Review

Progress of Application of Sedation Technique in Pediatric Ocular Examination

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Abstract

Pediatric ophthalmic test requires meticulous observation and precise measurement. However, children are unable to actively cooperate with the test. If they were forced to receive the examinations, it is difficult to deliver accurate diagnosis and treatment, and cause negative influence upon physical and mental health. Consequently, sedation technique plays an extremely vital role in pediatric eye examinations. This study was designed to summarize the application of chloral hydrate in pediatric eye examination and propose different methods of medicine administration for children of varying ages, aiming to improve the effect of sedation. In addition, the feasibility of use of dexmedetomidine, which had been proven to be effective in pediatric sedation examination, into pediatric ophthalmic sedation examination was evaluated, thereby offering more options for the development of pediatric ocular sedation test. (***Eye Science 2014; 29:186-192***)

Keywords: pediatric; eye examination; sedative; chloral hydrate; dexmedetomidine

Pediatric eye examination has been a long-term challenge for the ophthalmologists at home and abroad. At present, certain hand-held and/or non-contact test devices have been designed, such as hand-hold slit-lamp examination, hand-hold fundus camera and hand-held tonometer (Tonopen), which lower the requirement of the children´s cooperation. However, these hand-hold devices are inferior to traditional desktop equipments in terms of the clarity or precision of measurement results. Hence, desktop equipments are still necessary for pediatric eye examination. Common desktop devices used for eye examination include slit lamp, anterior segment photograph, fundus photography, Pentacam, IOLMaster, corneal topography and OCT, etc. During measurement, the examiners are required to be in a sitting position, keep their backs vertical with heads on the scaffold. The examinees should gaze forward and conduct eye movement according to the doctors' instructions. In addition, contact devices are adopted in most tests, such as B ultrasound, intraocular pressure measurement, retinoscopy, UBM, fundus fluorescence angiography, etc. The children are still unable to cooperate with the examination. To enhance examination efficacy and accuracy and alleviate the injury and fear by compulsory test, pediatric ophthalmologists are required to proficiently master sedation technique and perform different eye examinations for the asleep pediatric patients.

Current situation of application of sedation technique in pediatric examination

Different from adults, children constantly present with intense feelings of fear, pain and agitation due to poor degree of cooperation and concentration during different examinations. Such feelings of fear may endure until the adulthood[1]. More importantly, children are unable to cooperate with the examination, which may affect the accurate diagnosis and treatment of different pediatric diseases and severely suppress their physical and mental development. Consequently, pediatric sedation technique is an essential part of pediatric treatment (Table 1).

However, the medication and methods of sedation and anesthesia examination in pediatric ophthalmology have been rarely reported. Oral or rectal administration of chloral hydrate is the only selection for pediatric ophthalmologists probably due to the fol-

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Table 1 Examination items and characteristics of current pediatric sedation or anesthesia techniques in China

Examination and operation	Sedation medication	Dose	Administration method	Characteristics
Operation of different punctures	5% EMLA cream Compound lidocaine cream	1.5 g/10 cm^2	External application	Be able to infiltrate into the corium layer to achieve surface analgesia and anesthesia, and forbidden for children aged < 3 years
Lung function, eye examination, MRI, CT and B ultrasound	Chloral hydrate	0.5–0.8 ml/kg Total dose ⩽ 10 ml	Oral and rectal administration	Induce physiological sleep fast and safe, short duration, no incidence of residual effect or respiratory depression, no discomforts and is easily accepted by the relatives of the children. It tastes bitter and is likely to cause nausea and vomiting.
Gastroscope and oral examination	Midazolam Midazolam	0.5–0.75 mg/kg (oral administration) 0.2–0.6 mg/kg (nose drop) 0.08–0.1 mg/kg (intermuscular injection) 0.3–0.7 mg/kg (rectal administration)	Oral, nasal, rectal administration and intermuscular injection	With fast effect, short duration, quick recovery, convenient drug administration, safe and effective.
Oral examination	Nitrous oxide	The concentration ranging from 10%, 20% to 30% at a flow velocity of 3 L/min	Inhalation	Colorless gas, somewhat sweet taste, easy to use, quick effect (3 to 5 min in general), no respiratory depression or circulation function, safe without side effects and the children are sober and could cooperate with the treatment.The effect diminishes rapidly, no storage function or respiratory tract irritation and the children are likely to accept the examination.
MRI, CT, oral and eye examination	Dexmedetomidine	1–2 μg/kg	Oral and nasal administration	Sedation, analgesia, anti-depression and sympathetic nerve suppression effect, mild respiratory depression, low incidence of medication dependence and the most common adverse events are increases in blood pressure and heart rate.
Dressing changes and small surgery in outpatient	Ketamine	2 mg/kg (intravenous injection), and another dose of 1mg/kg can be delivered as necessary 3mg/kg (intermuscular injection)	Intermuscular and intravenous injection	Strong analgesic effect, slight inhibitory effect upon respiration and fast resuscitation; poor safety, abnormal responses may occur during resuscitation stage, such as involuntary limb movements, twitch or convulsion occasionally.

