Anesthesia in retinopathy of prematurity

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Abstract:

Retinopathy of prematurity (ROP) remains among the leading causes of childhood blindness. It affects mainly premature infants who tend to be systematically and clinically unstable and are more prone to complications and anesthesia related adverse effects when undergoing examination or treatment. A better comprehension of different analgesic and anesthetic methods used during screening and treatment may help in choosing a suitable option for ROP screening and treatment. An electronic search was done using MEDLINE, PubMed, and Embase databases. Search terms used included ROP, ROP, ROP screening, ROP treatment, analgesia, and anesthesia. All randomized clinical trials, large case series, and surveys were included in the review. Topical proparacaine is the most commonly used anesthesia during ROP screening and may significantly ease pain during ROP screening. Different comfort measures during screening may help infants recover faster but do not abolish pain. Topical tetracaine seems an effective pain-relieving option during intravitreal injections for ROP treatment. Photocoagulation of the peripheral retina under general anesthesia is considered the most common practice in the treatment of ROP. Further work is necessary to better understand the options of anesthesia methods offered for the treatment of ROP patients. This is a comprehensive review highlighting the available anesthetic methods for ROP patients to aid ophthalmologists in determining the most common and current anesthetic and analgesic practices.

Keywords:

Anesthesia, retinopathy of prematurity, retinopathy of prematurity

Introduction

Retinopathy of prematurity (ROP) is a leading cause of blindness in premature infants around the globe.[1] Over 20,000 infants are blinded yearly from ROP, and another 12,300 suffer from visual impairment.[2] Important risk factors associated with the development of ROP are infants with unstable clinical courses with low birth weight and gestational age, low Apgar score, and prolonged use of oxygen therapy.[3,4]

Untreated ROP can cause severe visual handicap. Thus, screening is very essential to identify the disease and reduce its burden by early intervention.[1] One important point to take into consideration when screening ROP patients, other than the age and weight, is the infant's clinical status.[5] Premature infants are unstable systemically compared to full-term infants of the same postnatal age, and are more prone to systemic complications such as apnea and bradycardia.[6,7] Respiratory distress syndrome, neonatal sepsis, anemia, thrombocytopenia, and multiple blood transfusions have also been significantly associated with preterm infants with ROP.[5] Thus, care must be taken during screening for ROP as pain and discomfort may result in low oxygen tension, bradycardia, and even apnea.

A wide variety of anesthetic techniques used for the treatment of ROP have been established. General anesthesia (GA) was found to be the most common type, especially during laser photocoagulation, followed by topical anesthesia.[8] Intravenous, oral, and rectal sedation using different anesthetic agents have also been reported.[9]

The aim of this study is to provide a focused comprehensive literature review aiming to highlight all available methods of anesthesia and analgesia used during ROP screening and treatment.

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Literature Search

We searched for the following keywords in PubMed, MEDLINE, and Embase databases in various combinations: ROP, ROP, ROP screening, ROP treatment, randomized controlled trials (RCTs), cohort, case series, analgesia, and anesthesia. Further studies were identified through citations, which were retrieved and examined for relevance, and included in this review. The medical subject heading search used terms relevant to the target disease, treatments, and study methods. Titles and abstracts of retrieved articles were read to identify possible RCTs, cohort, or case series. When in doubt whether to include a certain study, the full article in print was read before a decision was made. Further studies were identified through citations, which were retrieved and examined for relevance, and included in this review. Non-English papers, case reports, and animal-based studies were excluded.

