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Resurgence of combined intravenous Ketamine and regional anesthesia in pediatric ocular surgery in COVID-19 pandemic

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Purpose: The current pandemic of COVID-19 has made airway procedures like intubation and extubation, potential sources of virus transmission among health care workers. The aim of this work was to study the safety profile of combined ketamine and regional anesthesia in pediatric ocular surgeries during the COVID-19 pandemic. **Methods:** This prospective study included pediatric patients undergoing ocular surgery under general anesthesia from April to October 2020. Children were premedicated with oral midazolam (0.25–0.50 mg/kg) or intramuscular ketamine (7-10 mg/kg), ondensetron (0.1 mg/kg) and atropine (0.02 mg/kg). Anesthesia was achieved with intravenous ketamine (4–5 mg/kg) and local anesthesia (peribulbar block or local infiltration). The patient's vital signs were monitored. Serious complications and postoperative adverse reactions related to anesthesia were documented. **Results:** A total of 55 children (62 eyes) were operated. Lid tear was the most common surgical procedure performed [$n = 18$ (32.7%)]. Dose of ketamine needed ranged from 30 to 120 mg (66.67 ± 30.45). No intubation or resuscitation was needed. Four children complained of nausea and two needed an additional dose of intravenous ondansetron due to vomiting in the post-operative period. Incidence of postoperative nausea and vomiting was not affected by age, duration of surgery or dose of ketamine used ($P > 0.05$). There was no correlation between increase in pulse and dose of ketamine. **Conclusion:** Combined ketamine and regional anesthesia is a safe and effective alternative to administer anesthesia in a child during ocular surgeries.

Key words: COVID-19 era, ketamine, pediatric general anesthesia, regional anesthesia

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Coronavirus disease 2019 (COVID-19) is a pandemic caused by RNA virus named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[1] It has dramatically changed the way medicine is practiced, and the field of ophthalmology is no different. Worldwide, various guidelines have been put forward for the general ophthalmology practitioners.[2-5] Saxena *et al*., keeping in mind the unique challenges posed by the pediatric age group, published recommendations pertaining to listing conditions which need urgent care, precautions and technique of pediatric eye examination and a protocol for delivering a safe general anesthesia for a pediatric eye surgery.[6] A review by Lee-Archer *et al*. suggested that airway procedures such as bag-mask ventilation, intubation and extubation generate aerosols and are important routes of transmission of virus, particularly for healthcare workers.[7] Guidelines suggested so far include inhalational anesthesia for induction; precautions to be taken while intubating and extubating the child, inducing and maintaining the anesthesia were highlighted by Saxena *et al*.[6] Disadvantages include need of intubation and extubation, costly drugs and monitoring system and additional requirements like heat and moisture exchanging filters.[6] Intravenous (IV) anesthesia on the other hand, do not have these inherent problems.

Ketamine is considered among the oldest hypnotic agents for anesthesia because of its analgesic properties, minimal suppressive effects on respiration and stable hemodynamics.[8] It is a phencyclidine derivative used for general anesthesia in short surgical procedures. It is partially water soluble with high liquid solubility. It is metabolized by hepatic microsomal enzymes to nor-ketamine and hydroxylated to form hydroxy-nor-ketamine and excreted in the urine.[9] It causes a dissociative anesthesia with profound analgesia and crosses the blood-brain barrier rapidly, increasing cerebral blood flow and intracranial pressure.[9] It increases heart rate, cardiac output, and blood pressure, but relaxes bronchial smooth muscles.[9] Ketamine has a wide range of indications. It may be used as the sole anesthetic agent for short term procedures, and for induction and maintenance of anesthesia in high risk patients with respiratory and cardiac disorders and shock.[10] Adverse effects include an increase in lacrimation and salivation, dilation of pupil, increase in intraocular pressure, nausea and vomiting.[9] The dissociative

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experiences associated with ketamine (hallucinations) are often not unpleasant, and last only a short time.[10]

Ketamine has been in clinical use since long. Its safety profile in pediatric age group,[10,11] its empowerment of being able to do away with intubation and extubation and its low cost and investment, have made it a very useful agent in pediatric ocular surgeries (which are usually of shorter duration), especially in the developing regions of the world. There are recommendations that regional anesthesia (RA) should be preferred over general anesthesia (GA), if possible. And if general anesthesia is necessary, then it should be combined with RA, to decrease the strain on important drugs like midazolam, atracurium etc.[12] In this prospective single center observational study, we aim to study the safety profile of combined ketamine and RA in pediatric ocular surgeries during the COVID-19 pandemic.