lows: First, both parents and clinicians are cautious about the use of sedation and anesthesia medication during examination, which causes the difficulty of widespread application in clinical settings. Second, the development and economic profits of sedation medication are declining due to its low price. Third, most hospitals in China are lack of the specialty of pediatric ophthalmology and standard procedures for pediatric sedation and anesthesia examinations. Therefore, more studies focusing on pediatric sedation examination are urgently required to accommodate the development of pediatric ophthalmology.

Conventional application of chloral hydrate in pediatric sedation eye examination

Medication characteristics

Chloral hydrate is a colorless, volatile, lamellar crystalline solid with intense bitter smell and soluble in water. It is used for sedation, hypnosis and anticonvulsion, etc. It is commonly applied as a sedative in pediatric examination. Even if syrup is added, most children are unable to tolerate the taste of chlo-

ral hydrate solution. Pharmacokinetic analysis revealed that digestive tract or rectal administration could achieve rapid absorption, peak at 1 h after administration and maintain for 4-8 h. Chloral hydrate is rapidly metabolized in vivo to trichloroethanol, which is the main substance responsible for hypnosis. The plasma half-life of trichloroethanol is approximately 8 h. It is deactivated after binding with glucuronic acid, discharged from the kidney and has no delayed or accumulative properties. Use of chloral hydrate at a hypnosis dose for 30 min could induce physiologic insomnia and endure for 4-8 h. No discomforts or sequelae can be caused. It has been widely applied in pediatric sedation examination due to rapid effect, safety, short duration and mild adverse events. In addition, chloral hydrate does not lead to changes in nervous system, aqueous humor, muscular contraction or intraocular pressure[2]. Hence, it is widespread used as a sedative in pediatric eye examination.

Dose of administration

Liu et al[6]. adopted 10% chloral hydrate at a dose of 0.5 ml/kg. Zhou et al[7]. applied 10% chloral hydrate prior to newborn examination with a dose of 0.5 ml/kg for mature newborns and 0.3 ml/kg for premature infants. Wu et al[8]. delivered oral administration of 10% chloral hydrate at a dose ranging from 50 to 80 mg/kg and the maximum amount ≤ 2 g. Zou et al[9]. used syrup of 10% chloral hydrate with a dosage of 30-40 mg/kg and 50-60 mg/kg for 6% chloral hydrate. Sun et al[10]. adopted oral administration of 10% chloral hydrate at a dose of 0.8 ml/kg and the maximum quantity≤1.0 ml/kg. The dose of chloral hydrate should be determined according to age, body weight and individual situation of the children. In most cases, the safe dose of chloral hydrate is 0.3-0.5 ml/kg for premature infants and 0.5-0.8 ml/kg for healthy mature infants. The maximum quantity should be ≤ 10 ml. Our study demonstrated that the dose of 10% chloral hydrate was 0.8 ml/kg for most healthy mature infants, which took effect at 15-30 min after oral administration and the sedation time was approximately 30-60 min. Good sedation effect was obtained and multiple eye examinations could be successfully conducted.

