
4	A	+	HB	39	Yes	Yes
5	A	+	HB	21	Yes	No
6	A	+	HB	16	Yes	Yes
7	A	+	Air	16	No	Yes
8	A	+	HB	30	Yes	Yes
9	A	+	HB	33	Yes	Yes
10	A	+	Air	75	Yes	Yes
11	A	+	HB	20	No	Yes
12	A	–	Air	17	Yes	Yes
13	B	+	HB	45	Yes	No
14	B	–	Air	14	No	No
15	B	+	HB	46	Yes	Yes
16	B	+	HB	34	Yes	Yes
17	B	+	Air	26	Yes	No
18	B	–	Air	12	No	No
19	C	+	HB	42	Yes	No
20	C	+	HB	47	Yes	Yes
21	C	+	HB	28	Yes	Yes
22	C	+	Air	50	No	Yes
23	C	+	HB	53	No	No
24	C	+	IPPV	127	Yes	Yes
25	C	+	IPPV	143	No	Yes
26	C	+	HB	40	Yes	Yes
27	C	+	HB	54	Yes	Yes
28	C	–	Air	19	Yes	No
29	C	+	IPPV	144	Yes	No
30	C	+	HB	42	Yes	Yes

BPD, – = absent, + = present; HB = head box oxygen; IPPV = intermittent positive pressure ventilation; for surfactant and steroid treatment, Yes = drug administered, no = drug not administered.

The total study population was heterogeneous in terms of infant health. In order to make comparisons of post-treatment systemic stability between groups, we devised a scoring system based upon cardiovascular and respiratory variables. The system was designed to show changes in the overall systemic status of infants on a day to day basis. The details of this cardiorespiratory stability scoring are summarised in Table 2. In our NMU policy an apnoeic episode was defined as being equal to or greater than 20 seconds' duration and a bradycardiac episode was defined as a heart rate of equal to or less than 90 beats per minute. To reverse more significant apnoeic and bradycardiac episodes gentle stimulation (for example, touching a hand) or vigorous stimulation (for example, firmly rubbing a limb) was performed by neonatal staff. The daily oxygen requirement was calculated as the mean of the fractional inspired oxygen concentration (F_{IO₂}) values recorded for each day. Ventilatory support ranged from, in descending order, intermittent positive pressure ventilation (IPPV), to continuous positive airway pressure ventilation (CPAP), to head box oxygen, to air. Change in ventilation requirement of a baby was defined as a change in the level of ventilatory support—for example, from head box oxygen to CPAP. Scores were calculated for each 24 hour period starting 4 days preoperatively, to provide a baseline, and continuing for 7 days postoperatively. A score of greater than 1 indicates deterioration from baseline status (that is, increased instability) and a score of less than 1 indicates improvement (that is, decreased instability).

Statistical analysis was performed using one way and repeated measures analysis of variance (ANOVA) and Mann–Whitney U tests depending upon which groups of data were being compared. A p value of 0.05 or less was considered significant.

Results

The study population consisted of 30 babies in which there were 12 babies in group A, six in group B, and 12 in group C. Demographic data are shown in Table 3. No significant group differences were found for gestational age, birth weight, postmenstrual age at treatment, weight at treatment, or duration of treatment. The incidence of bronchopulmonary dysplasia, artificial ventilation at the time of treatment, duration of artificial ventilation, and treatment with surfactant and systemic steroids are shown in Table 4. All except four infants had bronchopulmonary dysplasia (BPD) with active chronic lung disease at the time of treatment. Analysis of duration of IPPV shows a significant difference between the groups (p = 0.019, Kruskal–Wallis one way ANOVA). Comparison of the three groups for duration of IPPV using Mann–Whitney U test shows that the difference occurs between groups A and C.

Two infants had other significant respiratory problems in the perioperative period. One baby in group A (patient no 5) developed pneumonia on the fifth postoperative day and one baby

Table 5 Cardiorespiratory stability scores for the study population. Details of the changes from baseline cardiorespiratory status which occurred during each 24 hour period are given next to the scores

