

Safety and Efficacy of Chloral Hydrate Sedation in Paediatric Sedation for Ophthalmic Procedures

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Abstract

Introduction: Chloral hydrate (CH) sedation is routinely used in paediatric ophthalmic examination in Singapore as an alternative to examination under general anaesthesia. Despite CH's traditionally high success rates and relatively low rate of adverse events, there is little data on its safety and efficacy as a sedative for ophthalmic procedures in an Asian population. **Materials and Methods:** A retrospective chart review was performed, including children who underwent CH sedation at the Singapore National Eye Centre from January 2012 to January 2015. Participants were given an initial dose of CH and a top-up dose if required. Univariate and multivariate analyses were performed on data collected. **Results:** CH sedation was successful in 144 of 153 children (94.1%). Of the 20 (13.0%) who required a top-up dose, 4 failed to sedate. The mean sedation onset was 29.4 minutes (SD: 24.3) and mean sedation duration was 56.5 minutes (SD: 24.0), with more than a third lasting more than 1 hour. The age of children, rather than initial dose of CH, was more relevant in determining success of sedation. Children who were >6 years old were 20.3 times more likely to fail sedation than those aged <2 years. During sedation, depression in the heart rate and a transient reduction of oxygen saturation was documented. All children recovered well post-sedation. **Conclusion:** CH is a very useful sedative for paediatric ophthalmic procedures, especially in younger children. Children over 4 years old were more likely to fail sedation and require top-up doses. Alternative means of sedation may need to be considered in these cases.

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Introduction

Sedation is often required to successfully conduct paediatric clinical ophthalmic examinations or diagnostic investigations when children are unable to cooperate due to anxiety or fear.¹ Chloral hydrate (CH) is commonly used for such situations. CH works by being metabolised into its pharmacologically active metabolite, trichloroethylene (TCE), which is postulated to work on the gamma-aminobutyric acid type A (GABAA) receptors in the central nervous system to achieve its sedative effects.² It can be orally administered, has high rates of success (88% to 100%) as a sedative and is relatively safe.³ However, it has a bitter taste and has been associated with adverse effects including nausea, vomiting, respiratory depression,

oxygen desaturation, paradoxical reaction, and rarely, deaths.^{1,4-7} It has also been associated with carcinogenesis in animal studies.⁸

Use of CH in ophthalmology was first described in 1974 when it was used to conduct electroretinography in children.⁹ Most studies have focused retrospectively on its safety and efficacy in dental and radiological procedures.¹⁰ The few studies regarding CH sedation for ophthalmic procedures suggest it is safe and effective as a paediatric sedative due to low incidences of adverse events and high sedation success rates.⁶

Recently, there has been a push worldwide to improve the quality of healthcare and safety of patients. As such, there has been an increasing concern with the use of CH in the

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outpatient setting, given its variable efficacy, long half-life and adverse effects profile, especially since newer sedative agents (e.g. intranasal dexmedetomidine) have been found to be as effective with minimal cardiorespiratory effects.⁴ The studies on CH thus far have focused on dental and radiological requirements, where the duration of sedation and invasiveness of procedures are greater and doses administered were consistently higher.¹⁰ In the ophthalmic setting, CH sedation was used sparingly and only when a short but thorough examination of the ocular structures or fundus was required (e.g. in cases of leucocoria, suspected glaucoma, postoperatively after cornea, glaucoma or retina surgery, and for electrophysiology tests). In this study, we reviewed children who underwent CH sedation at the Singapore National Eye Centre (SNEC) from January 2012 to 2015 with the aim of determining the safety and efficacy of CH sedation for ophthalmic procedures using a range of CH doses in a predominantly Asian paediatric population.

Materials and Methods

A retrospective chart review was performed for all children who underwent CH sedation between January 2012 and January 2105 at SNEC. Suitable patients were identified through our sedation record and relevant data was collected by tracing all case notes and CH sedation record forms. Data gathered comprised demographic data including age, weight and gender, and sedation parameters such as sedation dosage, top-up dosage, time of administration, sedation onset, sedation duration, vitals every 15 minutes during sedation, sedation score and presence of adverse effects. This study was done as part of a clinical audit in preparation of a Joint Commission International (JCI) inspection.