Retinopathy of Prematurity Screening

Pharmacological measures

Topical anesthesia

Screening and examining infants with ROP causes distress, discomfort, and pain.[10] Systemic effects such as apnea and bradycardia might be noted in those infants while they are being screened.[10] Minimizing such events is a priority for infants, examiners (ophthalmologists), and parents to achieve successful examinations. Deciding which comfort method to apply is still controversial and literature does not provide consensus as to which method is the most effective in reducing pain.[11]

An online survey was distributed to the American Association for Pediatric Ophthalmology and Strabismus members to identify the patterns of topical anesthetics used during ROP screening. Out of the 225 members, 82% utilized topical anesthetics and proparacaine was the most used agent of choice, representing 63%.[12]

In 1993, Saunders *et al*. performed a trial on premature infants undergoing ROP examination to assess the efficacy of topical anesthetic eye drops in decreasing infant stress. Infants were randomized to receive proparacaine 0.5% or normal saline eye drops. Results revealed no difference or advantage of topical anesthetic agents over normal saline. However, this study was not a cross-over study and did not apply validated pain score measures.[13] Later on, Marsh *et al*. carried out a cross-over trial, where all infants had been swaddled and held during examination. Premature infant pain profile (PIPP) scores were significantly higher in saline compared to proparacaine In addition, even though topical anesthetics decreased painful response in some infants, further comfort measures needed to be taken in cases where it was not as effective.[14] Moreover, Cogen *et al*. studied premature infants in a RCT where proparacaine 0.5% drops or artificial tear solution were administered, but comfort methods were abstained. The authors found that only 27% of proparacaine group experienced high PIPP scores, compared to 65% in placebo group. Thus, topical anesthetics could significantly decrease infants' pain.[15] Reviewed articles for topical anesthesia during ROP screening are summarized in Table 1.[12-18]

Other pharmacological agents

Providing safe and effective pain control measures is fundamental in every procedure including ophthalmology examination of newborns.[19] Morphine – an opioid – is an example of a drug commonly used for moderate-to-severe acute pain control. Nevertheless, the risk of developing respiratory depression, apnea, hypotension, and urinary retention with opioid use is higher in preterm neonates.[20] Hence, Hartley *et al*. conducted an RCT to establish the safety of oral morphine in reducing nonventilated infants' pain undergoing painful procedures. Subjects were allocated to get 100 μg/kg of oral morphine or placebo, swaddling was done before eye examination and proxymetacaine 0.5% was instilled preceding speculum insertion. No significant difference in pain score was noticed between morphine and placebo. Furthermore, 53% of infants who received morphine developed new-onset apnea or an increase in the number of apneic episodes highlighting the disadvantages of morphine in these settings and, thus, justifying the trial cessation.[19]

On the other hand, fentanyl has a better respiratory safety profile, favorable hemodynamics, shorter duration, and rapid onset compared to morphine. Sindhur *et al*. conducted the first trial aimed to investigate the efficacy of 50 mcg/ml intranasal fentanyl as an adjunct for pain management during ROP examination, all subjects received 24% oral sucrose and topical proparacaine 0.5%. Results illustrated that PIPP score, heart rate, and crying time during retinal examination were lower in fentanyl group compared to placebo. This study found that fentanyl significantly reduced pain scores but could not eliminate pain completely and cautioned against possible fentanyl side effects.[21]

In pediatric practice, paracetamol is used regularly due to its good safety profile and absence of significant side effects.

Table 1: Topical anesthesia during retinopathy of prematurity screening

Authors	Methods	Findings
Ahmed *et al*. (2016)[12]	Survey	82% utilized topical anesthetics Most reported agent was proparacaine (63%)
Saunders *et al*. (1993)[13]	RCT	No difference of topical anesthetic agents over normal saline
Marsh *et al*. (2005)[14]		Lower PIPP scores in proparacaine group
Cogen *et al*. (2011)[15]		Only 27% of proparacaine group experienced high PIPP score compared to 65% in placebo
Sekeroglu *et al*. (2013)[16]	Survey	92.1% of ophthalmologists preferred topical proparacaine prior to screening
Mehta *et al*. (2010)[17]	RCT	Lower PIPP scores in proparacaine group Older gestational age babies seem to tolerate stress better
Nesargi *et al*. (2015)[18]		Neither 0.5% proparacaine nor 25% dextrose was efficient in lowering painful events

RCT: Randomized controlled trial, PIPP: Premature infant pain profile

Kabataş *et al*. randomly assigned infants to either 15 mg/kg oral paracetamol or sterile water of the same volume, in addition to propracaine 0.5% eye drops before clinical examinations. During eye examination and speculum insertion, PIPP score was significantly lower in the intervention group, and no side effects were observed.[22]

