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Safety of hydroxyzine in the sedation of pediatric dental patients

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Hydroxyzine is one of the most popular oral sedatives used in pediatric dentistry. This study aimed to investigate the safety and possible side effects of sedation using hydroxyzine in pediatric dentistry. "Hydroxyzine," "Dental sedation," "Child," and "Safety" and their associated synonyms were searched using the Cochrane Library, Embase, PubMed, KISS, KMBASE, and KoreaMed databases. Academic information and portals of DBpia and RISS were also perused. Altogether, 340 papers were found, among which a total of 24 papers were selected according to the detailed criteria. Nine studies used hydroxyzine as monotherapy, and 10 studies compared its safety when hydroxyzine used as multitherapy. In addition, seven studies employed a drug regimen wherein hydroxyzine was one of the components. All these studies revealed that the adverse events specific to hydroxyzine usage were drowsiness and dryness of the mouth, and that there were respiratory complications due to a synergistic reaction of hydroxyzine. Although classified as a histamine blocker, hydroxyzine with its sedative, antiemetic, anticonvulsant, and anticholinergic properties is an oral sedative available without serious adverse events, If the proper dosage of the drug is used and its synergistic effects with other drugs are ascertained in the route of administration.

Keywords: Hydroxyzine; Pediatric Dentistry; Safety.

INTRODUCTION

If the degree of anxiety and fear in a child visiting a pediatric dentist is severe and it is difficult to treat with the generally used physical and psychological behavioral control method, sedation by drugs is often employed [1]. According to the level of sedation, it can be classified as minimal sedation or general anesthesia. Among these methods, general anesthesia is not preferred owing to its associated problems such as risks and costs. Thus, moderate sedation is often selected in pediatric dentistry wherever necessary [2]. Drugs for sedation can be administered through various routes such as oral, nasal, intramuscular, intravenous, subcutaneous, and inhalation [3]. Oral sedation is the most common method that is used by pediatric dentists [4,5].

According to a survey conducted in Korea in 2014, chloral hydrate, hydroxyzine, and N_2O/O_2 were the most frequently selected sedative drug combinations by pediatric dentists [6]. A study published by the American Academy of Pediatric Dentistry (AAPD) in 2016 reported that American dentists frequently used hydroxyzine alone or in combination with N_2O/O_2, chloral hydrate, meperidine, midazolam, etc. [7].

This study aimed to investigate the safety and side

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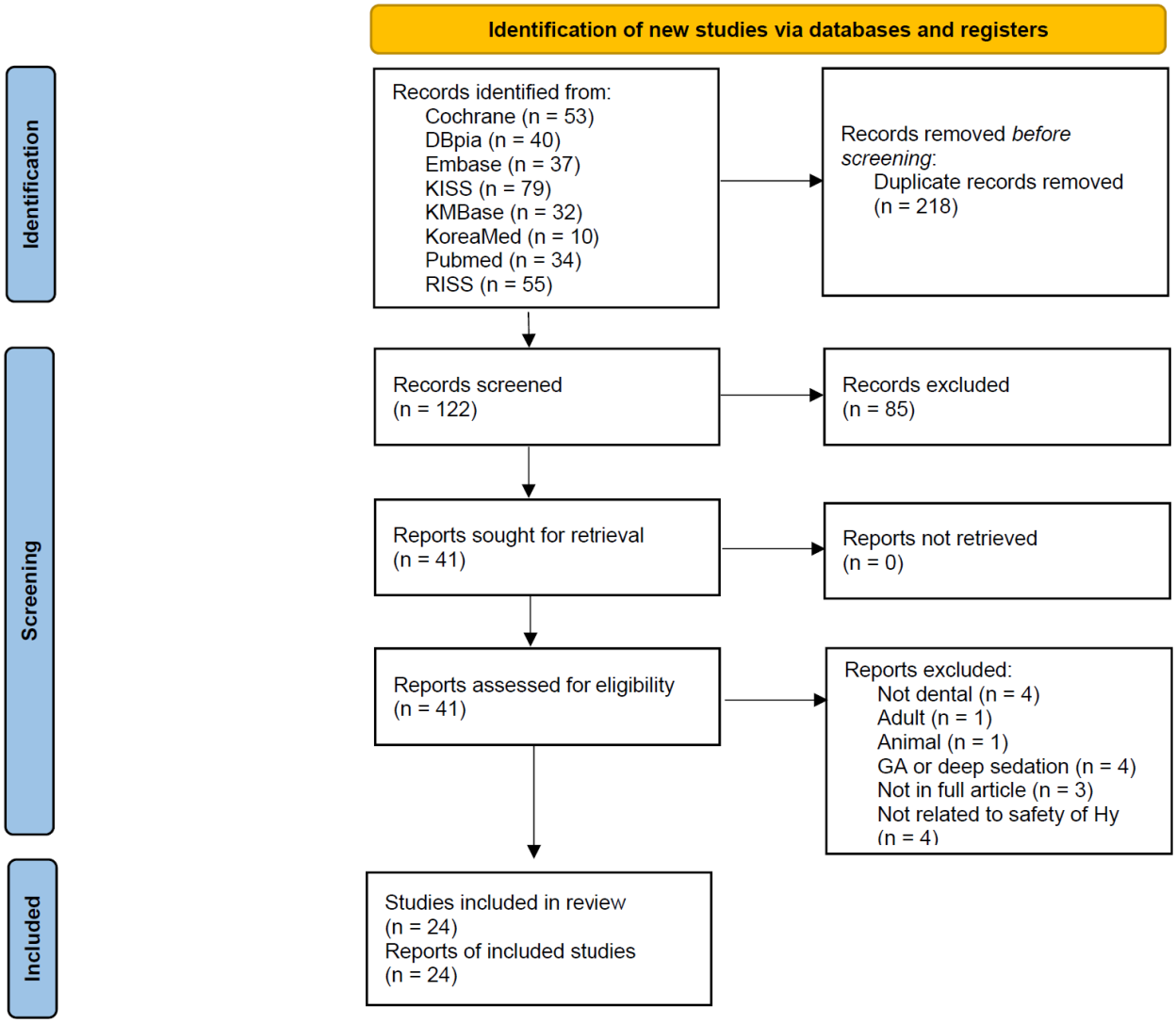

