***Corresponding author***

Dr Vivian M Yuen

Department of Anaesthesiology

University of Hong Kong

Room K-424, Queen Mary Hospital

102 Pokfulam Road, Pokfulam, Hong Kong

*Email: vtang131@hku.hk*

**A randomised controlled trial of oral chloral hydrate vs. intranasal dexmedetomidine before CT scans in children**

V. M. Yuen,1,5 B. L. Li,2 D. K. Cheuk,3 M. K. M. Leung,4 T. W. C. Hui,5 I. C. Wong,6 W. W. Lam,7 S. W. Cho8 and M. G. Irwin9

*1 Consultant, Department of Anaesthesiology, Hong Kong Children’s Hospital, Hong Kong*

*2 Attending Anaesthesiologist, Department of Anaesthesiology, Guangzhou Women and Children’s Medical Centre, Guangzhou, China*

*3 Associate Consultant, Department of Paediatric and Adolescent Medicine, 4 Associate Consultant, 5 Consultant, Department of Anaesthesiology, 7 Consultant, Department of Radiology, Queen Mary Hospital, Hong Kong*

*6 Professor, UCL School of Pharmacy, London, UK*

*8 Postdoctoral Fellow, 9 Professor, Department of Anaesthesiology, University of Hong Kong, Hong Kong*

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**Key Words:** Chloral Hydrate, Dexmedetomidine, Intranasal, Pediatric, Sedation, Tomography.

**Summary**

Chloral hydrate is commonly used to sedate children for painless procedures. Children may recover more quickly after sedation with dexmedetomidine, which has a shorter half-life. We randomly allocated 196 children to chloral hydrate syrup 50 mg.kg-1 and intranasal saline 0.9% spray, or placebo syrup and intranasal dexmedetomidine spray 3 µg.kg-1, 30 min before computerised tomography studies. More children resisted or cried on drinking chloral hydrate syrup than placebo syrup, 72/107 (67%) vs. 42/87 (48%), respectively, p = 0.009, but there was no difference after intranasal spray with saline vs. dexmedetomidine, 49/107 (46%) vs. 40/87 (46%), p = 0.98. Sedation was satisfactory in 81/107 (76%) children after chloral hydrate and 64/87 (74%) children after dexmedetomidine, p = 0.74. Of the 173 children followed up for at least four hours 38/97 (39%) recovered normal function after chloral hydrate and 32/76 (42%) after dexmedetomidine, p = 0.76. Six children vomited after chloral hydrate syrup and placebo spray vs. none after placebo syrup and dexmedetomidine spray, p = 0.03.

**Introduction**

Globally, chloral hydrate is one of the most widely used sedatives in young children undergoing imaging studies. Although it is associated with a reasonably high success rate for procedural sedation in young children [[1](#_ENREF_1),[2](#_ENREF_2)], the gastrointestinal [[3](#_ENREF_3)] and post-discharge side effects are significant and, possibly, underappreciated [[1](#_ENREF_1),[4](#_ENREF_4)]. The common post-discharge side effects include persistent sleepiness (for more than 4 hours), unsteady gait, hyperactivity, poor appetite and vomiting [[1](#_ENREF_1)]. This may be explained by the active metabolite of chloral hydrate, trichloroethanol, which has a peak effect approximately 2.2 h after administration and a half-life of 9.7 h in children [[5](#_ENREF_5)].

Dexmedetomidine is a highly selective alpha-2 agonist. It has been extensively used for paediatric sedation [[6-11](#_ENREF_6)] and used as the sole intravenous sedative agent for computerised tomography (CT) and magnetic resonance imaging (MRI) in children [[7](#_ENREF_7),[8](#_ENREF_8)]. It has also been administered intranasally to produce sedation before anaesthesia induction [[12-14](#_ENREF_12)], for CT [[15](#_ENREF_15)] and transthoracic echocardiography in children [[16](#_ENREF_16),[17](#_ENREF_17)]. The elimination half-life in children has been reported to range from 96 to 139 minutes [[18](#_ENREF_18),[19](#_ENREF_19)] and is much shorter than chloral hydrate.