Inhalational anesthetic agents have been widely used in day surgery due to their favorable safety profile and efficacy in inducing and maintaining anesthesia. Two papers studied sevoflurane and nitrous oxide (N2O) in reducing infant discomfort during ophthalmology examination. Yu *et al.* concluded that 6% of inhaled sevoflurane can be safely used in preventing infant movements during eye examination, and no side effects were reported during or after the procedure.[23] Mandel *et al*. studied inhaled equimolar mixture of N2O (EMONO) and oxygen (EMONO) via nasal cannula for pain relief. All infants received standard care measures, including: swaddling, 24% of oral sucrose, and one drop of proparacaine HCl 0.5%. EMONO did not provide extra beneficial pain relief over the currently used measures which was argued to be due to mode of delivery, nasal cannula versus facemask, and the inherent minimal anesthetic and analgesic properties of EMONO. Nevertheless, EMONO was tolerated without any side effects.[24] Table 2 summarizes studies related to pharmacological agents used in ROP screening.[19,21-24]

Nonpharmacological measures

Oral glucose

Despite the use of topical anesthetics prior to infant eye examination, ROP screening remains painful to infants. Orally administered dextrose has a role in relieving newborns' pain, mechanism of action is still unknown, but it is thought to be related to indirect endogenous opioid or dopamine release. Oral glucose is a safe and widely available solution used in infants undergoing stressful procedures.[25,26] There are four RCTs which employed oral dextrose in premature neonates undergoing ROP examination. Two of them found no significant effect for oral glucose over sterile water or expressed breast milk.[25,27] Another study found that 1 ml of 25% oral glucose was significantly effective in pain prevention.[28] Similarly, Sagheb *et al*. found that 25% dextrose and topical anesthesia reduced the PIPP score significantly when compared to water and nothing by mouth.[26] These studies stressed on the need of further studies to properly evaluate the efficacy and safety of higher doses of glucose or dextrose as a pain prevention measure during ROP screening.

Table 2: Other pharmacological agents used during retinopathy of prematurity screening

Authors	Methods	Findings
Hartley *et al*. (2018)[19]	RCT	100 μg/kg oral morphine had harmful effects on studied infants rather than providing analgesic effects
Sindhur *et al*. (2020)[21]		Intranasal fentanyl significantly reduced pain scores
Kabataş *et al*. (2016)[22]		PIPP score was significantly lower in the paracetamol group
Yu *et al*. (2011)[23]	Non-RCT	6% of inspired sevoflurane can be safely used in preventing infant movements during eye examination
Mandel *et al*. (2012)[24]	RCT	EMONO did not provide extra beneficial pain relief over the currently used measures

*RCT: Randomized controlled trial, PIPP: Premature infant pain profile, EMONO: Equimolar mixture of oxygen and nitrous oxide

Oral sucrose

It is hypothesized that sucrose activates lingual sweet taste receptors leading to endogenous opioid release, and combination with nonnutritive sucking (NNS) can activate nonopioid mechanism, thus reducing pain and stress.[29] RCT results varied with studies concluding no analgesic effect at all as compared to sterile water with a possibility that only a pacifier may decrease pain/stress associated with ROP, to other studies finding a clear benefit of oral sucrose in reducing immediate procedural pain response compared to placebo. Other studies even suggested the need to provide both oral sucrose and a pacifier to decrease behavioral and physiological pain responses.[30-35] Seifi *et al*. compared oral sucrose to paracetamol and found lower PIPP scores at the beginning of eye examination.[36] They found that better PIPP scores at the end of eye examination can be achieved by repeating the dose or increasing the volume of sucrose.[36]