Fig. 1. PRISMA 2020 flow diagram showing the search results from the databases included in the study. Abbreviations: GA, general anesthesia; Hy, hydroxyzine; n, number; PRISMA, preferred reporting items for systematic reviews and meta-analyses.

effects of hydroxyzine by reviewing previously published literature.

METHODS

To obtain relevant papers, the Cochrane Library, Embase, and PubMed databases were searched for foreign literature. For reports within the Korean literature, the databases KISS, KMBASE, and KoreaMed were perused in addition to academic information and portals from DBpia and RISS. Until June 2022, the data from each of these databases were searched using the following keywords: "Hydroxyzine," "Dental sedation," "Child," and safety, Besides, synonyms for these words were also used as keywords.

After the first search, 198 papers were found using domestic search engines and portals, and 142 papers were found using foreign search engines. Subsequently, 41 papers were selected by excluding duplicate papers and checking the titles and abstracts of the papers as a secondary screening process. Finally, articles unrelated to the safety of hydroxyzine or for which the original text was unavailable were excluded. The method employed

Table 1. Selected studies

First author	Publication year	Classification
Lang LL [8]	1965	Hydroxyzine monotherapy
Yoon DK [9]	1976	Hydroxyzine monotherapy
Doring KR [10]	1985	Hydroxyzine regimen
Moody Jr EH [11]	1986	Hydroxyzine multitherapy
Lee KY [12]	1990	Hydroxyzine multitherapy
Park HS [13]	1990	Hydroxyzine multitherapy
Kwon OY [14]	1994	Hydroxyzine multitherapy
Kim SH [15]	1997	Hydroxyzine monotherapy
Kupietzky A [16]	1998	Hydroxyzine monotherapy
Avalos-Arenas V [2]	1998	Hydroxyzine multitherapy
Ram D [17]	1999	Hydroxyzine monotherapy/multitherapy
Lee IC [18]	2001	Hydroxyzine multitherapy
Jung JH [19]	2001	Hydroxyzine regimen
Leelataweedwud A [20]	2001	Hydroxyzine regimen
Lee JH [21]	2002	Hydroxyzine regimen
Lima ARDA [22]	2003	Hydroxyzine multitherapy
Faytrouny M [23]	2007	Hydroxyzine monotherapy
Torres-Pérez J [24]	2007	Hydroxyzine monotherapy/multitherapy
Costa LRDRSD [25]	2007	Hydroxyzine multitherapy
Kim KH [26]	2007	Hydroxyzine regimen
Baygin O [27]	2010	Hydroxyzine monotherapy
Lenahan M [28]	2015	Hydroxyzine regimen
Kim GM [29]	2020	Hydroxyzine regimen
Pouliquen A [30]	2021	Hydroxyzine monotherapy

for the selection and exclusion of studies in each stage has been outlined in Fig. 1.