Sedation Procedure

Sedation was performed with the supervision of trained nurses and ophthalmologists at the outpatient clinic. Patients were fasted for 3 hours prior to sedation. The ophthalmologist in charge assessed fitness for sedation; patients with unstable medical conditions, abnormal airway or respiratory disorders, degenerative neuromuscular disease, and patients on medications that may cause drowsiness such as antiepileptics or opiates were not sedated. Informed consent was obtained from parents or legal guardians before sedation. Baseline vital signs (heart rate [HR], blood oxygen levels and respiratory rate) were documented by nurses. A single dose of oral CH, ranging from 30 mg/kg to 75 mg/kg, was administered and if necessary, a top-up dose of less than half of the original dose was added. Once the children fell asleep, a pulse oximeter was used to monitor HR and blood oxygen levels continuously.

The clinic was fully equipped with resuscitation equipment and the support of trained personnel. Sedation score and vital signs were recorded before sedation, every 15 minutes during sedation till patients were fully awake and every 30 minutes post-procedure until the discharge criteria was met. We measured sedation using the Ramsey Sedation Scale – 1: when the child is anxious or restless or both; 2: when the child is cooperative, orientated and tranquil; 3: when the child responds to commands; 4: a brisk response to stimulus; 5: sluggish response to stimulus; and 6: no response to stimulus.¹¹ The procedures were performed when patients were adequately sedated. After arousal, patients were discharged only when they met the criteria of having vital signs within normal limits (O_2 level >90% or pulse rate >80 beats per minute), being conscious and alert, able to tolerate fluids and to sit or stand or walk according to their age.

Sedation success, need for a top-up dose and incidence of any adverse event during or post-sedation were measured. We defined sedation success as the achievement of adequate sedation for procedures to be performed, with a Ramsay scale of at least 4 (i.e. a brisk response to light glabellar tap or loud auditory stimulus).¹¹ This could have been achieved with a single dose or an additional top-up dose. Top-ups were considered if child was still awake 45 minutes after the medication was administered, especially if the child spat or vomited a sizeable amount of the medication.

Statistical Analysis

Continuous variables were reported with their mean, median, standard deviation (SD) and range, whereas categorical data were reported with their percentages. We ran statistical analyses on continuous variables using Student's *t*-test and on categorical data using Pearson's chi-square test. Variables with a *P* value <0.05 were deemed statistically significant.

Results

Patient Demographics

Over a 3-year period, 153 children received CH sedation; 62.1% were males, with a mean age of 2.4 years (SD: 1.7; age range, 1 month to 97 months) (Fig. 1). Most patients were Chinese (42.4%), followed by Indian (14.3%), Malay (4.6%) and patients of other races (Table 1).

Sedation Success and Failure

Of the 153 patients, 144 (94.1%) were successfully sedated. Twenty children (13.0%) required a top-up. Sedation failed in 9 children (5.9%), of which 4 failed despite top-ups (Table 2). Sedation was successful in 95.8%

Table 1. Demographics, Dose, Sedation Onset, Duration, and Baseline Vital Signs in Children of Different Age Groups

Variable	Total No. (n = 153*)	<2 Years Old (n = 69)	2–4 Years Old (n = 62)	>4 Years Old (n = 22)	P Value <2 vs 2–4 Years Old	P Value <2 vs >4 Years Old	P Value 2–4 vs >4 Years Old
Gender (Male, %)	95 (62.1%)	41 (59.4%)	41 (66.1%)	13 (59.1%)	0.428	0.487	0.554
Chinese (%)	65 (42.5%)	29 (42.0%)	29 (46.8%)	7 (31.8%)	0.277	0.602	0.218
Mean initial dose, mg/kg (SD)	49.5 (5.4)	48.7 (6.3)	50.2 (5.0)	50.1 (2.8)	0.159	0.338	0.944
Need to top-up (%)	20 (13.1%)	9 (13.0%)	4 (6.5%)	7 (31.8%)	0.277	0.116	0.002
Mean total dose, mg/kg (SD)	51.3 (7.5)	51.0 (9.2)	51.0 (5.7)	53.3 (6.0)	0.957	0.290	0.113
Sedation onset, minutes (SD)	29.4 (24.3)	22.8 (13.5)	28.4 (16.1)	58.8 (49.4)	0.035	<0.001	0.001
Sedation duration, minutes (SD)	56.5 (24.0)	57.0 (26.2)	56.9 (21.9)	53.5 (23.4)	0.982	0.620	0.582
Failed to sedate (%)	9 (5.9%)	2 (2.9%)	2 (3.2%)	5 (22.7%)	0.001	0.009	0.004
Baseline heart rate (SD)	109.3 (19.4)	120.0 (18.4)	100.6 (14.6)	101.0 (17.4)	<0.001	<0.001	0.839
Heart rate <80% of baseline during sedation	44 (32.8%)	20 (31.7%)	14 (25.9%)	10 (58.8%)	0.489	0.090	0.012
Oxygen saturation <95% during sedation	5 (3.7%)	4 (6.3%)	1 (1.9%)	0 (0%)	0.222	0.554	0.579
Baseline respiratory rate (SD)	25.5 (2.0)	26.0 (2.2)	25.3 (1.5)	24.7 (1.8)	0.039	0.011	0.117
Respiratory rate <90% of baseline during sedation	16 (11.9%)	9 (14.1%)	6 (11.1%)	1 (5.9%)	0.605	0.980	0.541