Breast milk

Breast milk has been found to be a good analgesic agent in painful procedures, and might have more advantages over other analgesics. It is a natural, safe, feasible, and cost-effective agent, and contains high concentration of tryptophan, an essential amino acid with pain-relieving properties.[25] Rosali *et al*. assessed whether expressed breast milk is an effective pain control measure during eye examination. Findings revealed that expressed breast milk has the ability to reduce infant pain, as assessed by PIPP scale, during the procedure and for 5 min afterward.[37] Ribeiro *et al*. performed a quasi-experimental study, the intervention group was given 2 ml of breast milk, whereas the control received 25% of oral sucrose (0.5 ml/kg), all infants received proxymetacaine eye drops before the examination. Crying time, salivary cortisol, and heart rate did not yield statistical significance between the two groups; hence, breast milk is as effective as sucrose in relieving acute pain during ROP screening.[38]

Articles assessing nonpharmacological measures during ROP screening are shown in Table 3.[25-28,30-41]

Comfort measures

To date, numerous analgesic methods have been implemented to control infant pain during ROP examination including nonpharmacological techniques such as swaddling and nonnutritive suckling. Such measures have a clear analgesic effect by distracting newborns and preventing pain from transmitting to the cerebral cortex.[42]

A trial to determine if comfort care measures would ameliorate infant pain during ROP examination has been conducted. All groups were instilled with 0.5% proparacaine, the intervention

Table 3: Nonpharmacological measures used during retinopathy of prematurity screening

Authors	Methods	Findings
		Oral glucose
Nayak *et al*. (2020)[25]	RCT	No significant effect for 30% oral glucose over sterile water nor expressed breast milk
Sagheb *et al*. (2020)[26]		25% oral glucose was significantly effective in pain prevention
Olsson *et al*. (2011)[27]		No significant effect for 30% oral glucose over sterile water
Costa *et al*. (2013)[28]		25% oral glucose was significantly effective in pain prevention
		Oral sucrose
Boyle *et al*. (2006)[30]	RCT	No difference between sucrose and placebo
Gal *et al*. (2005)[31]		PIPP scores were lower in sucrose group than placebo
Mitchell *et al*. (2004)[32]		PIPP scores were lower in sucrose group than placebo
Dilli *et al*. (2014)[33]		Combining sucrose with NNS and swaddling is effective in decreasing pain responses
O'Sullivan *et al*. (2010)[34]		Combining sucrose with NNS and swaddling is effective in decreasing pain responses
Grabska *et al*. (2005)[35]		Infants enrolled did not benefit from 24% oral sucrose despite high sucrose doses
Seifi *et al*. (2013)[36]		Compared to paracetamol, sucrose group had lower PIPP scores at the beginning of eye examination
Wang *et al*. (2020)[41]	Non-RCT	Oral sucrose and simple comfort measures can alleviate pain associated with mydriatic eye drops instillation
		Breast milk
Rosali *et al*. (2015)[37]	RCT	Expressed breast milk can reduce infant pain during the procedure and for 5 min afterward
Ribeiro *et al*. (2013)[38]	Non-RCT	Breast milk is as effective as sucrose in relieving acute pain during ROP screening
Taplak *et al*. (2017)[39]	RCT	Breast milk group recovered and reached their initial baseline (physiologically and behaviorally) more rapidly than sucrose
		Breast milk has a longer duration in reducing pain
Mirlashari *et al*. (2021)[40]		Breast milk has superiority in coping with stress over sucrose group

RCT: Randomized controlled trial, PIPP: Premature infant pain profile, NNS: Nonnutritive sucking, ROP: Retinopathy of prematurity

group were swaddled, given 24% sucrose pacification, and were held by a nurse, whereas the control group did not receive any relieving measures. The authors could not recommend the routine use of the aforementioned techniques as effective in reducing infant pain; instead, they advised ophthalmologists to perform ROP examination as quick and safe as possible and to use topical anesthetics prior to eye examination.[43]

Newborn Individualized Developmental Care and Assessment Program (NIDCAP) in reducing infant pain during retinal examination was investigated by Kleberg.[44] NIDCAP care consisted of dimmed lighting, reduced sound and activity levels, and standard bed support; this intervention did not abolish infant pain but helped subjects to recover faster after examination as indicated by a faster decrease in cortisol level.[44] Chuang *et al*. compared the modified developmental care bundle versus standard care in decreasing premature pain and stress during eye examination. The modified developmental care bundle included environmental modifications, positioning and containment, oxygen supplementation, interaction and approach, and cue-based individual care, applied before, during, and after the ROP examination. They stated that recovery time was significantly shorter in the intervention group; moreover, bundle of comfort measures significantly reduced pain and stress during ophthalmic examination and 1 h afterward.[45]