RESULTS

Altogether, 24 papers met the criteria, and Table 1 lists them by the year of their publication. The contents in parentheses are citations that indicate the side effects reported for each of the articles. 1. Hydroxyzine Monotherapy (Table 2)

The reported side effects of moderate sedation using hydroxyzine alone in dental treatment of pediatric patients were drowsiness (age: 2.5–12 y, dose: 30 mg [9]), dryness of mouth (mean age: 6 y 3 mo, dose: 30 mg [8]), superficial thrombophlebitis (age: 4 y 6 mo, dose: 0.5 mg/kg [15]), nausea/vomiting, and cough (mean age: 5.33 y, dose: 1 mg/kg with 40%–60% N_2O-O_2 [27]). As hydroxyzine is classified as a histamine blocker with antiemetic action, nausea/vomiting is not likely to be a side effect caused by hydroxyzine. Superficial thrombophlebitis was treated by self-healing without special treatment. Oxygen desaturation was not reported in all studies that monitored oxygen saturation using a pulse oximeter, and physiological variables, including heart rate, were also within the normal range.

1. Multitherapy with Hydroxyzine (Table 3)

Among the literature that confirmed side effects or safety of administering hydroxyzine and other drugs in combination, only those that can be compared depending on the use of hydroxyzine were reviewed. A side effect that was found to be induced upon the use of only hydroxyzine was dryness of the mouth, which was mentioned in one study (mean age: 33.2 mo, dose: chloral hydrate 70 mg/kg, hydroxyzine 1–3 mg/kg [13]).

2. Regimen with hydroxyzine (Table 4)

Although there was no comparative analysis on the side effects of hydroxyzine usage in pediatric patients,

Table 2. Hydroxyzine monotherapy

Publication year/ First Author	Mean age	Sample size	Sedative drugs	Administration	Monitoring equipment/ interval	Adverse effects
1965 Lang LL [8]	6 y 3 mo	21	Hy: 50 mg (tablet)	60 min before appointment pO		Sleepy/Drowsy: 9 Dryness of mouth: 2
		21	Hy: 50 mg (syrup)			
	6 y 7 mo	20	Placebo tablet			Sleepy/Drowsy: 4 Nausea and vomiting: 3
		18	Placebo syrup			
1976 Yoon DK [9]	2.5 y~12 y	23	Hy: 30 mg syrup	30~45 min before appointment pO		Drowsiness: 4
		20	Placebo			Drowsiness: 3
		19	Control group			Drowsiness: 2
1997 Kim HS [15]	4 y 6 mo	1	Hy: 0.5 mg/kg	IV	PO	Superficial thrombophlebitis Prolonged sedation
1998 Kupietzky A [16]	30 mo	24	GA	50 min before treatment	PO, PC - PR, SaO_2, RR, Color - 15min	
	35 mo	30	Hy: 5 mg/kg (Max. 100 mg), N_2O-O_2: 50%-50%			
1999 Ram D [17]	29 mo	30 (each drug once)	Met: 5 mg, Hy: 3.7 mg/kg, N_2O-O_2: 50%-50%	60 min before treatment (Met first, Hy 5~8 min later)	PO, PC - PR, SaO_2 - 5min	
			Hy: 3.7 mg/kg, N_2O-O_2: 50%-50%			
2007 Faytrouny M [23]	61.9 mo	15	Hy: 20 mg, Hy 3.7 mg/kg, N_2O-O_2: 50%-50%	24 hour before treatment (Hy 20 mg), 60 min before treatment (Hy 3.7 mg/kg)	PO - HR, SaO_2 - 5min	
	53.7 mo	15	Hy: 3.7 mg/kg, N_2O-O_2: 50%-50%			
2007 Torres-Pérez J [24]	3.9 y	18	Hy: 2 mg/kg, Hy: 1 mg/kg	2 hour before treatment (Hy 2 mg/kg) 20 min before treatment (Hy 1 mg/kg)	- CR, SaO_2 -	
	2.83 y	18	Mid: 0.5 mg/kg, Hy: 1.5 mg/kg	20 min before treatment		
	2.94 y	18	CH: 50 mg/kg, Hy: 1.5 mg/kg	20 min before treatment		SaO_2 < 90: 1
2010 Baygin O [27]	5.33 y	15	Hy: 1 mg/kg, N_2O-O_2: 40%-60%	60 min before treatment	PO, BIS - SpO_2, HR	Nausea and Vomiting: 1 Cough: 4
	5.27 y	15	Mid: 0.7 mg/kg, N_2O-O_2: 40%-60%	60 min before treatment		Nausea and vomiting: 2 Cough: 4 Hiccough: 1 Enuresis: 2 Bronchospasm: 1
	5.2 y	15	Ket: 3 mg/kg, Mid: 0.25 mg/kg, N_2O-O_2: 40%-60%	15 min before treatment		Nausea and vomiting: 3 Hypersalivation: 8 Hallucination: 2
	5.53 y	15	No medication, N_2O-O_2: 40%-60%			Nausea and vomiting: 4 Hiccough: 5 Otalgia: 2 Epistaxis: 1
2021 Pouliquen A [30]	6.8 y	184	Hy: 1-2 mg/kg (1.63 mg/kg mean)	90 min before treatment		