SD: Standard deviation

*Total number may not add up to 153 children for vital signs measurements as 10 patients failed to sedate and 10 patients were uncooperative and did not allow baseline measurements to be taken at onset.

of children weighing <15 kg compared to 87.8% in those weighing >15 kg ($P = 0.085$).

The initial and total doses given were similar in different age groups with a mean initial dose of 49.5 ± 5.4 mg/kg (range, 19.5 mg/kg to 60.8 mg/kg) (Table 1). Overall, 16 (10.5%), 111 (72.5%), 26 (17.0%) children received <45 mg/kg, 45 mg/kg to 50 mg/kg, and >55 mg/kg of CH, respectively. Logistic multivariate analysis suggested that the odds of sedation failure or requiring a top-up increased with age, and was 20.3 times more likely in children >6 years old than in those aged <2 years ($P = 0.010$) with initial dose used being less relevant ($P > 0.389$).

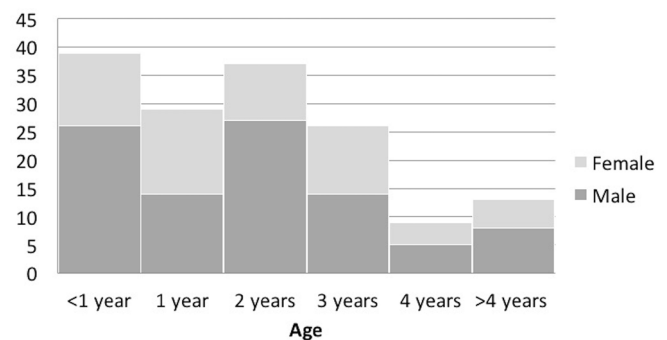


Fig. 1. Patient demographics (n = 153).

Table 2. Comparative Sedation Data

	Total (n = 153)	Success			Failure		
		Total (n = 144)	Without Top-up (n = 128)	After Top-up (n = 16)	Total (n = 9)	Despite Top-up (n = 4)	Without Top-up (n = 5)
Mean age, years (SD)	2.4 (1.7)	2.3 (1.6)	2.2 (1.4)	3.0 (2.4)	3.8 (2.5)	4.4 (3.7)	3.4 (2.0)
Mean weight, kg (SD)	12.1 (4.2)	11.9 (4.0)	11.8 (3.8)	12.5 (5.5)	15.3 (5.9)	14.6 (5.2)	15.9 (6.9)
Chinese	42.4%	43.1%	43.8%	37.5%	33.3%	75.0%	0%
Initial dose, mg/kg (SD)	49.5 (5.4)	49.8 (4.7)	49.7 (4.9)	50.4 (4.7)	45.2 (10.9)	41.6 (14.7)	48.2 (7.1)
Total dose, mg/kg (SD)	51.3 (7.5)	51.5 (7.3)	49.7 (4.9)	65.4 (8.6)	49.2 (10.5)	50.5 (15.0)	48.2 (7.1)

