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. Over 20,000 infants are blinded yearly from ROP, and another 12,300 suffer from visual impairment. 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.

Untreated ROP can cause severe visual handicap. Thus, screening is very essential to identify the disease and reduce its burden by early intervention. One important point to take into consideration when screening ROP patients, other than the age and weight, is the infant’s clinical status. Premature infants are unstable systemically compared to full-term infants of the same postnatal age, and are more prone to systemic complications such as anemia and bradycardia. Respiratory distress syndrome, neonatal sepsis, anemia, thrombocytopenia, and multiple blood transfusions have also been significantly associated with preterm infants with ROP. 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. Intravenous, oral, and rectal sedation using different anesthetic agents have also been reported.

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.
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.

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%.

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. 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. 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.

Reviewed articles for topical anesthesia during ROP screening are summarized in Table 1.

Other pharmacological agents

Providing safe and effective pain control measures is fundamental in every procedure including ophthalmology examination of newborns. 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. 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.

On the other hand, fentanyl has a better respiratory safety profile, favorable hemodynamics, shorter duration, and rapid onset compared to morphine. Sindur 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.

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

**Note:** 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.

#### 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.[30-33] 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.[35] 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% propracaine, the intervention

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

| Authors         | Methods | Findings                                                                 |
|-----------------|---------|--------------------------------------------------------------------------|
| Hartley et al.  | RCT     | 100 μg/kg oral morphine had harmful effects on studied infants rather than providing analgesic effects |
| Sindhur et al.  | RCT     | Intrasinal fentanyl significantly reduced pain scores                    |
| Kabataş et al.  | RCT     | PIPP score was significantly lower in the paracetamol group              |
| Yu et al.       | Non-RCT | 6% of inspired sevoflurane can be safely used in preventing infant movements during eye examination |
| Mandel et al.   | 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
Table 3: Nonpharmacological measures used during retinopathy of prematurity screening

| Authors            | Methods   | Findings                                                                 |
|--------------------|-----------|--------------------------------------------------------------------------|
| Nayak et al. (2020) | RCT       | No significant effect for 30% oral glucose over sterile water nor expressed breast milk |
| Sagheb et al. (2020) | RCT       | 25% oral glucose was significantly effective in pain prevention          |
| Olsson et al. (2011) | RCT       | No significant effect for 30% oral glucose over sterile water             |
| Costa et al. (2013)   | RCT       | 25% oral glucose was significantly effective in pain prevention          |

Oral sucrose

- PIPP scores were lower in sucrose group than placebo
- PIPP scores were lower in sucrose group than placebo
- Combining sucrose with NNS and swaddling is effective in decreasing pain responses
- Combining sucrose with NNS and swaddling is effective in decreasing pain responses
- Infants enrolled did not benefit from 24% oral sucrose despite high sucrose doses
- Compared to paracetamol, sucrose group had lower PIPP scores at the beginning of eye examination
- Oral sucrose and simple comfort measures can alleviate pain associated with mydriatic eye drops instillation

Breast milk

- Expressed breast milk can reduce infant pain during the procedure and for 5 min afterward
- Breast milk is as effective as sucrose in relieving acute pain during ROP screening
- 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
- 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

Infant’s position and body posture play an important role in increasing the sense of security which, in turn, reduces energy expenditure. 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. 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 settings: Slevin et al.). 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. In addition, lower heart rate and shorter crying time were noticed compared to the control group who received a pacifier only. 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. Table 4 summarizes studies assessing comfort measures during ROP screening.

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. 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]

**Table 4: Comfort measures during retinopathy of prematurity screening**

| Authors | Methods | Findings |
|---------|---------|----------|
| Sun *et al.* (2020)[62] | RCT | PIPP scores were lower in babies receiving gentle human touch compared to the control group |
| Rush *et al.* (2005)[61] | Case series | Using 24% sucrose, pacifier, swaddling, and holding could not be recommended as effective pain relieving method |
| Kleberg *et al.* (2008)[60] | RCT | NIDCAP did not abolish infant pain but helped subjects to recover faster |
| Chuang *et al.* (2019)[61] | Case series | Bundle of comfort measures significantly reduced pain and stress at ophthalmology examination and 1 h afterward |
| Zeraati *et al.* (2016)[61] | Case series | Multisensory stimulation program is effective in reducing infant pain |
| Slevin *et al.* (1997)[61] | Case series | Nesting is a beneficial method in reducing infant discomfort, movements, activity, and crying time |
| Metreş *et al.* (2019)[61] | 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)[61] | 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)[61] | RCT | Skin-to-skin contact and parental support did not give extra pain relief compared to standard care |