BIS, bispectral index; CH, chloral hydrate; CR, cardiac rate; GA, general anesthesia; HR, heart rate; Hy, hydroxyzine; IV, intravenous; Ket, ketamine; mo, months; Met, metoclopramide; Mid, midazolam; N_2O, nitrous oxide; O_2, oxygen; PC, precordial stethoscope; pO, per oral; PO, pulse oximeter; PR, pulse rate; RR, respiratory rate; SaO_2, blood oxygen saturation; SpO_2, peripheral oxygen saturation; y, years.

desaturation (mean age: 30 mo, dose: chloral hydrate 60 mg/kg, hydroxyzine 25 mg [19]) was the major side effect found in literature that investigated the safety of employing a regimen containing hydroxyzine. In addition, there were apnea, prolonged sedation, vomiting (mean age: 47 mo, dose: chloral hydrate 50 mg/kg, meperidine 1.5 mg/kg, hydroxyzine 25 mg with 100% O_2 [20]), fever (mean age: 30 mo, dose: chloral hydrate 70 mg, hydroxyzine 2 mg/kg [26]), and rash (dose: meperidine 1–2.2 mg/kg, hydroxyzine 0.5–2.2 mg/kg with 50%–50%

Table 3. Multitherapy with hydroxyzine

Publication year/ First Author	Mean age	Sample size	Sedative drugs	Administration	Monitoring equipment/interval	Adverse effects
1986 Moody Jr EH [11]	39.6 mo	10	CH: 50 mg/kg, N_2O-O_2: 50%-50%	30 min before treatment Oral	PC, PO - PR, SaO_2 - 5 min	
	42 mo	10	CH: 50 mg/kg, N_2O-O_2: 50%-50%	30 min before treatment Rectal		
	38.4 mo	10	CH: 30 mg/kg, Hy: 25 mg, N_2O-O_2: 50%-50%	30 min before treatment Oral		
1990 Lee KY [12]	37 mo	15	CH: 75 mg/kg	Rectal	PO, Manometer - BP, PR, RR, SaO_2 - 5 min	Oxygen saturation < 95% more than 5sec.: 2 Excitement: 2
		15	CH: 75 mg/kg, Hy: 20 mg	1 hour before treatment (Hy), 30 min before treatment (CH) Oral		Oxygen saturation < 95% more than 5sec.: 2 Excitement: 1 Nausea: 1 Fever: 1
		15	CH: 75 mg/kg, Dzp: 3~4 mg	Rectal (CH) IM (Dzp)		Oxygen saturation < 95% more than 5sec.: 4 Vomiting: 2 Diarrhea: 1
1990 Park HS [13]	36.65 mo	20 (each drug once)	CH: 50 mg/kg	Oral	BPC, Manometer, PC - BP, HR, Respiratory reflex - 10 min	Vomiting: 1
			CH: 50 mg/kg, Hy: 25 mg	Oral		Xerostomia: 9
			CH: 50 mg/kg	Rectal		Vomiting: 1 Xerostomia: 1
1994 Kwon OY [14]	21-45 mo	22 (each drug once)	CH: 75 mg/kg	45 min before treatment	PO - HR, SaO_2	Vomiting: 3 Nausea: 2 Diarrhea: 1
			CH: 50 mg/kg, Hy: 25 mg			Nausea: 1 Diarrhea: 1