The study was designed to test the hypothesis that children sedated with intranasal dexmedetomidine would resume normal activity quicker than those who received oral chloral hydrate. The primary objective was to compare the proportion of children who could resume normal activity within 4 hours after discharge. Secondary outcomes included the success rate of sedation, incidence of poor behaviour with oral and nasal drug administration, incidence of vomiting with drug administration, adverse respiratory and haemodynamic events, time to onset of sedation, wake up time and discharge time after sedative administration. The incidence of post-discharge side effects including restlessness, hyperactivity/agitation, motor imbalance, respiratory difficulties and gastrointestinal upset were also recorded and analysed.

**Methods**

The Institutional Review Boards approved this randomised, controlled trial at Queen Mary Hospital, Hong Kong and the Guangzhou Women and Children’s Medical Centre, China. We recruited children ASA physical status 1 or 2 scheduled for computerised tomographic (CT) studies under sedation between March 2013 and February 2015. The parents or the legal guardian gave informed consent, with the child’s assent if he or she was mature enough to understand and discuss sedation. We did not study children allergic to a study drug or those with cardiac arrhythmia, congenital heart disease or severe organ dysfunction.

The Hong Kong University Department of Pharmacy and Pharmacology generated and kept a random sequence by computer, allocating children to oral chloral hydrate and intranasal placebo or oral placebo and intranasal dexmedetomidine. Hospital pharmacists prepared the study drugs: oral aloe vera syrup with concentrated sodium chloride solution, or chloral hydrate 200 mg.ml-1 (Hong Kong) or 100 mg.ml-1 (China); atomised nasal saline 0.9% or dexmedetomidine 100 µg.ml-1 (MAD®; Teleflex Medical China, Shanghai). Recruited subjects were assigned a subject number and pharmacist was informed of the number of subjects recruited. Pharmacist assigned randomization number to each subject recruited and prepared the study drug according to the allocation sequence. Ten (in Hong Kong) or 20 (in China) ml of chloral hydrate and oral placebo were prepared in 10 ml syringes (Hong Kong) or 20 ml syringes (China). One ml of dexmedetomidine or 0.9% saline were prepared in 1ml syringe. The study drugs were labelled with subject and randomization number. The active drugs and placebo were indistinguishable and the research nurses were blinded to group allocation. Since the received study drug were always in excess, research nurse would discard the excess drug according to subject’s body weight. Thirty minutes before the CT study children drank 1 ml.4kg­-1 syrup (Hong Kong) or 2 ml.4kg-1 syrup (China) and received 0.03 ml.kg-1 nasal spray. We recorded whether the child’s reaction was unacceptable (crying or resisting) or acceptable (anxious but accepting or calm and cooperative).

Research nurses recorded blood pressure, pulse rate and oxygen saturation before drug administration and then every five minutes, along with sedation (University of Michigan Sedation Scale): awake and alert; sleepy with appropriate responses to voice; somnolent, roused by touch; asleep, roused by significant stimulation; not rousable. We also recorded episodes of: vomiting; SpO2 < 95%; airway interventions; and heart rate or blood pressure 20% less than normal [20]. We judged children as adequately sedated once at least somnolent. It is departmental policy in Hong Kong that all children received sedation for CT would have intravenous cannula inserted by paediatric resident before sedation. The radiologist (Hong Kong) or paediatric anaesthesiologist (China) could give additional sedative: intravenous midazolam (Hong Kong); or intranasal dexmedetomidine (China). We continued to monitor children after the CT study until ready for discharge: and Aldrete score at least nine and no more sedated than sleepy. During the first 24 h at home parents recorded how sleepy were their children and whether they were unsteady, hyperactive, anorexic or vomiting. Parents specifically recorded when children had recovered normal activity, defined as no more than sleepy, able to drink, walk or stand and talk normally.

We estimated 93 children in each group would have 80% power to detect an increase in the proportion of recovered children four hours after discharge from 46% to 66% at p < 0.05 [[1](#_ENREF_1)]. We tested proportions with the Fisher exact test and cumulative recovery rates with the Tarone-Ware test for equality of time-to-event distributions. The relationship between drug and successful sedation was assessed by binomial logistic regression. We used SPSS for Windows version 20.0 (SPSS Inc., Chicago, IL, USA) for analyses. We considered p < 0.05 significant.