Methods

This was a prospective study conducted in a tertiary eye care center in Ahmednagar, India from April 2020 to September 2020. All the pediatric patients undergoing ocular surgery under general anesthesia were included in the study. They were asked to fast for 6 hours and to maintain nil by mouth (NBM) status for 4 hours prior to the operation. Surgery was performed by a pediatric ophthalmologist and anesthesia was administered by an anesthetist experienced in pediatric airway management and resuscitation, thereby minimizing the surgical time and time under anesthesia.

Every child was screened prior by the treating pediatrician to rule out any systemic infection and the anesthetist to screen for conditions that could interfere with administering safe anesthesia. Every child was given a surgical cap and 3ply mask, irrespective of the age. Nil by mouth status was confirmed with parents. While the child was with the mother, oral midazolam was given in the dosage of 0.25-0.50 mg/kg or ketamine was given intramuscularly in a dose of 7-10 mg/kg, helped us to put scalp vein or catheter IV in the operation theatre. Ondensetron was added in a dose of 0.1 mg/kg to avoid postoperative nausea and vomiting (PONV) slow IV over 30 seconds. Atropine was given at a dose of 0.02 mg/kg. The aim was to reduce salivation which would reduce the chances of aspiration. All patients received intravenous Midazolam at a dose of 0.05 mg/kg 10 minutes before induction.

All the necessary drugs for anesthesia and resuscitation were made ready before taking the patient inside the operation theatre (OT), including oxygen cylinder, laryngoscope, endotracheal tube of appropriate size, masks, and ambu bag. All the other unnecessary equipments were removed, as suggested by the guidelines on pediatric airway management.[1] This helps to reduce the need for anesthetist to search the anesthesia trolley drawers and bins once the patient has entered the OT. Trash cans and sharps containers were kept open near the OT table to avoid dropping equipment on the floor, which can increase viral dispersion.

Once the necessary arrangements were made, the child was taken to the operating theatre where an intravenous line or scalp vein (depending on the duration of surgery) was positioned. A splint was placed to stabilize the hand. Anesthesia was induced with intravenous ketamine, 4-5 mg/kg given slowly, a diluted dose was then used for maintenance according to the surgical stimulus response. Once the child was under the effect of ketamine, supplemental local anesthesia in the form of peribulbar block or local infiltration was administered, depending upon the case. A disposable nasal catheter was secured below the nose to deliver oxygen at a rate of 1.5–2 liters/min. The patient's vital signs were monitored using a pulse oximeter. Changes of heart rate (HR) and blood oxygen saturation (SpO2) pre-anesthesia, intra- and post-surgery were observed using the pulse oximeter.

Once the surgery was over, oxygen delivery was stopped and SpO2 concentration was observed during spontaneous breathing for 2-3 minutes. The child was shifted to the ward if the SpO2 levels were more than 98%. The vital signs of the child were monitored in the ward as well using pulse oximeter. After 3 hours of NBM, the child was given fluids in slow increments to watch for nausea or vomiting. In absence of any untoward reaction/ complication, the intravenous line was removed and the child was discharged. The occurrence of various postoperative adverse reactions such as nausea and vomiting, suctioning, shiver, dysphoria and lethargy were documented. General doses of ketamine and vital signs of every patient were documented.

The primary outcome measure was the incidence of serious complications and post-operative nausea and vomiting (PONV). Secondary outcome measures included association of PONV with background characteristics i.e., age, gender, eye involved, duration of surgery and dose of ketamine, and the association between increase in pulse (maximum intraoperative value minus preoperative value) with dose of ketamine/ duration of surgery and age. Descriptive and inferential statistical analyses were carried out in the present study. The results were analyzed by using SPSS version 18 (IBM Corporation, SPSS Inc., Chicago, IL, USA). Results on continuous measurements were presented on Mean ± SD (Min-Max) and results on categorical measurements were presented in Frequency (Percentage). Normality of the data was assessed using Shapiro-Wilk test. Inferential statistics like Chi-square test/Fischer Exact test, Independent t test & Pearson Correlation was used. P value less than 0.05 was considered to be significant.

Results

A total of 55 children (62 eyes) were operated, ranging in age from 6 months to 10 years (mean 3.7 years, SD 2.8). The gender distribution and descriptive are mentioned in Tables 1 and 2. There were 43.6% girls (n = 24 out of 55) and 56.4% boys (n = 31 out of 55). The time required to perform these procedures ranged from 10 minutes to 75 minutes (35.92 ± 20.49). Dose of ketamine needed ranged from 30 mg to 120 mg (66.67 ± 30.45). Table 3 lists the indications for surgery. Lid tear was the most common procedure performed [n = 18 out of 55 (32.7%)], followed by probing and syringing [n = 14 out of 55 (25.5%)]. All patients maintained SpO2 more than 95%, intraoperatively as well as in the postoperative period.