1998 Avalos-Arenas V [2]	28.58 mo	40	CH: 70 mg/kg, Placebo	1 hour before treatment	PC, Manometer - HR, RR, BP, SaO_2 - 15 min	At least 10% of children had an SaO_2 of < 90%
			CH: 70 mg/kg, Hy: 2 mg/kg			
1999 Ram D [17]	29 mo	30 (each drug once)	Met: 5 mg, Hy 3.7 mg/kg, N_2O-O_2: 50%-50%	60 min before treatment (Met first, Hy 5~8 min later)	PO, PC - PR. SaO_2 - 5 min	
			Hy: 3.7 mg/kg, N_2O-O_2: 50%-50%			
2001 Lee IC [18]	33.2 mo	50 (each drug once)	CH: 70 mg/kg, Placebo		PO, BPC - HR, BP, SaO_2 - 5 min	Vomiting: 6 Respiratory depression: 1
			CH: 70 mg/kg, Hy: 1 mg/kg			Vomiting: 1 Xerostomia: 4 Respiratory depression: 1
			CH: 70 mg/kg, Hy: 2 mg/kg			Vomiting: 1 Xerostomia: 6
			CH: 70 mg/kg, Hy: 3 mg/kg			Vomiting: 2 Xerostomia: 6 Respiratory depression: 2
2003 Lima AR [22]	40 mo	37 case (11 child)	Placebo	30 min before treatment	PO - RR, HR, SaO_2 - 15 min	
			Mid: 1 mg/kg			
			Mid: 0.75 mg/kg, Hy: 2 mg/kg			

N_2O-O_2 [28]) in different cases. Among them, apnea was due to the respiratory depressive effect of the narcotic used in combination. However, that could also be a result of a synergistic reaction of hydroxyzine.

Table 3. Multitherapy with hydroxyzine (continued)

Publication year/ First Author	Mean age	Sample size	Sedative drugs	Administration	Monitoring equipment/interval	Adverse effects
2007 Torres-Pérez J [24]	3.9 y	18	Hy: 2 mg/kg, Hy: 1 mg/kg	2 hour before treatment (Hy 2 mg/kg) 20 min before treatment (Hy 1 mg/kg)	- CR, SaO_2 -	
	2.83 y	18	Mid: 0.5 mg/kg, Hy: 1.5 mg/kg	20 min before treatment		
	2.94 y	18	CH: 50 mg/kg, Hy: 1.5 mg/kg	20 min before treatment		SaO_2 < 90: 1
2007 Costa LR [25]	40.6 mo	35 case (12 child)	Placebo	30 min before treatment	PO, BPC	
			CH: 75 mg/kg		- RR, HR, SaO_2, BP - 15min	Irritation: 7 Sleepiness: 9 Nausea, Vomiting: 3
			CH: 50 mg/kg, Hy: 2 mg/kg			Irritation: 5 Sleepiness: 8 Nausea, Vomiting: 1

BP, blood pressure; BPC, blood pressure cuff; CH, chloral hydrate; CR, cardiac rate; Dzp, diazepam; HR, heart rate; Hy, hydroxyzine; IM, intramuscular; mo, months; Met, metoclopramide; Mid, midazolam; N_2O, nitrous oxide; O_2, oxygen; PC, precordial stethoscope; PO, pulse oximeter; PR, pulse rate; RR, respiratory rate; SaO_2, blood oxygen saturation; y, years.