Multisensory stimulation program (visual, taste, tactile, and smell stimulations) had been studied on premature infants undergoing retinal examination by Zeraati who concluded that multisensory stimulation program is a safe, simple, and effective method in reducing infant stress and pain, and suggested future studies comparing this program with other nonpharmacological methods in reducing pain associated with eye examination.[46]

Infant's position and body posture play an important role in increasing the sense of security which, in turn, reduces energy expenditure.[47] Three articles assessed the concept of infant's settings: Slevin *et al*. evaluated the role of nesting, Padhi *et al*. examined the effect of reverse kangaroo mother care (R-KMC), and Metreş and Yıldız determined the result of ROP position.[47-49] Nesting appears to be a beneficial method in reducing infant discomfort and crying time.[47] The pilot study of R-KMC (baby is rotated 180° and lies supine on the mother's chest) revealed that most of the infants were comfortable or had just a transient mild-to-moderate pain during ROP examination.[48] Furthermore, a randomized trial was conducted to study the efficacy of ROP position (he infant will be held in an ideal position, the nurse will support the infant's lower extremities in a cocoon shape while keeping the head immobilized). Findings showed lower PIPP scores at the beginning, at the end of screening, and after the examination. In addition, lower heart rate and shorter crying time were noticed compared to the control group who received a pacifier only.[49] A meta-analysis was conducted by Disher *et al*. reported that topical anesthetics combined with multisensory pain interventions (e.g.; sweet taste in addition to NNS, or sweet taste in addition to familiar odor) is more likely to be the optimal method in lowering premature infants pain undergoing eye examination.[50] Table 4 summarizes studies assessing comfort measures during ROP screening.[42-47,49-51]

Retinopathy of prematurity treatment

Topical/local anesthesia

Laser treatment under topical/local anesthesia for ROP has been the preferred method in developing countries due to the absence of specialized pediatric anesthetists and inaccessibility to GA.[52,53] However, topical anesthesia is insufficient for laser treatment and may raise the risk of life-threatening

events including cardiorespiratory instability.[54] Sub-Tenon local anesthesia appears to suppress the oculocardiac reflex which minimizes cardiorespiratory instability till few hours after treatment. Moreover, it enhances pupillary dilatation as pupils are resistant to pharmacological dilatation due to iris vasculature engorgement.[54]

Parulekar *et al*. and Novitskaya *et al*. tested the efficacy of sub-Tenon anesthesia and oral/rectal sedation for laser treatment of ROP. Findings suggest that sub-Tenon anesthesia with oral/rectal sedation can sufficiently control pain during ROP laser treatment, and it is believed to be an alternative to GA with lesser morbidity.[54,55] Peribulbar block, using lidocaine or bupivacaine or combination of both, in conjunction with GA for infants undergoing vitreoretinal surgery for ROP was studied by Sinha and Maitra All subjects were hemodynamically stable intraoperatively, none had apnea or desaturation, no one required postoperative neonatal intensive care unit (NICU) admission, and none required analgesia postoperatively. They concluded that peribulbar block is safe, and its sparing effects are speculated to be the reason for the low incidence of postoperative complications.[56]

A trial by Kataria *et al*. tested oral dextrose (25%) plus topical anesthesia to reduce pain associated with laser treatment for ROP. PIPP scores during laser treatment were high irrespective of oral dextrose or topical anesthesia use. It also did not seem to provide any additional pain relief.[57]

Intravitreal injections have been used for infants with aggressive ROP, it could be carried out under topical anesthesia as it is a quick procedure. Castellanos *et al*. performed a noncomparative trial to assess pain response during intravitreal bevacizumab injections for ROP under topical anesthesia. Tetracaine 0.5 g/ml has been used and was found to be effective, as the majority of infants experienced mild discomfort only.[58] Studies evaluating topical/local anesthesia during ROP treatment are shown in Table 5.[54-58]