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

| Authors | Methods | Findings |
|---------|---------|----------|
| Parulekar *et al.* (2008)[64] | Case series | Sub-Tenon anesthesia with oral/rectal sedation sufficiently controlled infant pain |
| Novitskaya *et al.* (2013)[63] | Case series | Sub-Tenon anesthesia with oral/rectal sedation sufficiently controlled infant pain |
| Sinha *et al.* (2016)[60] | 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)[61] | Case series | Tetracaine is an effective pain-relieving method during Intravitreal injections |

**RCT:** Randomized controlled trial, PIPP: Premature infant pain profile, NIDCAP: Newborn Individualized Developmental Care and Assessment Program
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. 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. In addition, But et al. concluded that sevoflurane–N₂O 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. Table 6 illustrates reviewed sedoanalgesia articles during ROP treatment.

**Table 6: Sedoanalgesia during retinopathy of prematurity treatment**

| Authors         | Methods   | Findings                                                                 |
|-----------------|-----------|--------------------------------------------------------------------------|
| Kirwan et al. (2007) | Case series | Morphine is an effective sedoanalgesia and can be used alternative to GA |
| Piersigilli et al. (2019) | Case series | Fentanyl is an effective sedoanalgesia and can be used alternative to GA   |
| Örge et al. (2013) | Case series | Fentanyl is safer when compared to morphine                                |
| Dannelley et al. (2018) | Case series | Fentanyl and midazolam achieved successful procedures with no adverse events |
| Miller et al. (2018) | Case series | Fentanyl and midazolam achieved successful procedures with no adverse events |
| Saylan et al. (2020) | Case series | Majority of infants had successful and uneventful laser procedures under ketamine sedation |
| Lyon et al. (2008) | Case series | Majority of infants had successful and uneventful laser procedures under ketamine sedation |
| Jiang et al. (2017) | RCT       | Both GA and sedoanalgesia are well tolerated                               |
| But et al. (2012) | RCT       | Sevoflurane-N₂O and midazolam–remifentanil anesthesia techniques can be safely used |
| Sethi et al. (2020) | Case series | Low fentanyl dose (1 μg/kg/h) is an effective pain-relieving method compared to 24% oral sucrose |
| Sammartino et al. (2003) | Case series | Use of opioids and benzodiazepines appear to be valid and feasible analgesia protocol |
| Demirel et al. (2014) | Case series | Use of opioids and benzodiazepines appear to be valid and feasible analgesia protocol |
| Ulgey et al. (2015) | RCT       | Sedation using 1 mg/kg ketamine and 1 mg/kg propofol provided hemodynamic stability compared to GA |
| Novitskaya et al. (2020) | Survey   | Most frequent anesthetic practice was sedation (47.8%)                     |

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. 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. 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. 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.

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. A summary of reviewed GA studies during ROP treatment is shown in Table 7.

**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) | Survey          | GA was employed in the majority of neonatal units (57%)                   |
| Chen et al. (2007)     |                 | Majority (50%) of ophthalmologists preferred GA for laser treatment      |
| Sekeroglu et al. (2013) |                 | 72.7% of the ophthalmologists preferred GA                              |
| Klein et al. (2013)    |                 | Most of the practitioners (60%) preferred Intravenous sedation followed by GA (19%) |
| Sato et al. (2015)     | Non-RCT         | Air, oxygen, and sevoflurane inhalation should be adopted as the best anesthetic protocol |
| Ugur et al. (2021)     | Case series     | General anesthesia with sevoflurane can be safely used in infants undergoing laser photocoagulation |
| Kaur et al. (2020)     |                 | General anesthesia with sevoflurane can be safely used in infants undergoing laser photocoagulation |
| Aoyama et al. (2010)   |                 | Half of the patients were successfully extubated in the operation room, no postoperative complications after early vitrectomy |
| Sinha et al. (2014)    |                 | Only 5.36% of studied subjects undergoing vitrectinal surgery under general anesthesia using sevoflurane with atracurium and fentanyl had postoperative apnea which is lower than the literature |
| Tokgöz et al. (2013)   |                 | General anesthesia with sevoflurane can be safely used in infants undergoing bexacizumab injections |
| Gutierrez-Padilla et al. (2015) | Survey | Combining IV Fentanyl and propofol without muscle relaxant for laser photocoagulation is useful and offers rapid recovery |
| Anand et al. (2007)    |                 | 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                 |
| Guene et al. (2011)    | 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)    |                 | 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)       |                 | 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 |

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