Table 4. Regimen with hydroxyzine

Publication year/ First Author	Mean age	Sample size	Sedative drugs	Administration	Monitoring equipment/ interval	Adverse effects
1985 Doring KR [10]	51.4 mo	36 case (26 child)	Alp: 0.6 mg/kg, Hy: 0.3 mg/kg, N_2O-O_2: 40%-60%	6min before treatment Submucosal (Maxillary vestibule)	ECG, PO, BPC - HR, BP, SaO_2 - 3 min	
2001 Jung JH [19]	30 mo	92 case (71 child)	CH: 60 mg/kg, Hy: 25 mg	45~60 min before treatment	PO	SpO_2 < 95%: 42
2001 Leelataweedwud P [20]	47 mo	195 case (111 child)	CH: 50 mg/kg, Mep: 1.5 mg/kg, Hy: 25 mg, 100% O_2	45 min before treatment	PO, PC, Capnography - $EtCO_2$, PR, RR, SpO_2 - 5 min	True apnea: 1 Prolonged sedation: 3 Vomiting: 1 True desaturation: 1
2002 Lee JH [21]	42.2 mo	40	CH: 60 mg/kg, Hy: 25 mg		PO, PC - - 5min	True desaturation: 0~3 times for each patient
2007 Kim KH [26]	30 mo	171 case (94 child)	CH: 70 mg/kg, Hy: 2 mg/kg, (N_2O-O_2 induction if child not sedated in 60min)		- SpO_2, HR, RR - 5 min	Vomiting: 2 Fever: 1 Desaturation: 1
2015 Lenahan M [28]		248 case	Mep: 1~2.2 mg/kg (Max 50 mg), Hy: 0.5~2.2 mg/kg (Max. 50 mg), (N_2O-O_2: 50%-50% for 238 case)	45~60 min before treatment	PO, BPC, PC - BP, PR, SaO_2 - 5 min	Nausea, Vomiting, Rash, Minor desaturation: 14
2020 Kim G [29]	36.4 mo	188 case (149 child)	CH: 50~70 mg/kg, Hy: 25 mg, N_2O-O_2: 55%-45% (mean)	30~60 min before treatment	PO, Capnography - SpO_2, HR, RR, $EtCO_2$ - 15 min	Vomiting during procedure: 27 Vomiting after procedure: 4 Desaturation: 4

Alp, Alphaprodine; BP, blood pressure; BPC, blood pressure cuff; CH, chloral hydrate; ECG, electrocardiograph; $EtCO_2$, end tidal carbon dioxide; HR, heart rate; Hy, hydroxyzine; mo, months; Max, maximum; Mep, meperidine; N_2O, nitrous oxide; O_2, oxygen; PC, precordial stethoscope; PO, pulse oximeter; PR, pulse rate; RR, respiratory rate; SaO_2, blood oxygen saturation; SpO_2, peripheral oxygen saturation.

DISCUSSION

Hydroxyzine is classified as a histamine blocker (H1), but has sedative, antiemetic, anticonvulsant, and anticholinergic properties. After oral administration, it is absorbed through the gastrointestinal tract, and its clinical action is observed within 15–30 minutes. The maximum action is observed 2 hours after administration [31]. The sedative action of hydroxyzine is initiated when the hypothalamic nuclei are inhibited and then subsequently, the sympathetic part of the autonomic nervous system [32]. Since it amplifies the central nervous system depression of drugs such as barbiturates, narcotics, alcohol, sedative-hypnotics, and anxiolytics, the dose of these drugs in combination or hydroxyzine alone should be reduced to 50% [33].

Although the dosage of hydroxyzine has not been determined precisely, Ayd [34] described in 1957 that 25 mg was effective in children with neurotic and hyperkinetic disorders. In addition, Kopel [35] reported in 1959 that satisfactory results were obtained when 30–50 mg of the drug was taken at bedtime, a day before the appointment; and the same dose when taken one hour before treatment in "high-strung" children. In 1965, Lang [8] reported that a single dose of 50 mg of the drug was effective when it is taken one hour before the treatment. On the other hand, in 1992, Shapira et al. [36] reported that, since hydroxyzine (50 mg) prescription in heavier children showed high failure rates, an effective mg/kg ratio should be used. They also added that the 3.7 mg/kg ratio used along with 50% N_2O-O_2 was the most appropriate. Tafaro et al. [37] used 2 mg/kg, and Needleman et al. [38] used 1 mg/kg in their studies. Kupietzky and Blumenstyk [16] reported no side effects even with higher doses of hydroxyzine (5 mg/kg, 100 mg max).

Among the side effects that were investigated in this study, drowsiness and dryness of the mouth are considered to be caused by hydroxyzine. These phenomena are considered to be helpful for pediatric treatment.