**Results**

We recruited 211 children, of whom 196 participated in the study (Fig. 1). The median (IQR [range]) age and weight of the 108 children (67 boys, 63%) allocated to oral chloral hydrate were 24 (14-36 [8-70]) months and 11.6 (10-13.7 [7.5-20]) kg, whilst the respective values for the 88 children (63 boys, 72%) allocated intranasal dexmedetomidine were 32.5 (19.8-39 [2-79]) months and 12.0 (10.4-15 [5-22]) kg.

 The mean (SD) time to sedation after chloral hydrate was 22.4 (7.8) min and 19.6 (6.6) min after dexmedetomidine, a difference (95% CI) of 2.8 (0.7-4.9) min, p = 0.03. The median (IQR [range]) time to recovery of normal activities after drug administration was 5.0 (2.2-8.8 [0-32]) h after chloral hydrate and 4.3 (3.3-6.7 [0.8-26]) h after dexmedetomidine, (Tarone-Ware test for equality of time-to-event distributions, p = 0.357) (Fig. 2), with 38/107 and 32/87 recovered at four hours, respectively, p = 0.76. Chloral hydrate syrup upset more children and caused more vomiting than placebo syrup, whilst intranasal dexmedetomidine caused more bradycardia (Table 1). No child received treatment for hypotension or bradycardia. After discharge 6/97 (6%) children were unsteady and 0/76 after dexmedetomidine, p = 0.03, whilst three and two children, respectively, were restless, p = 0.88, and five children and four children, respectively, were agitated, p = 0.98.

**Discussion**

This is the first study to compare the effectiveness and post sedation recovery profile in children who received oral chloral hydrate and intranasal dexmedetomidine as primary sedatives for computed tomography imaging studies. Although dexmedetomidine has a much shorter half-life, overall than chloral hydrate, the time to resumption of normal activities was similar after both drugs. The rate of successful sedation was similar in children who received oral chloral hydrate at 50 mg.kg-1 or intranasal dexmedetomidine at 3 µg.kg-1. Although not popular in the UK, chloral hydrate is globally the most commonly used sedative for non-painful procedures in young children [[4](#_ENREF_4),[20](#_ENREF_20),[21](#_ENREF_21)], particularly in less economically developed countries because of its low cost and high success rate [[1](#_ENREF_1),[2](#_ENREF_2)]. Nevertheless, administration can be problematic as chloral hydrate is bitter to taste and has a pungent odour. Spitting and even vomiting is a problem, therefore, some clinicians have tried to resolve this by administering chloral hydrate via the rectum which is relatively invasive and undesirable [[22](#_ENREF_22)]. Our study shows that intranasal dexmedetomidine has a similar success rate to chloral hydrate and is more acceptable to administer.

In a recently published double blind, randomized, controlled trial, intranasal dexmedetomidine 2-3 µg.kg-1 produced a similar sedation success rate when compared with oral chloral hydrate 50 mg.kg-1 in children undergoing transthoracic echocardiography [[23](#_ENREF_23)]. Intranasal dexmedetomidine 3-4 µg.kg-1 was more successful than chloral hydrate 50 mg.kg-1 in children undergoing auditory brainstem response examinations [[24](#_ENREF_24),[25](#_ENREF_25)]. Dexmedetomidine administered orally or intravenously has been shown to be more effective than oral chloral hydrate for children undergoing electroencephalogram studies [[26](#_ENREF_26),[27](#_ENREF_27)]. Intranasal dexmedetomidine was also used as rescue sedative with high success rate in failed chloral sedation [[28](#_ENREF_28)].