Patient No	Group	Time (days)										
		-4	-3	-2	-1	1	2	3	4	5	6	7
1	A	1	1	1	1	4 Emergency intubation	3 HB to IPPV	3 IPPV	3 IPPV	2 CPAP	3 IPPV	2 Extubated 5B gs
2	A	1	1	1	1	4 Suction bag and mask	3 ↑O ₂ >50%	2 5B gs	3 HB to IPPV	3 IPPV	3 IPPV	2 Extubated 7AB gs
3	A	1	1	1	1	4 Suction bag and mask	3 HB to IPPV	3 IPPV ↑O ₂ >50%	3 CPAP 7AB vs	3 CPAP	2 Extubated 6B gs	2 8AB gs
4	A	1	1	1	1	3 Air to IPPV	3 IPPV	3 IPPV	3 IPPV	2 CPAP	2 Extubated 9AB gs	1
5	A	1	1	1	1	2 5B gs	2 8B gs	2 7AB gs	3 13B gs 6AB vs	3 6B vs	2 11B gs	2 5B gs ↑O ₂ >20%
6	A	1	1	2 ↑O ₂ >20%	1	2 6B gs	1	3 7AB vs	1	0 ↓O ₂ >20%	0 ↓O ₂ >20%	0 ↓O ₂ >20%
7	A	1	1	1	1	2 7B gs	2 ↑O ₂ >20%	1	1	1	1	1
8	A	1	2 6B gs	1	1	1	2 7 AB gs	1	2 ↑O ₂ >20%	1	3 15AB vs CPAP	1
9	A	1	1	1	1	1	2 ↑O ₂ >20%	1	1	1	1	1
10	A	1	1	1	1	1	1	1	1	1	1	1
11	A	1	1	1	1	1	1	1	1	1	1	1
12	A	1	1	1	1	1	1	1	1	1	1	1
13	B	1	1	1	1	3 Elective IPPV	3 IPPV	3 IPPV	2 Extubated 9AB gs	2 12AB gs	1	1
14	B	1	1	1	1	2 8A gs	1	1	1	1	1	1
15	B	1	1	1	1	1	0 ↓O ₂ >20%	0 ↓O ₂ >20%	0 ↓O ₂ >20%	0 ↓O ₂ >20%	0 ↓O ₂ >20%	0 ↓O ₂ >20%
16	B	1	1	1	1	1	1	1	2 5B gs ↑O ₂ >20%	1	1	1
17	B	1	1	1	1	1	1	1	1	1	1	1
18	B	1	1	1	1	1	1	1	1	1	1	1
19	C	1	1	1	1	2 ↑O ₂ >20%	2 6B gs	1	1	1	1	1
20	C	1	1	1	1	2 ↑O ₂ >20%	2 5AB gs	1	3 14AB vs	2 7AB gs	2 11AB gs ↑O ₂ >20%	1
21	C	1	1	1	1	2 9A gs	0 ↓O ₂ >20%	0 ↓O ₂ >20%	1	0 ↓O ₂ >20%	1	1
22	C	1	1	1	1	2 9B gs	1	1	1	1	1	1
23	C	1	1	1	1	2 ↑O ₂ >20%	1	1	0 ↓O ₂ >20%	0 ↓O ₂ >20%	0 ↓O ₂ >20%	1
24	C	1	1	2 7B gs	1	1	0 IPPV to CPAP	1	1	1	1	1
25	C	1	1	1	1	1	1	2 ↑O ₂ >20%	1	1	1	1
26	C	1	1	1	1	1	1	1	1	1	1	1
27	C	1	1	1	1	1	1	1	1	1	1	1
28	C	1	1	1	1	1	1	1	1	1	1	1
29	C	1	1	1	1	1	0 ↓O ₂ >20%	1	0 IPPV to CPAP	1	1	1
30	C	1	1	1	1	0 ↓O ₂ >20%	1	1	2 ↑O ₂ >20%	2 ↑O ₂ >20%	1	1

Days -4 to -1 are preoperative and days 1 to 7 are postoperative. HB = head box oxygen; IPPV = intermittent positive pressure ventilation; CPAP = continuous positive airway pressure ventilation; A = apnoea; B = bradycardia; gs = gentle stimulation; vs = vigorous stimulation; ↑ = increased; ↓ = decreased; O₂ = oxygen.

in group C (patient no 19) had a coexistent chest infection with mucus plugging at the time of treatment.

The cardiorespiratory stability scores and details of the changes from baseline cardiorespiratory status are shown in Table 5. In group A five babies showed mild instability and four babies showed marked instability in the first 48 hours after treatment. Of the four babies showing marked instability, three suffered life threatening events at the time of treatment (patient nos 1-3, Table 5), and all three of these infants required resuscitation. One infant underwent emergency endotracheal intubation followed by IPPV for 4 days. The other two needed airway suction, bag, and mask oxygen and were later intubated requiring IPPV for

several days. In these three cases following resuscitation, the cryotherapy procedure was abandoned and necessitated repeat treatment as a result of failure of ROP regression. Ultimately, successful regression of neovascularisation was achieved in all study subjects.