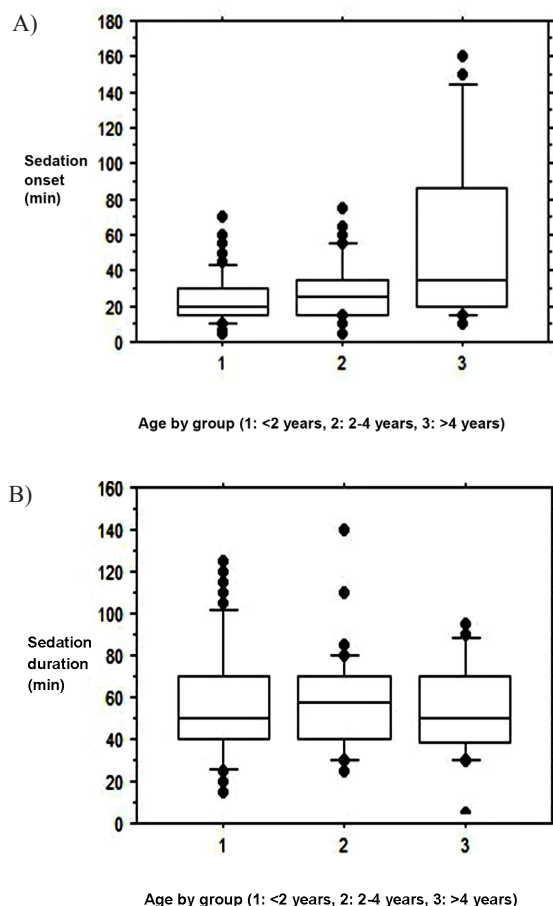


Fig. 2. A) Box plot of sedation onset and B) duration versus age.

Sedation Onset and Duration

The mean sedation onset for successful cases was 29.4 ± 24.3 minutes (range, 5 to 160 minutes). A total of 102 children (70.8%) were sedated within 30 minutes, and 93.0% within 1 hour. The mean sedation duration was 56.5 ± 24.0 minutes (range, 5 to 140 minutes). Ten children (6.9%) had a sedation onset of more than 1 hour while 52 children (36.1%) remained sedated for more than 1 hour. Those who remained sedated for >100 minutes were all below 3 years of age.

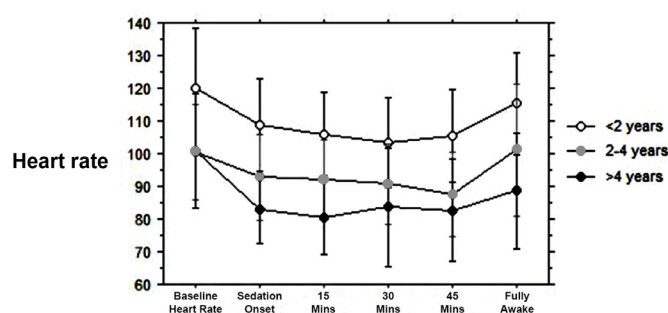


Fig. 3. Change in heart rate over time (line-chart).

Univariate analysis suggested that older children took longer to sedate, but duration of sedation was similar across ages (Fig. 2). Multivariate analysis confirmed this (Table 3), and further suggested that duration of sedation was not affected by gender or initial dose used.

Change in Vital Signs

Baseline vitals were present in all but 10 children who resisted attempts to measure their vitals prior to sedation. In general, younger children had a higher baseline HR than older children (Table 1). A reduction in HR was noted at sedation onset, remained stable over the period of sedation, and returned to baseline on waking (Fig. 3). A total of 55.2% of children ($n = 74$) had a fall of HR >10 beats per minute from baseline, with children >4 years old having the greatest decrease in HR. However, none had HR that decreased below age-related normal ranges.¹²

Respiratory rate (RR) remained relatively stable throughout sedation across all age groups (Fig. 4). Measurements of oxygen saturations showed a transient reduction in oxygen saturation, which recovered by the 15-minute assessment with none requiring oxygen supplementation (Fig. 5). Only 1 of the 5 children whose oxygen saturations dropped below 95% had a baseline saturation of 94%; the rest had >95% baseline saturation. The lowest oxygen saturation encountered during sedation was 92%. Oxygen levels often improved after a readjustment of child's head position.

Table 3. Multivariate Analysis of Onset and Duration of Sedation

	Onset of Sedation $-\beta$	95% CI	P Value	Duration of Sedation β	95% CI	P Value
Male	-0.32	-7.78 to 7.13	0.932	-0.67	-9.15 to 7.81	0.876
Initial dose, mg/kg	-0.09	-0.83 to 0.63	0.791	-0.18	-1.01 to 0.65	0.668
Age	10.34	6.34 to 14.34	0.000	-0.10	-4.6 to 4.43	0.965

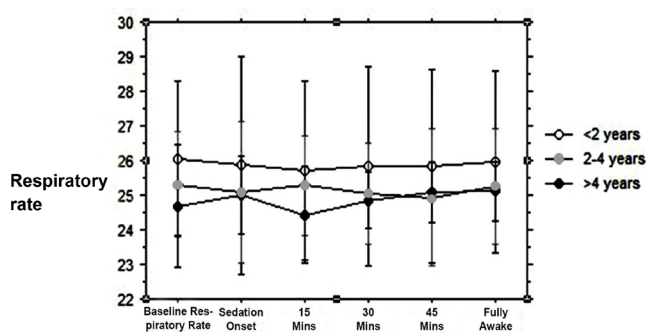


Fig. 4. Change in respiratory rate over time (line-chart).