Complications: There were no serious side effects from ketamine, either intraoperatively or postoperatively. None of the patient required intubation, and no resuscitations were necessary. Four children complained of nausea and two needed an additional dose of intravenous ondansetron due to vomiting

Table 1: Gender Distribution

Gender	Frequency	Percentage
Female	24	43.6
Male	31	56.4
Total	55	100

Table 2: Descriptives

	Range	Mean±SD
Age (Years)	0.50-10	3.67±2.79
Dose	30-120	66.67±30.45
Duration	5-90	35.92±20.49

Table 3: Indications for surgical procedure

Indication for surgery	Number of patients	Percentage (%)
Open globe injury	6	10.9
Lid tear	18	32.7
Probing	14	25.5
Ptosis	2	3.6
Squint	4	7.3
Cataract	8	14.5
Others	3	5.5
Total	55	100

in the post-operative period. Table 4 shows that the incidence of PONV was not affected by age and gender of the patient, eye involved, duration of surgery or dose of ketamine used ($P > 0.05$). Pearson Correlation was used to see the relationship/ correlation/ association between the variables (age, dose of ketamine and duration of surgery with increase in pulse). Mild correlation was observed between the variables but was not statistically significant [Table 5].

Discussion

Various bodies across the globe have issued recommendations pertaining to protocols for delivering a safe general anesthesia for pediatric surgery, including the All India Ophthalmological Society.[6] Though inhalational induction was traditionally being preferred in children,[13] intravenous induction is becoming increasing popular.

Velly L *et al*. in their article have enlisted the procedures that increase the risk of aerosolization.[12] These include endotracheal intubation and extubation, performing a tracheotomy and endotracheal suctioning without a closed suction system. They also suggested that in children, RA and infiltration techniques used in combination with general anesthesia, can reduce the use of drugs that are in short supply.[12] It will also allow postoperative follow-up directly in the ward without going through the recovery room in accordance with regulations. This facilitates compliance with distancing measures specific to the current epidemic context.[12] However, intubating the child does not make it possible to bypass the recovery room. This is again facilitated by using ketamine which does not need intubation in the OT. So, it is imperative that for ophthalmic procedures at least; which are usually of shorter duration, we should employ a technique of delivering general anesthesia which takes endotracheal intubation and extubation out of the equation. Hence, we decided to use intravenous ketamine along with regional or local infiltration.

AIOS guidelines recommend using a transparent box (COVID-19 GA box) to induce the child.[6] This was first described by a doctor in Taiwan which consists of a transparent plastic cube designed to cover a patient's head that has two circular ports through which the person performing the tracheal intubation places their hands.[14] However, Kearsley in his correspondence in Anesthesia raised concerns regarding safety of the staff and patient with respect to the use of these boxes.[15]

Ketamine is a noncompetitive NMDA receptor antagonist, which blocks the phencyclidine binding site on NMDA receptor thereby stopping depolarization of neuron.[11] These NMDA receptors are located at the spinal, thalamic, limbic and cortical levels. Hence, ketamine interferes with sensory input to higher centers of central nervous system, affecting pain and emotional responses as well as memory. It also has some secondary effects on opiod receptors, catecholamines, alpha and beta receptors.

In a developing world like India, ketamine fulfils many requirements of an ideal pediatric anesthetic agent. It has a rapid onset, rapid offset, and ease of administration. Its duration of action is long enough to allow completion of contemplated surgical procedures.[10] It does not cause significant respiratory or cardiac suppression, but also offer immobilization of the patient and good analgesia. Additionally, it is cheap. Administration of ketamine for pediatric ophthalmology has been studied since past couple of decades[10,16,17] Green *et al*. in their study attempted to quantify ketamine use in low-middle income countries, found a serious complication rate, i.e.; death, cardiac arrest, apnea, laryngospasm and aspiration, of only 0.15% in more than 12,000 administrations of ketamine.[11] This low rate of complications was seen in varied levels of skill of practitioners and monitoring, which points towards a high safety margin of ketamine in these situations.[9] But the study subjects were not limited to children, and it included a variety of short, non-ophthalmic procedures. In a series of 679 children of Tilganga Eye hospital, Kathmandu, the authors did not report a single incident of need of resuscitation or intubation while performing intraocular or extraocular pediatric procedures.[10]

Since ketamine is a potent bronchodilator, it is a good induction agent for asthmatic patients.[9] It functionally "dissociates" the thalamus (which relays sensory impulses from the reticular activating system to the cerebral cortex) from the limbic cortex (which is involved with the awareness of sensation). Characteristically, while some brain neurons are inhibited, others are tonically excited and clinically, this state of dissociative anesthesia causes the patient to appear conscious but unable to process or respond to sensory input.[18] Ketamine inhibits morphine metabolism to increase the duration of analgesia, thereby exercising its intrinsic anti-inflammatory effects.[19]