In group B one baby showed mild and one showed marked instability during the first 48 hours after treatment. In group C five babies showed mild instability only, during the first 48 hours after treatment. Five infants in group B were extubated within the first 24 hours after surgery. One infant in group B (patient no 13, Table 5) was maintained on IPPV for 3 days following elective intubation at the time of surgery. Eleven infants in group C were extubated within the first 24 hours and one (patient no 19, Table 5) was extubated 40 hours after surgery. In babies in groups B and C postoperative systemic instability was noted to occur after extubation, typically lasting for several hours. No life threatening events were encountered in babies from groups B or C.

The mean cardiorespiratory stability scores pre- and postoperatively (Table 6) were plotted for each day (Fig 1). The graph obtained indicates good baseline stability for the 4 days

Table 6 Mean cardiorespiratory stability scores (taken over each 24 hour period) from 4 days preoperatively (-) to 7 days postoperatively

	Time (days)										
	-4	-3	-2	-1	1	2	3	4	5	6	7
Group A	1.00	1.08	1.08	1.00	2.17	2.00	1.83	1.92	1.58	1.67	1.25
Group B	1.00	1.00	1.00	1.00	1.50	1.17	1.17	1.17	1.00	0.83	0.83
Group C	1.00	1.00	1.08	1.00	1.33	0.92	1.00	1.08	1.00	1.00	1.00

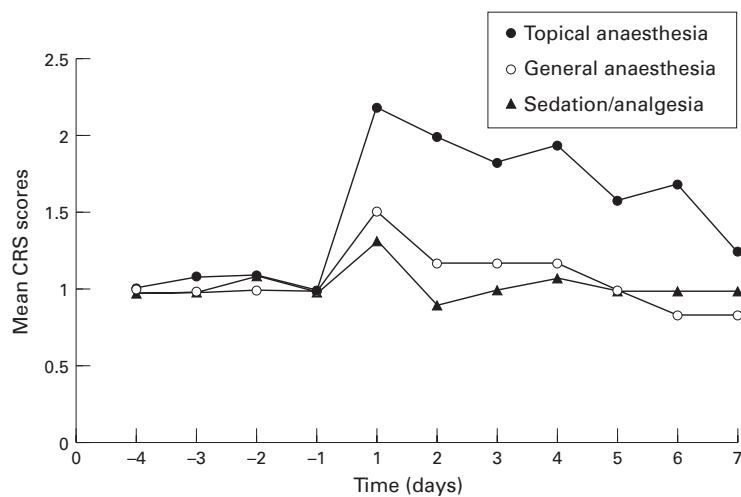


Figure 1 Mean cardiorespiratory stability (CRS) scores from 4 days preoperatively (–) to 7 days postoperatively. Scores above 1 indicate deterioration from baseline status (that is, increased instability) and scores below 1 indicate improvement (that is, decreased instability).

preoperatively and divergence of the groups postoperatively with group A showing greatest instability. Analysing the data on individual days there is a significant difference between the groups for the cardiorespiratory stability scores on days 2 and 3 ($p = 0.013$ and 0.045 respectively, Kruskal–Wallis one way ANOVA). Further analysis using Mann–Whitney U test shows that the differences occur between groups A and C on days 2 and 3. Analysis over the whole study period gives a significant difference between the three groups (repeated measures ANOVA $p = 0.018$) and again this difference occurs between groups A and C.

Discussion

Preterm infants show increased cardiovascular and respiratory instability when compared with their full term counterparts.^{6 7 13 14} Infants requiring treatment for ROP are among the most vulnerable, since the prevalence of ROP is highest for very premature and very low birth-weight babies. Systemic complications have been well documented following cryotherapy for ROP.^{9–11} However, no studies have hitherto compared the postoperative course between infants receiving different modalities of anaesthesia when undergoing cryotherapy.

Although the total study population is somewhat heterogeneous in terms of infant health, this variation occurred within groups rather than between groups and we found groups to be broadly comparable (Tables 3 and 4). In the absence of an ideal method for comparing postoperative stability in infants with differing health problems, we devised our cardiorespiratory scoring system as a tool to allow comparisons of postoperative systemic outcome between the groups. The scoring system incorporates details from daily 'apnoea/bradycardia charts' in routine use on the NMU and mirrors standard monitoring practice.

The three groups were similar in terms of gestational age, birth weight, postmenstrual age at treatment, and duration of surgery. In those babies showing instability at the time of

ROP treatment, systemic complications usually occurred soon after starting cryotherapy and this has been reported by others.¹⁰ All babies received similar postoperative analgesia and eyedrops.

Search for perioperative confounding factors, which may have resulted in increased cardiorespiratory instability unrelated to the ROP treatment, revealed only one case of respiratory infection in the week following surgery in each of groups A and C. All three groups had a high incidence of bronchopulmonary dysplasia (BPD), but there is a trend (NS) towards more severe BPD in group C; patients 24, 25, and 29 requiring artificial ventilation for very prolonged periods since birth. However, contrary to expectation group C had a significantly better outcome. The three groups were comparable in terms of treatment with surfactant and systemic steroids. The severe BPD in the three infants, which required prolonged artificial ventilation, probably reflects their extreme prematurity and low birth weight rather than specific differences in treatment.