Other Effects

Six children (3.9%) vomited or spat out medication at the time of administration. Sedation was still successful after the vomiting/spitting out, except in 1 case where the child's parents decided not to proceed. No cases of paradoxical hyperactivity were noted.

Discussion

In this study, CH sedation for ophthalmic procedures was highly successful. Failure to sedate and need for top-up was more likely in older children, particularly in those more than 4 years old. We also noted minimal changes in vital signs and that all children recovered well from sedation. No other major adverse effects requiring hospitalisation or paradoxical hyperactivity were documented.

Efficacy

Our sedation success rate of 94.1% was similar to those of 96.7% and 97.9% cited in West et al¹ and Wilson et al¹⁰, respectively. It was also within the 88% to 100% success ranges noted in older publications and in radiological and dental literature.^{6,7,13} Variability in success rates may be partially due to patient selection and doses used (as high as 80 mg/kg to 100 mg/kg in some studies). In this study, we also noted that sedation in children >6 years old were 20.3 times more likely to fail or require top-up doses than those aged <2 years. This is consistent with existing literature, where failure rates were higher in those aged 48 months and above.^{1,14} Our findings are also in line with the current National Institute for Health and Care Excellence (NICE) guidelines, which recommends CH as an agent for mild to moderate sedation during painless procedures for children under 15 kg; our success rate for sedation for those <15 kg was 95.8%, compared to 87.8% in those >15 kg.¹⁵ Possible explanations include older children metabolising the drug faster, as the half-life of CH does decrease with age,¹⁶ and older children being more aware and anxious, and thus,

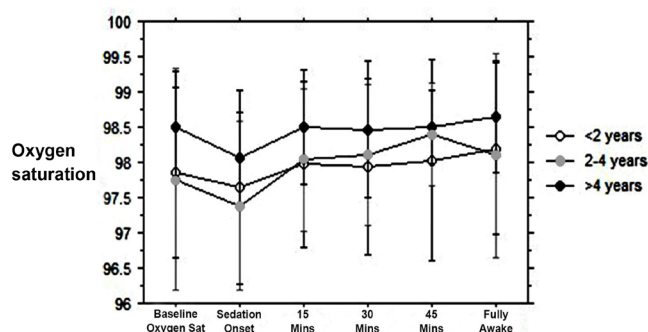


Fig. 5. Change in oxygen saturation over time (line-chart).

more likely to resist the effect of sedation. Hence, older children may benefit from alternative means of sedation.

Although the approximate time for sedation onset and duration was 30 minutes and 60 minutes, respectively, the range of onset and duration was quite wide and unpredictable. Jaafar and Kazi⁷ reported a mean sedation onset of 25 minutes and sedation duration of 60 minutes using 100 mg/kg of CH for the first 10 kg and 50 mg/kg, respectively, for every additional kg while West et al¹ quoted 28.8 minutes and 53.4 minutes on 80 mg/kg of CH. Similar to other studies, these sedation durations appear to be independent of doses used.¹⁷ In this study, 6.9% had a sedation onset of more than 1 hour, while 36.1% remained sedated for more than 1 hour. Those who remained sedated for >100 minutes were all younger than 3 years old. Other studies also noted delayed recovery in children <1 years old, and prolonged sedation >2 hours in 3.3%.¹⁸ The prolonged effect of CH in younger children may be due to differences in CH metabolism with age.