Administration of medicine

At present, two administration methods of chloral hydrate are available including oral and rectal administration. Yang et al[3]. divided the children into three groups based on age and compared the clinical efficacy between oral and rectal administration, concluding that oral administration of 10% chloral hydrate is suitable to infants and rectal administration applies to babies and school age children. Feng[4] delivered oral administration of chloral hydrate to 102 children with retinoblastoma and rectal administration to 101 counterparts. The sedation efficacy was observed between two groups. The results demonstrated that during auxiliary examination for children with retinoblastoma, oral administration had better sedation effect compared with rectal administration. Zhang et al[5]. delivered chloral hydrate via oral administration for 50 children with hand-foot-mouth disease and rectal administration for 70 counterparts and found that rectal administration was significantly superior to oral administration in terms of clinical efficacy, safety and sedative effect. Therefore, oral administration is suitable for infants considering their immature perception, sense of taste and control of excretion. However, rectal administration applies for babies and preschoolers because their sense of taste and fear may affect the absorbed dose and sedation effect of medication. For premature infants with cleft palate, laryngomalacia complex congenital heart disease, severe pneumonia, vomiting, cough and swallowing dysfunction, oral administration is likely to cause adverse events and negatively influence sedation effect. Therefore, rectal administration should be considered instead.

The conventional and modified administration methods are described as follows. Conventionally, the nurses instructed the parents to administer the medicine using a cup. However, the children are reluctant to cooperate with the administration by spraying or throwing up the drugs. The absorption dose could not be evaluated and the sedation effect is poor. By modified methods, the nurses or parents use a spoon to suppress the tongue of the children and deliver the medicine or absorb the medicine using a syringe, take off the syringe head and slowly deliver the medicine solution via the mouth. Thus, the absorption dose can be evaluated. Both children

and parents are likely to accept this method of administration. Wang et al[11]. compared the conventional and modified oral administration and the results revealed that modified oral administration could improve sedation effect and ease gastrointestinal discomforts. After administration, the parents should make the children fall asleep and then perform the examination. Conventional rectal administration has the following limitations. The diameter of the anal canal is thick and hard, which irritates the anus, causes pain and discomforts and defecation reflex and affects clinical efficacy. Recently, the anal canal is substituted by disposable scalp needle without the syringe (approximately 25 cm in length) in modified rectal administration. It uses a thin and soft needle, which merely causes slight stimulation, unlikely to lead to defecation reflex and alleviate the discomforts. Wang et al[12]. proposed to inject the medicine solution by insertion depth of 15-20 cm, gently rubbed the anus using the toilet tissue and removed the catheter after retaining for 3-5 min, which ensured the retention time of medicine solution in the sigmoid colon. We equally recommend this administration method, which favors medication retention, represses defecation reflex and improves sedation effect. The temperature of the medicine solution should be kept at 39-41 ℃, similar to the temperature of colon. It not only contributes to retention and absorption of medicine solution, but also reduces the incidence of diarrhea after rectal administration. The children should be kept in a lying or lateral position to prevent the overflow of medication and the incidence of administration failure.

Besides, the following methods could enhance the success rate of sedation examination. First, parents should wake up the children 2-3 h earlier than usual. If the examination was scheduled at the afternoon, the children can not sleep until the examination. The effect of sedation could be significantly enhanced when the children are under sleepy and fatigue status. Second, the children should not be fed too full prior to oral administration. The medication is easily absorbed under empty stomach and it prevents the incidence of vomiting. Third, medicine should be administered after defecation, which decreases anal stimulation and reduces the incidence of discharge of medication and excrement mixture. Fourth, oral administration should be recommended if diarrhea occurs. Taken together, correct medicine administration could improve sedation effect, enhances the success rate of drug administration and eases pain, which is easily accepted by both children and their parents.