Our results indicate that cardiac and respiratory adverse events are more common using topical anaesthesia. More importantly, life threatening events during treatment were encountered only in the topical anaesthesia group. In each instance when resuscitation was required, the cryotherapy was abandoned to allow recovery and stabilisation of the infant, with potentially serious implications in terms of arresting progression of sight threatening retinopathy. The three babies suffering these serious episodes needed to undergo a further cryotherapy procedure several days later. Following repeat treatment satisfactory neovascular regression was achieved. Otherwise no ocular complications were encountered that could be attributable to variation in anaesthetic support.

Episodes of bradycardia did occur during cryotherapy in groups B and C, but these were of short duration and none required resuscitative measures. Control of the airway and assisted ventilation in groups B and C were other factors in achieving this increased stability during treatment. Group A provided the worst scenario when respiratory arrest had occurred; the anaesthetist in attendance having to gain control of the airway and assist ventilation very rapidly to prevent profound hypoxia. If laryngospasm occurs during resuscitation, the situation becomes extremely hazardous and significantly increases the risk of infant death. Elective intubation, employed in groups B and C, can be performed safely after preoxygenation of the baby.

Several investigators have described systemic instability of preterm infants in the early postoperative period, concentrating attention on the first 24 hours after surgery.^{13 14} Our results indicate that instability after treatment may be much more prolonged in some babies. Four babies in group A were unstable for 7 days postoperatively. In contrast, most babies in groups B and C had returned to pretreatment

baseline cardiorespiratory status by day 2, and indeed some showed improvement from baseline.

We have attributed the differences in degree and duration of instability between the three groups largely to the stress of the cryotherapy procedure itself, where significant differences in outcome appear to relate to the type of anaesthesia employed. Every effort should be made to avoid protracted systemic instability, since there is evidence that recurrent or prolonged apnoeic episodes may result in permanent neuronal damage and consequent impaired neurological development.^{15 16}

Cryotherapy is a painful procedure and adequate analgesia is essential. Fentanyl, an opioid analgesic, is effective in suppressing the stress response to surgery⁴ and this drug has been used widely in neonatal anaesthesia.¹⁷⁻²⁰ The half life of fentanyl is shorter than morphine, but if necessary any effects of respiratory depression can readily be reversed with intravenous naloxone. Inhalational general anaesthesia provides analgesia and reduces the stress response,⁵ and a further reduction in the stress response has been demonstrated by adding fentanyl to the anaesthetic regimen.⁴ It is unlikely that topical anaesthesia alone provides sufficient analgesia to suppress the stress response to cryotherapy. The preferred method of providing analgesia for ROP treatment has not been determined, and clearly it is an area worthy of further study.

Although the safety of the infant is paramount, a further consideration is that of achieving optimal conditions for the surgeon to apply treatment. Retinal ablation for ROP can be a difficult technique, made easier if the baby is still. Under suitable conditions treatment application should be quicker and more accurate. Both general anaesthesia and sedation with muscle relaxation provide these conditions.

In many centres where laser is increasingly employed in preference to cryotherapy the latter is still used, either as 'backup' or when laser proves difficult because of miosed pupils. Laser application also has potential to induce stress when scleral indentation is necessary or in cases of inadvertent deeper retinal and pupil margin burns in eyes with rigid, poorly dilated pupils. Unwanted ocular movement increases the risk of visual damage due to accidental treatment of posterior retina. Hence, in many cases, some form of anaesthetic support remains desirable with laser use.

Finally, there are other considerations when providing a service for the treatment of ROP. In some units a specialised paediatric anaesthetic service may not be readily available or may be based in another hospital necessitating transfer of babies needing treatment. Use of topical anaesthesia is a simple approach, although in our practice a paediatric anaesthetist was still required to remain in attendance during treatment. In our hospital the sedation/analgesia technique used in group C is carried out in the NMU in a dedicated treatment room. Intubation and administration of drugs are performed by a neonatologist, and we and

others²¹ have found this approach works well. In the neonatal intensive care unit there is ready access to all emergency support and the complications associated with transportation are eliminated.

In conclusion, use of topical anaesthesia alone for the treatment of ROP is associated with more severe cardiorespiratory complications during and after surgery. The systemic instability following cryotherapy with topical anaesthesia is more protracted than with general anaesthesia or sedation/analgesia. The study by Schulenburg and Bloom¹² indicates that, currently, up to 43% of units in the UK may be employing local anaesthesia in the treatment of ROP.

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