Sedoanalgesia

Many institutes prefer the use of sedation/analgesia at the bedside in the NICU settings rather than GA to improve patient stability and avoid intubation and transportation to the operation room, thus reducing risk of hypothermia.[9,59-62] Opioids such as fentanyl, morphine, and remifentanil have been used and tested for this purpose. Kirwan *et al*. concluded that morphine is a safe and effective sedoanalgesia in laser treatment for ROP, and can be used as an alternative to GA with a good hemodynamic record.[60]

Örge *et al*. revealed that fentanyl is safer when compared to morphine in infants undergoing laser photocoagulation.[63] Dannelley *et al*. found that fentanyl and midazolam continuous infusions achieved successful results when applied in laser treatment procedures.[64] Opioids (fentanyl and morphine) and neuromuscular agents (vecuronium and rocuronium) in conjunction with midazolam were tested for the first time by Miller *et al*. for infants receiving intravitreal bevacizumab injections. Majority of infants had successful procedures, defined as no procedural interruption nor cardiopulmonary adverse events.[65]

Ketamine is a short-acting agent with a prolonged analgesic effect, protects laryngeal and pharyngeal reflexes, and has a bronchodilator effect; hence, it is the preferred drug of choice in pediatric anesthesia.[66,67] Lyon *et al*. supported the use of ketamine sedation for infants undergoing ophthalmic laser procedure; despite the few intra- and postoperative complications and excessive infant movements, the majority of infants had successful and uneventful

Table 4: Comfort measures during retinopathy of prematurity screening

Authors	Methods	Findings
Sun *et al*. (2020)[42]	RCT	PIPP scores were lower in babies receiving gentle human touch compared to the control group
Rush *et al*. (2005)[43]		Using 24% sucrose, pacifier, swaddling, and holding could not be recommended as effective pain reliving method
Kleberg *et al*. (2008)[44]		NIDCAP did not abolish infant pain but helped subjects to recover faster
Chuang *et al*. (2019)[45]		Bundle of comfort measures significantly reduced pain and stress at ophthalmology examination and 1 h afterward
Zeraati *et al*. (2016)[46]		Multisensory stimulation program is effective in reducing infant pain
Slevin *et al*. (1997)[47]	Case series	Nesting is a beneficial method in reducing infant discomfort, movements activity, and crying time
Metreş *et al*. (2019)[49]	RCT	Lower PIPP scores throughout the examination, in addition to lower heart rate and shorter crying time compared to the control group
Disher *et al*. (2018)[50]	Meta-analysis	Topical anesthetics combined with multisensory pain interventions is more likely to be the optimal method in lowering infants pain undergoing eye examination
Kristoffersen *et al*. (2019)[51]	RCT	Skin-to-skin contact and parental support did not give extra pain relief compared to standard care

RCT: Randomized controlled trial, PIPP: Premature infant pain profile, NIDCAP: Newborn Individualized Developmental Care and Assessment Program

Table 5: Topical/local anesthesia during retinopathy of prematurity treatment

Authors	Methods	Findings
Parulekar *et al*. (2008)[54]	Case series	Sub-Tenon anesthesia with oral/rectal sedation sufficiently controlled infant pain
Novitskaya *et al*. (2013)[55]		Sub-Tenon anesthesia with oral/rectal sedation sufficiently controlled infant pain
Sinha *et al*. (2016)[56]		Peribulbar block is a safe anesthetic technique
Kataria *et al*. (2015)[57]	RCT	PIPP scores during laser treatment were high irrespective of oral dextrose or topical anesthesia use
Castellanos *et al*. (2013)[58]	Case series	Tetracaine is an effective pain-relieving method during Intravitreal injections

RCT: Randomized controlled trial, PIPP: Premature infant pain profile

procedures.[68] Comparably, Saylan *et al*. reported that most of their subjects (86.2%) had successfully completed the laser treatment for ROP and achieved spontaneous ventilation under ketamine and midazolam protocol.[66] In both aforementioned studies, atropine was used to minimize salivation and to suppress the oculocardiac reflex produced by ketamine.