Adverse events and safe nursing

The most common adverse event of chloral hydrate is gastrointestinal mucous irritation, which is likely to arouse nausea, vomiting and diarrhea. Xiao et al[13]. delivered 10% chloral hydrate for 5500 children. Upon the day of examination, the amount of diet and sleep were reduced. In total, 5480 children had no adverse events, 8 presented with redness at the corner of the mouth which disappeared 3-4 h later, 5 systemic roseola, which was alleviated within 24 h, 6 presented with cyanosis, which could be mitigated by corresponding measures (lung and heart color ultrasound) and 1 had endocardium defects and respiration obstruction and subsequently transfered to ICU. Hu et al[14]. administered 10% chloral hydrate for 30 children and found that varying degree of throat noise was heard within 30 min in most cases. The younger the age was, the louder the whining noise was, especially during breast feeding. The throat noise was alleviated after the drug effect was absent. Albeit chloral hydrate has been applied in clinical settings for years, close monitoring and nursing should be addressed. First, chloral hydrate should be used at a rational and safe dose. A large dosage of chloral hydrate exerts inhibitory effect on cardiac muscle, decreases blood pressure, causes respiratory depression and induces damages to liver and kidney. For those discharged the medicine solution during rectal administration and vomiting during oral administration, the dose of drugs should not be supplemented because excessive dose may cause severe adverse events[15]. Second, the children should be closely observed after drug administration, such as facial complexion, respiration and heart rate, etc. The children presenting with respiratory depression, allergic reaction or alternative abnormality should be subject to emergency rescue. The safety of drug administration should be guaranteed. Our previous studies demonstrated that the success rate of chloral hydrate sedation was not satisfactory, approximately 30% of

children were unable to complete sedation examination. Consequently, an alternative administration method, which is more suitable for children, convenient to administer and high effect, is urgently required.

Dexmedetomidine as a novel drug for pediatric sedation examination

Medication property

Dexmedetomidine is a selective agonist of α2-adrenergic receptors, as a sedative medication used by intensive care units and anesthesiologists. Dexmedetomidine is mainly metabolized in the liver and discharged from urine and excrement.Compared with other sedatives, dexmedetomidine exerts less influence upon respiratory system. It has been applied as a sedative in CT and MRI for pediatric patients and yields high sedative effect.

Medication administration

Four administration methods are available for dexmedetomidine: intravenous drip, intermuscular injection, oral administration and mucosa administration including intranasal and oral routes. Intravenous drip or intermuscular injection yields more stable hemodynamics, whereas the children's parents are unwilling to accept these approaches. The bioavailability of oral administration is merely 15.6%[20], and it should not be used for dexmedetomidine administration. The bioavailability of mucosal administration of dexmedetomidine is up to 82%[20]. However, the sedative effect of oral mucosal administration is lower than that of nasal administration. In addition, it requires the children adapt to wear the masks[21]. The nasal administration shares similar pharmacologic effects with intravenous drip. Therefore, nasal administration of dexmedetomidine is the optimal administration approach for pediatric sedation and hypnosis. Previous studies demonstrated that the onset time of intranasal administration of dexmedetomidine is 25-30 min and endures for approximately 55-100 min in 100 children aged 1-12 years[18]. Prior to intranasal administration, the doctors should explain the whole procedures to the parents, advise them to embrace the children tight and fix the children's head to cooperate with the medicine administration. The speed of nasal administration should be 2-3 drops per second along with the wall of nasal cavity as possible, thereby enlarging the contacted area of solution and nasal mucous membrane and enhancing the sedative effect. The drug should be administered for both nostrils in turn for the purpose of good absorption.

Dose of administration and adverse events

Mason et al[16]. conducted sedation CT (dose of 2.4 μg/kg) and MRI (2.9 μg/kg) via intermuscular injection of dexmedetomidine in 65 children and obtained favorable sedation and hypnosis without bradycardia, blood pressure elevation, pulse oxygen saturation reduction and alternative adverse events. However, the incidence of hypotension was up to 14%. Yuen et al[17]. conducted a double-blind cross study and performed intranasal administration of dexmedetomidine for 54 healthy children aged 2-12years. The results prompted that nasal administration of dexmedetomidine at a dose of 1 μg/kg could cause effective sedation and good tolerance. Another study reported that the pediatric patients' degree of satisfaction about the sedative effect at a dose of 2 μg/kg was higher compared with 1 μg/kg of dexmedetomidine, whereas no obvious influence upon hemodynamics was observed[19]. Previous studies reported that the incidence of bradycardia was as high as 16% at a dose of 2-3 μg/kg dexmedetomidine in 747 children during MRI, significantly higher than 1.5-2 μg/kg. Younger children presented with a higher incidence of bradycardia[23]. Another study reported 2 cases presenting with significant blood pressure elevation and resuscitation delay after rapid administration of dexmedetomidine at an excessive dose[24]. Hypotension and bradycardia are the most common adverse events of dexmedetomidine administration. Strict control of the dose of dexmedetomidine (1-2 μg/kg), intranasal administration combined with observation of cardiovascular adverse events could guarantee the relative security of dexmedetomidine administration for children. Dexmedetomidine and chloral hydrate have respective advantages and limitations during pediatric sedation examination.