Although dexmedetomidine is more expensive than chloral hydrate, it is easier to administer and is associated with less aversive behaviour. While it was difficult to determine the incidence of nausea associated with oral chloral hydrate, approximately 5% of the children vomited after administration in this study. While in one report the incidence of gastrointestinal side effects was reported to be 3% after chloral hydrate sedation [[4](#_ENREF_4)], nausea and vomiting was reported to be as high as 8.3% and 17.5% in children who had 50 and 100 mg.kg-1, respectively [[26](#_ENREF_26)]. It was 30% in another study [[3](#_ENREF_3)]. The difference in incidence may be secondary to the difference in dose, formula or reporting threshold. Nevertheless, nausea and vomiting have not been reported with intranasal dexmedetomidine administration.

No children who received intranasal dexmedetomidine in this study had adverse respiratory events and less than 2% who received chloral hydrate experienced oxygen desaturation requiring oxygen therapy, similar to results reported in two previous studies [[4](#_ENREF_4),[26](#_ENREF_26)]. However, in a crossover comparison where children had chloral hydrate for electroencephalography, the incidence of airway obstruction and desaturation were reported to be as high as 47% and 17.6%, respectively [[27](#_ENREF_27)]. This could be secondary to the use of a higher dose in children with epilepsy disorders who were already on anti-epileptic medications. No respiratory depression was reported in the same group of children when they received dexmedetomidine for the same procedure. The absence of respiratory depression with dexmedetomidine is an important advantage over chloral hydrate.

Similar to previous reports, the most common complications associated with chloral hydrate after discharge were motor imbalance and, although low, this was significantly higher than in children who received dexmedetomidine.

Although chloral hydrate is the most common sedative used in younger children, it is not recommended for those over 4 years of age or with neurodevelopmental disorders because of the increased risk of adverse events and treatment failure [[29](#_ENREF_29)]. On the other hand dexmedetomidine has been used safely in infants, children and adults for sedation, although this use is “off-label” [[30](#_ENREF_30),[31](#_ENREF_31)]. Chloral hydrate has a narrow therapeutic range and higher doses are associated with an increased incidence of adverse events. Although uncommon, there are case reports of severe morbidity and mortality with chloral hydrate sedation [[32](#_ENREF_32)]. In contrast, dexmedetomidine has a wide therapeutic window and has been used in high doses in both adults [[33](#_ENREF_33)] and children [[34](#_ENREF_34)] for airway procedures with no untoward effects. When compare with chloral hydrate, intranasal dexmedetomidine is safer and attractive method of sedation in children [[35](#_ENREF_35)].

One limitation of this study was the collection of post-sedation data. The reporting of time to resume normal activities and other sedation related complications could be subjective and inaccurate. Although we have given verbal and written guidance to parents, and they are the best source of information on post-sedation recovery, it is difficult to control for bias and lapses in reporting. Parental under-reporting could also be a concern.

In summary, intranasal dexmedetomidine at a dose of 3 µg.kg-1 and oral chloral hydrate at 50 mg.kg-1 are associated with a similar success rate for sedation in young children undergoing CT studies. Dexmedetomidine is associated with better behaviour and less gastrointestinal side effects.

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**Table 1** Secondary outcomes after sedation for CT scanning in 194 children, 107 of whom received oral chloral hydrate and intranasal placebo and 87 of whom received oral placebo and intranasal dexmedetomidine. Values are number (proportion).

|  |
| --- |
|  |
|  | **Oral choral hydrate, nasal placebo (n = 107)** | **Oral placebo, nasal dexmedetomidine (n = 87)** | **p value** |
| **Crying or resisting**  |  |  |  |
|  **Oral syrup** | 72 (67%) | 42 (48%) | 0.009 |
|  **Intranasal spray** | 49 (46%) | 40 (46%) | 0.98 |
| **Successful sedation** | 81 (76%) | 64 (74%) | 0.74 |
| **Vomiting** | 6 (6%) | 0 | 0.03 |
| **Hypotension** | 9 (8%) | 9 (10%) | 0.80 |
| **Bradycardia** | 3 (3%) | 14 (16%) | 0.002 |
| **Supplemental oxygen** | 2 (2%) | 0 | 0.19 |

**Figure 1** CONSORT diagram following the recruitment of 211 children for sedation before scheduled CT studies.

**Figure 2** Time to resume normal activities after oral chloral hydrate () or intranasal dexmedetomidine ().