Jiang *et al*. compared three techniques of anesthesia (topical anesthesia, IV Fentanyl sedation, and GA using Halothane), results revealed that both GA and sedoanalgesia are well tolerated and no life-threatening events were reported compared to topical anesthetics. However, in terms of financial and time costs, fentanyl analgesia appears to be the most practical.[69] In addition, But *et al*. concluded that sevoflurane–N_2O and midazolam–remifentanil anesthesia techniques had similar hemodynamics, intraoperative complications, and extubation times, thus both can be safely used for premature infants during laser treatment for ROP.[70] Table 6 illustrates reviewed sedoanalgesia articles during ROP treatment.[60,62-66,68-75]

General anesthesia

Types and forms of anesthesia during ROP treatment vary widely between different eye institutes; therefore, several observational studies have been conducted to evaluate the most commonly employed form of anesthesia for ROP treatments. In 1995, Schulenburg screened all neonatal units in the UK, and concluded that most of the units were using cryotherapy for ROP treatment and GA was employed in the majority of units (57%).[8] Moreover, Chen *et al*. surveyed ophthalmologists in the UK and found that majority (50%) of them preferred GA for laser treatment followed by intravenous sedation with topical anesthesia (37%). The remaining (3% each) used oral sedation combined with topical anesthesia, rectal chloral hydrate and paracetamol combined with topical anesthesia, intravenous ketamine combined with topical anesthesia, or sub-Tenon's local anesthesia. This variation in practice might be related to different beliefs, experiences, safety concerns, and resource limitations of individual physicians.[9] In a Turkish survey, 72.7% of the ophthalmologists preferred GA, while 20.5% used intravenous sedation combined with topical anesthesia.[16]

Table 6: Sedoanalgesia during retinopathy of prematurity treatment

Authors	Methods	Findings
Kirwan *et al*. (2007)[60]	Case series	Morphine is an effective sedoanalgesia and can be used alternative to GA
Piersigilli *et al*. (2019)[62]		Fentanyl is an effective sedoanalgesia and can be used alternative to GA
Örge *et al*. (2013)[63]		Fentanyl is safer when compared to morphine
Dannelley *et al*. (2018)[64]		Fentanyl and midazolam achieved successful procedures with no adverse events
Miller *et al*. (2018)[65]		Fentanyl and midazolam achieved successful procedures with no adverse events
Saylan *et al*. (2020)[66]		Majority of infants had successful and uneventful laser procedures under ketamine sedation
Lyon *et al*. (2008)[68]		Majority of infants had successful and uneventful laser procedures under ketamine sedation
Jiang *et al*. (2017)[69]		Both GA and sedoanalgesia are well tolerated
But *et al*. (2012)[70]	RCT	Sevoflurane-N_2O and midazolam-remifentanil anesthesia techniques can be safely used
Sethi *et al*. (2020)[75]		Low fentanyl dose (1 mcg/kg/h) is an effective pain-relieving method compared to 24% oral sucrose
Sammartino *et al*. (2003)[71]	Case series	Use of opioids and benzodiazepines appear to be valid and feasible analgesia protocol
Demirel *et al*. (2014)[72]		Use of opioids and benzodiazepines appear to be valid and feasible analgesia protocol
Ulgey *et al*. (2015)[73]	RCT	Sedation using 1 mg/kg ketamine and 1 mg/kg propofol provided hemodynamic stability compared to GA
Novitskaya *et al*. (2020)[74]	Survey	Most frequent anesthetic practice was sedation (47.8%)

RCT: Randomized controlled trial, GA: General anesthesia, N_2O: Nitrous oxide

Sato *et al*. concluded that air, oxygen, and sevoflurane inhalation should be adopted as the best anesthetic protocol compared to local anesthesia, intravenous pentazocine, and intravenous fentanyl.[76] Sevoflurane is a good agent for day surgery and widely used in infants, as it enables rapid induction and recovery and does not cause respiratory irritation.[77,78] In two recent retrospective studies, results revealed that GA with sevoflurane can be safely used in infants undergoing argon/diode laser photocoagulation for ROP. However, it carries moderate rates of intraoperative hypotension and postextubation apnea.[79,80] Likewise, for aggressive ROP requiring vitrectomy, studies have shown that half of the patients were successfully extubated in the operating room, no postoperative complications were observed, and that early vitrectomy is effective despite the perioperative risks.[81]