The main side effects, limiting its use during shorter procedures, are agitation and emergence symptoms, both of

Table 4: Association of post-operative nausea and vomiting with background characteristics

Variables		Post-operative Nausea and Vomiting			
		Yes	No	Total	*P*
Gender	Male	4	27	31	0.589
	Female	2	22	24	
Eye operated	RE	3	15	18	0.795
	LE	3	27	30	
	BE	0	7	7	
Age	Mean (SD)	6 (2.94)	3.27 (2.73)	3.72 (2.89)	0.086
Dose of ketamine	Mean (SD)	92.50 (22.17)	61.50 (29.61)	66.66 (30.45)	0.061
Duration	Mean (SD)	43 (7.70)	34.50 (22.05)	35.92 (20.49)	0.461

Table 5: Pearson Correlation between increase in pulse with different variables

Pulse difference	Correlation coefficient	*P*
Dose of ketamine	0.397	0.055
Duration of surgery	0.179	0.401
Age	0.159	0.459

which are common with high doses.[9] Hence, we routinely premedicate the child with low doses of midazolam. This reduces the incidence of these phenomenon and do not cause any additional problems either. In addition, in every case we also use local anesthesia in conjunction with ketamine, which helps to reduce the doses of ketamine. This not only preserves the supply of important drug, ketamine, but also seems to improve analgesia, and allows improved postoperative recovery.

Ketamine increases salivary secretions, which in turn may increase the incidence of laryngospasm.[20] Hence, it is recommended to premedicate the patient with a small dose of atropine or glycopyrrolate. Ketamine has been shown to increase the incidence of PONV, while also increasing the severity of nausea.[21] Habib *et al*.[22] proposed a multimodal approach to reduce PONV, that consists of preoperative anxiolysis (midazolam), prophylactic antiemetics, total IV anesthesia with propofol, and local anesthetic infiltration and ketorolac with no nirous oxide usage. According to them, this approach had 80% complete response rate as compared to 43% to 63% among patients receiving either inhaled drug or total IV anesthesia alone. We employed following steps to prevent PONV: Minimize the doses of ketamine (performing the surgeries quickly and using local anesthesia in addition to ketamine), prophylactic use of ondansetron before ending the surgery and preoperative midazolam. Out of 55 children, we encountered incidence of PONV to be 10.9% (n = 6, 4 patients complained of nausea and other 2 had an episode of vomiting, requiring additional medications postoperatively). Ketamine appears to stimulate sympathetic nervous system leading to increased cardiac output, tachycardia and increased blood pressure.[9] We divided the patients in three groups depending upon the increase in the pulse and did not find a significant correlation with the dose of ketamine used or age or the duration of surgery. This is probably again due to lower doses of ketamine used and using local anesthesia in addition to ketamine.

A unique concern of IV anesthesia includes a crying child at the time of induction. Because inhalational induction may increase exposure to respiratory droplets and aerosols, the Pediatric Difficult Intubation Collaborative (PeDI-C) members agreed that IV induction is preferred.[1] However, clinicians should assess the child's disposition to IV catheter placement as struggling to place a catheter may result in higher exposure to respiratory droplets if the child cries. They have advised clinicians to consider the routine use of preprocedural sedatives to reduce anxiety and increase compliance when an intravenous (IV) is placed awake. Additionally, premedication may reduce the risk of vigorous crying.[1] They have deemed nasal administration of premedication undesirable because of the potential for high viral loads and the risk of coughing and sneezing.[1] We gave oral midazolam or intramuscular ketamine depending on the cooperation of the child when he/she was with their mother. An experienced anesthetist is useful in this situation as well as he was able to put a scalp vein or IV catheter in a single attempt. Every child irrespective of their age was given a disposable three-ply face mask during this procedure as well which further reduces the dissemination of aerosols.

The main limitation of the study is a smaller sample size. However, the pandemic allowed us to operate only emergency cases. Further studies are required with more sample size to validate the results of the present study. The ideal way to perform the study would have been to conduct a randomized controlled trial and compare inhalational versus ketamine with RA to look for the actual virus spread. However, it was not possible in clinical setting.

Conclusion

To conclude, ketamine in itself is a safe drug to administer for general anesthesia in children. In addition, it obviates the need of intubation and hence, intubation box and extubation to a large extent. Additional filters need not be attached to breathing circuit. Requirement of gases, oxygen and nitrous oxide decreases. Postoperative monitoring decreases as well. Lesser manpower is needed. The drug and the monitoring system is cheap, in environment where there is already a significant financial crunch. The two main disadvantages are a crying child during induction and PONV. But with due precautions these can be easily managed as well. Hence, combined ketamine and regional anesthesia is a safe and effective alternative to administer anesthesia in a child during ocular surgeries.

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Conflicts of interest

There are no conflicts of interest.

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