The goal of sedation in pediatric patients is to ensure patient safety and minimize discomfort, anxiety, and psychological trauma. It is also aimed at maximizing the potential of amnesia, controlling behaviors for the safe completion of procedures, and ensuring safe discharge from the hospital [39]. The side effects of sedation treatment can cause brain damage or even death, and these side effects are mainly caused by respiratory failure [40]. Normal arterial oxygen saturation of healthy children in room air is 97–100%, and an oxygen saturation of 95% or more can provide oxygen to tissues at a normal level. Mild hypoxemia refers to an oxygen saturation of 91–95%, moderate hypoxemia an oxygen saturation of 75–90%, and severe hypoxemia an oxygen saturation of less than 75% [41]. An oxygen saturation of less than 95% does not occur under normal physiological conditions. Cyanosis of nails or mucous membranes is useful for detecting hypoxia, and changes in heart rate, electrocardiogram, and blood pressure can also be signs of hypoxemia [42]. However, these were not observed until the oxygen saturation fell from a moderate to a severe level [43]. When an overdose of drugs is used or inappropriate anesthesia is practiced, cardiovascular complications may also occur during sedation. However, these processes occur less frequently than when only local anesthesia is used [44]. Hypotension or hypertension refers to a case in which a patient's blood pressure changes by 20% or more from the baseline. When the cardiac rhythm is different from the patient's baseline sinus rhythm, it can be considered as arrhythmia [45].

To prevent such a situation, the patient should be continuously monitored by professional personnel using appropriate equipment before, during, and after the procedure [46]. According to the American Society of Anesthesiologists (ASA) guidelines, ventilatory and cardiovascular functions are not affected in cases of minimal sedation. Thus, no interventions other than observation or intermittent assessment of the sedation level are necessary. Moreover, for moderate sedation, no

interventions are required for airway maintenance or spontaneous ventilation. However, even in cases where minimal sedation is intended, individuals can be moderately sedated, which can progress to deep sedation. Therefore, it is stated that an operator needs to prepare the necessary equipment for deep sedation [39,45]. It should be able to monitor heart rates and oxygen saturation continuously, and capnography or precordial stethoscopes are recommended to monitor ventilation [39].

No serious adverse events induced by hydroxyzine were reported in this study. However, it was reported in 1994 that second-generation antihistamines could induce QT interval prolongation. Besides, some first-generation antihistamines (including hydroxyzine) could also cause ventricular fibrillation, which may result in torsades de pointes (TdP), leading to death [47]. Such QT interval prolongation is thought to be caused by cardiac potassium channel blockage involved in repolarization, and increased repolarization time and T wave disturbances have been reported with the use of hydroxyzine. However, since these adverse events only occur when the drug is overdosed and do not appear in most cases, hydroxyzine should not be administered to patients with hereditary long QT syndrome or cardiovascular disease [48]. In this regard, there was a pharmacovigilance review of hydroxyzine in 2017, in which [49] all 59 cases with QT prolongation and/or TdP reported from 1995 to 2016 had underlying risk factors (daily dose of 100 mg or more, systemic disease, concomitant medications).

CONCLUSIONS

Hydroxyzine was developed in 1956 and has been widely used in over 30 countries. It is the 70th most-used drug with over 10 million prescriptions in the US in 2020. It is safe to use, with a very low incidence of side effects. Besides, there have been rare cases of fatal overdose, and no reported withdrawal symptoms following long-term treatment.

Upon the selection of an appropriate route and dose, there are no side effects except for drowsiness and dryness of the mouth when used alone. Since hydroxyzine can amplify central nervous system depression due to other drugs, more satisfactory sedative effects can be obtained by reducing nausea and vomiting and other side effects of drugs such as chloral hydrate.

However, the use of hydroxyzine alone is limited to the management of children with mild to moderate fear. Therefore, when used in combination with other drugs for pediatric patients who are more fearful, the patient's vital signs should be meticulously monitored before, during, and after treatment to maintain sedation at a minimal to moderate level.

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Taegyeom Kim: Writing - original draft, Writing - review & editing
Keoungah Kim: Supervision
Seungoh Kim: Supervision
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REFERENCES