Evaluation of the perioperative and postoperative courses in neonates undergoing vitreoretinal surgery for ROP under GA using sevoflurane with atracurium and fentanyl was performed by Sinha *et al*. and concluded that as low as 5.36% of studied subjects had postoperative apnea. This is thought to be due to reduced intraoperative opioid doses with the use of paracetamol and topical anesthetics.[82] A summary of reviewed GA studies during ROP treatment is shown in Table 7.[8,9,16,59,76,79-88]

Conclusion

Achieving a universal standard of care for pain control measures during ROP screening is still controversial and has yet to be established. However, implementing topical anesthesia, NNS, swaddling, and sweet solution during ROP examination was observed as a common effective practice in many institutes. Laser treatments using GA and sedoanalgesia are the most preferred protocols. Numerous neonatal units lack the availability of specialized anesthesiologists, thus sedoanalgesia was noted to be the second most common technique. Further studies are required to determine the best standard of care and the most appropriate guideline for the

Table 7: General anesthesia during retinopathy of prematurity treatments

Authors	Methods	Findings
Schulenburg *et al*. (1995)[8]	Survey	GA was employed in the majority of neonatal units (57%)
Chen *et al*. (2007)[9]		Majority (50%) of ophthalmologists preferred GA for laser treatment
Sekeroglu *et al*. (2013)[16]		72.7% of the ophthalmologists preferred GA
Klein *et al*. (2013)[59]		Most of the practitioners (60%) preferred Intravenous sedation followed by GA (19%)
Sato *et al*. (2015)[76]	Non-RCT	Air, oxygen, and sevoflurane inhalation should be adopted as the best anesthetic protocol
Ugur *et al*. (2021)[79]	Case series	General anesthesia with sevoflurane can be safely used in infants undergoing laser photocoagulation
Kaur *et al*. (2020)[80]		General anesthesia with sevoflurane can be safely used in infants undergoing laser photocoagulation
Aoyama *et al*. (2010)[81]		Half of the patients were successfully extubated in the operation room, no postoperative complications after early vitrectomy
Sinha *et al*. (2014)[82]		Only 5.36% of studied subjects undergoing vitreoretinal surgery under general anesthesia using sevoflurane with atracurium and fentanyl had postoperative apnea which is lower than the literature
Tokgöz *et al*. (2013)[83]		General anesthesia with sevoflurane can be safely used in infants undergoing bevacizumab injections
Gutierrez-Padilla *et al*. (2015)[84]	Survey	Combining IV Fentanyl and propofol without muscle relaxant for laser photocoagulation is useful and offers rapid recovery
Anand *et al*. (2007)[85]		Out of 14 neonatal units 6 units were following the protocol of sedoanalgesia 5 units implementing GA 3 units were following local anesthesia and/or sedation
Gunenc *et al*. (2011)[86]	Case series	LMA is superior to ETT and it can be used safely for infants undergoing laser photocoagulation LMA has less and minimal complications including desaturation and apnea compared to ETT
Zhang *et al*. (2019)[87]		LMA is superior to ETT and it can be used safely for infants undergoing ROP surgeries LMA has less and minimal complications including desaturation and apnea compared to ETT
Lönnqvist (1995[88]		LMA is superior to ETT and it can be used safely for infants undergoing cryotherapy LMA has less and minimal complications including desaturation and apnea compared to ETT

RCT: Randomized controlled trial, GA: General anesthesia, LMA: Laryngeal mask airway, ETT: Endotracheal intubation, ROP: Retinopathy of prematurity

type of anesthesia/analgesia during different ROP treatment interventions.

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Conflicts of interest

There are no conflicts of interest.

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