Comparison of clinical application of dexmedetomidine and chloral hydrate is illustrated in Table 2. Zhu et al[12]. randomly divided 120 children under-

Table 2 Comparison of clinical application of dexmedetomidine and chloral hydrate

Medication	Concentration	Medicine administration	Onset time	Duration	Optimum time	Age	Disadvantages	Adverse events	Parents' degree of acceptance
10% chloral hydrate	0.5–0.8 ml/kg (maximum amount ≤ 10 ml)	Oral administration	10–20 min	3–4 h	Empty stomach	1 year below	Bitter taste, stinky smell, difficult to intake and low success rate of sedation	Nausea and vomiting	Moderate
		Rectal administration	10–20 min	3–4 h	After defecation	1 year above	Easy discharge of medication, pain and low success rate of sedation	Diarrhea	Low
Dexmedetomidine	1–2 μg/kg	Intranasal drop	25– 30 min	55–100 min	No requirement	1 year above	Close monitoring of blood pressure and heart rate	Hypotension and bradycardia	High

going MRI into two groups: oral administration of 50 mg/kg chloral hydrate and intranasal administration of 2 μg/kg dexmedetomidine. The results revealed that the sedation effect of intranasal administration of dexmedetomidine was slightly better. Five cases had bradycardia and were mitigated without any treatment. Much attention should be paid to monitoring heart rate changes when applying dexmedetomidine in sedation and hypnosis. Along with widespread use of sedatives in pediatric clinical examination, the influence of sedation under anesthesia upon pediatric intelligence development captivates much attention[27]. Zhang et al[25]. found that chloral hydrate could damage the study and memory capability of the mice in a short time, whereas exert no significant effect on physical growth. Bo et al[26].demonstrated that dexmedetomidine had less effect on nerve cells and study and memory function in young animals compared with midazolam. At present, the studies analyzing the influence of anesthesia medication on pediatric intelligence are still lacking. Such research is urgently required to offer evidence for proper use of sedatives.

Prospect

Along with the rapid progress of medical techniques and eye examinations, pediatric patients have a higher demand of sedation and anesthesia effect during eye examination. Nowadays, no optimal sedatives are available for pediatric sedation examination. Both dexmedetomidine and chloral hydrate have respective advantages and limitations. In clinical practice, the anesthetists have attempted to use dexmedetomidine as a sedative during pediatric eye examination and obtained high success rate and good sedation effect. However, the short- and long-term safety, the dose of medication and administration method remains to be elucidated. The standard system of sedation and anesthesia examination should be established as soon as possible including reasonable individualized treatment scheme, drug administration, informed consents, health education flier, observation sheet, *etc*. The physicians and nurses should improve their skills in terms of use of sedatives, emergent treatment of adverse events. All these efforts aim to meet the demand of diagnosis and treatment of pediatric eye diseases.

References

1 Zhao LX, Lu P, Chen YJ. Progress in research on children's dental clinic sedation.Nursing Journal of Chinese People's Liberation Army,2011,4,28:4.

2 Chen CY, Wu SH, Wu HK. Effect observation and nursing of children IOL measuring inspection with Chloral hydrate.Modern Clinical Nursing,2006,15,4:24.

3 Yang YX, Lin MS, Hu SX, et al. Anesthetic Effects of Chloral Hydrate Given by Different Routes in Children before 0Phthalmic Examination.Journal of Nursing Science,2003,18,11:20.

4 Feng HP, Zhang FH, Liu Y, et al. Comparison of sedative effects of chloral hydrate given via different routes on babies with retinoblastoma.Medical Journal of the Chinese People's Armed Police Forces,2008,6:19.