Safety

CH is absorbed by the gastrointestinal tract and reaches peak serum concentrations in 30 to 60 minutes, and later metabolised to TCE by alcohol dehydrogenase in the liver. TCE causes the sedative effect of CH and has a half-life of approximately 8 to 12 hours.⁵ The long half-life of TCE is especially of concern as it has been shown to be 3 to 4 times longer in neonates and infants than in older children.¹⁶ Mayers et al also demonstrated that TCE half-life was 27.8 hours in term infants and 9.67 hours in older children, with peak TCE concentrations decreasing with age. This may explain the prolonged sedation and delayed recovery in younger children and the higher failure rates in older children.¹⁹

Although CH has a relatively good safety profile, its long half-life means that it may still have a sedative effect even after discharge.¹⁸ Post-discharge side effects include

sleepiness lasting >8 hours in 11% of children, unsteadiness in 48% and hyperactivity in 29%.¹⁹ Nordt et al⁵ has also documented 3 cases of major adverse events, including 2 incidences of over-sedation and 1 death. One was the result of an accidental overdose, while the other child had pre-existing neurological problems. The fatal episode occurred after discharge with prolonged sedation. These further emphasise the need for strict sedation guidelines that account for pre-existing medical problems, monitoring under professional supervision and proper discharge counselling of parents.

We also found that CH sedation resulted in general depression of HR within normal age-related parameters and a transient reduction in oxygen saturation. In contrast, respiratory rates remained relatively stable over time.

Under normal physiological conditions, HR often slows during sleep.²⁰ In our study, HR decreased at the onset of sedation and plateaued, reverting to baseline on awakening, and none were outside of normal age-related parameters.¹⁴ About 32.8% of children had a fall of HR of >20% during sedation, with the children aged >4 years recording greater falls. This may be due to the older children being more aware of the situation and having a higher baseline HR due to anxiety or fear, thus having a greater fall in HR during sedation.²¹ Our findings corresponded to Heistein et al,¹⁸ who found that 24% of patients had a greater than 20% departure from their baseline HRs, of which only 1.7% had a drop lower than the normal range for their age. Intervention was also not needed in our study for the transient bradycardia recorded, suggesting that reductions in HR did not impair protective airway reflexes.¹⁸

Of more concern was the transient fall of oxygen saturation at the time of sedation onset, although oxygen saturation of <95% was noted in 3.7% of the children. In almost all cases, oxygen saturations had returned to baseline by the 15-minute assessment period. Vade et al²² reported a higher rate of hypoxia, with departure of oxygen saturation <95% in 9% of the children, which spontaneously recovered by 5 to 10 minutes. Other studies had lower published rates of hypoxaemia of between 0.99% and 0.26%, which were possibly due to their larger sample size and children who were only either ASA class 1 (healthy) or 2 (mild systemic disease).^{1,10} The transient fall in oxygen saturation may reflect the presence of respiratory suppression or obstruction of the airway. In most cases, proper positioning of the child could rectify this. We suggest maintaining close vigilance with a readiness to act (e.g. by suctioning of airway or oxygen supplementation) as necessary.

The other most common adverse effect was vomiting or spitting out medication. Our rates of vomiting/spitting out (3.9%) were in the range of other studies (0.53% to 20%).^{1,7} Other adverse effects, including paradoxical reaction, airway obstruction, apnoea, hypotension, and

rarely, cardiac arrhythmias and death, were not noted in our study.¹⁶ Overall, CH was demonstrated to be a safe sedative with low rates of gastrointestinal irritation and transient decreases in HR and oxygen saturation that recovered without medical intervention. Surprisingly, we did not have any cases of paradoxical reaction or excess irritability despite it being a common adverse effect of CH sedation, with rates of 1.5% to 6.3%.¹ This might be a limitation of the study being retrospective, with inadequate accounting of certain events or agitation being subjectively dependent on observer interpretation.

Strengths and Limitations

Other limitations of the study include the lack of evaluation of blood pressure, post-discharge events, such as re-admission to hospital or persistent excessive drowsiness, and history of multiple sedations, as these were not included in our protocol forms. Another limiting factor was that standard dosing was not employed, as different consultants adopted varying dosing regimens, although majority administered an initial dose of approximately 50 mg/kg. However, the strengths of the study lie in its consistent recording of sedation cases with a standardised proforma, with well documented adverse effects. We also used specified validated scales (Ramsay Sedation Scale) to determine adequate sedation.

Conclusion

CH is a very useful sedative for paediatric ophthalmic examinations, especially in younger children. The age of children, rather than initial dose of CH, was more relevant in determining success of sedation in our predominantly Asian population. Children over 4 years of age were more likely to fail sedation and require top-up doses. Alternative means of sedation may need to be considered in these cases. To ensure patient safety, continuous monitoring during sedation is useful, and parents need to be made aware of the side effects, long half-life and care required in the post-sedation period. Adequate education and training of doctors and nurses is needed to ensure awareness of their individual roles and responsibilities, and ability to react in case of emergency.

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