5 Zhang Q, Zhang HX, Kong LY. Clinical observation of sedative effect of chloral hydrate given via different routes before babies's EEG administration. China Health Vision,2013,21,10:14.
6 Liu Y, Yan HY. Pediatric applications of chloral hydrate. China Practical Medicine,2007,2,4:80.
7 Zhou YE, Zhang H. Safety nursing of neonates with chloral hydrate.Journal of Nurses Training,2009,24,19: 1771-1772.
8 Wu FY. Comparison of sedative effect of chloral hydrate via two kinds of routes before children's administration on EEG.Journal of Nurses Training,2007,22,1:95.
9 Zhou J. Observation of effect on infants with chloral hydrate via orally and rectally route.China herald of Medicine,2008,5,26:160.
10 Sun L, Liu SX. Effect of reasonable induction for chloral hydrate sedation for infants.Chinese Nursing Research, 2013,1,27:3.
11 Wang CJ. Application of chloral hydrate two oral methods of pulmonary function test in infants.Today Nurse,2008, 7:42-43.
12 Wang SL, Meng SL. Observation on Both Inserting Length and Retainning Time of the Catheter for Chloral Hydrate Retention-Enema in Children. Chinese Nursing Research,2001,15,3:167.
13 Xiao QY, Chen WJ, Peng QY. To investigate security of oral administration of 10% chloral hydrate sedation for the infant inspection.China Health Industry,2013,19:5.
14 Hu XL, Ma YF. Oral administration of 10% chloral hydrate can cause children to laryngeal stridor. Chinese Journal of Nursing,2001,36:5.
15 Hui RB, Zhao JN. Application of retention enema with Chloral hydrate in neonatal inspection. Public Medical Forum Magazine,2010,14,9:16.
16 Mason KP, Lubisch NB, Robinson F, et al. Intramuscular dexmedetomidine sedation for pediatric MRI and CT. AJR AM J Roentgenol,2011,197,3:720-725.
17 Yuen VM, Irwin MG, Hui TW, et al. A double-blind crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine.Anesth Analg,2007,105, 2:374-380.
18 Yuen VM, HUI TW, Irwin MG, et al. Optimal timing for the administration of intranasal dexmedetomidine for premedication in children.Anesthesia,2010,65,9:922 - 929.
19 Yuen VM, Hue TW, Irwin MG, et al. A randomized comparison of two intranasal dexmedetomidine doses for premedication in children.Anesthesia,2012,67,11:1210-1216.
20 Attila M, Pettily J, Hemline A, et al. Bioavailability of dexmedetomidine after extravascular doses in healthy subjects.Br J Clin Pharmacol,2003,56,6:691-693.
21 Cimen ZS, Hanci A, Sivrikaya GU, et al. Comparison of buccal and nasal desmedetomidine premedication for pediatric patients.Paediatr Anaesth,2013,23,2:134-138.
22 Zhu QX. Sedation nursing care of childrenW's MR via Dexmedetomidine.Guangzhou Medical Journal,2013,44: 6.
23 Mason KP, Zurakowski D, Zgleszewski SE, et al. High dose dexmedetomidine as the sole sedative for pediatric MRI.Paediatr Anaesth,2008,18,5:403-411.
24 Salgado PF, Sabbag AT, Silva PC, et al. Synergistic effect between dexmedetomidine and 0.75% ropivacaine in epidural anesthesia. Rev Assoc Med Bras,2008,54,2: 110-115.
25 Zhang KX, Zhao JJ, Li HC. Effects of Chloraldurate on the Growth, Learning-memory and Therapeutic Index of Mice. Journal of Jinggangshan University (Natural Sciences Edition),2011,32:2.
26 Bo P,Wu XD,Yan D.Influence of multiple sedation of dexmedetomidine and midazolam on young rats′nervous injury and learning and memory ability after grow up. Chongqing Medicine,2013,5:25.
27 Sun LS, Li G, Dimaggio C, et al. Anesthesia and neurodevelopment in children. Time for an answer.Anesthesiology,2008,109:757-761.
28 De Wolf AM, Fragen RJ, Avmm MJ, et al. Th8 phacokinetics of dexmedetomidine in volunteers with severe renal impatient. Anesthesia & Analgesia,2001,93:1205-1209.