1. Korean Academy of Pediatric Dentistry. Textbook of Pediatric Dentistry. 5th ed. Seoul, Yenang INC. 2014, pp 225
2. Avalos-Arenas V, Moyao-García D, Nava-Ocampo AA, Zayas-Carranza RE, Fragoso-Ríos R. Is chloral hydrate/hydroxyzine a good option for paediatric dental outpatient sedation?. Curr Med Res Opin 1998; 14: 219-26.
3. Mason KP. Pediatric sedation outside of the operating

room: a multispecialty international collaboration. 3rd edition. Boston, Springer. 2021, pp 171-91.
4. Chopra R, Mittal M, Bansal K, Chaudhuri P. Buccal midazolam spray as an alternative to intranasal route for conscious sedation in pediatric dentistry. J Clin Pediatr Dent 2013; 38: 171-3.
5. Primosch RE, Guelmann M. Comparison of drops versus spray administration of intranasal midazolam in two-and three-year-old children for dental sedation. Pediatr Dent 2005; 27: 401-8.
6. Yang Y, Shin T, Yoo S, Choi S, Kim J, Jeong T. Survey of sedation practices by pediatric dentists. J Korean Acad Pediatr Dent 2014; 41: 257-65.
7. Wilson S, Houpt M. Project USAP 2010: use of sedative agents in pediatric dentistry-a 25-year follow-up survey. Pediatr Dent 2016; 38: 127-33.
8. Lang LL. An evaluation of the efficacy of hydroxyzine (Atarax-Vistaril) in controlling the behavior of child patients. J Dent Child 1965; 32: 253-8.
9. Yoon DK. Studies on the clinical efficacy of hydroxyzine hydrochloride in dentistry for children. J Korean Acad Pediatr Dent 1976; 3: 41-7.
10. Doring KR. Evaluation of an alphaprodine-hydroxyzine combination as a sedative agent in the treatment of the pediatric dental patient. J Am Dent Assoc 1985; 111: 567-76.
11. Moody EH Jr, Mourino AP, Campbell RL. The therapeutic effectiveness of nitrous oxide and chloral hydrate administered orally, rectally, and combined with hydroxyzine for pediatric dentistry. ASDC J Dent Child 1986; 53: 425-9.
12. Lee KY, Yang KH. Clinical studies on the effect of premedicants for behavior management in uncooperative children. J Korean Acad Pediatr Dent 1991; 18: 11-22.
13. Park HS, Kim YK. Clinical study on the effect of chloral hydrate and hydroxyzine in sedating child patients for dental treatment. J Korean Acad Pediatr Dent 1990; 17: 1-14.
14. Kwon OY, Lee KH. Comparison of chloral hydrate with and without hydroxyzine HCl in the sedation of pediatric dental patients. J Korean Acad Pediatr Dent 1994; 21: 159-73.
15. Kim HS, Han GJ, Lee CS, Lee SH. Clinical study on the side effects of the conscious sedation. J Korean Acad Pediatr Dent 1997; 24: 823-9.
16. Kupietzky A, Blumenstyk A. Comparing the behavior of children treated using general anesthesia with those treated using conscious sedation. J Dent Child 1998; 65: 122-7.
17. Ram D, Mamber E, Chosack A, Fuks AB. The effect of metoclopramide and hydroxyzine in sedation of infants undergoing dental treatment. ASDC J Dent Child 1999; 66: 49-52.
18. Lee IC, Kim JS, Kwoon SW. The comparative study on the efficacy of chloral hydrate and hydroxyzine of different doses in sedating young pediatric dental patients. J Korean Acad Pediatr Dent 2001; 28: 430-40.
19. Jung JH, Park KT. Evaluation of success rate and temporary hypoxia in pediatric dental sedation using chloral hydrate and hydroxyzine. J Korean Acad Pediatr Dent 2001; 28: 337-44.
20. Leelataweedwud P, Vann WF Jr. Adverse events and outcomes of conscious sedation for pediatric patients: study of an oral sedation regimen. J Am Dent Assoc 2001; 132: 1531-9.
21. Lee JH, Park HW. Assessment of vital signs in pediatric dental sedation using chloral hydrate and hydroxyzine. J Korean Acad Pediatr Dent 2002; 29: 455-62.
22. Lima AR, Costa LR, da Costa PS. A randomized, controlled, crossover trial of oral midazolam and hydroxyzine for pediatric dental sedation. Pesqui Odontol Bras 2003; 17: 206-11.
23. Faytrouny M, Okte Z, Kucukyavuz Z. Comparison of two different dosages of hydroxyzine for sedation in the paediatric dental patient. Int J Paediatr Dent 2007; 17: 378-82.
24. Torres-Pérez J, Tapia-García I, Rosales-Berber MÁ, Hernández-Sierra JF, Pozos-Guillén Ade J. Comparison of three conscious sedation regimens for pediatric dental patients. J Clin Pediatr Dent 2007; 31: 183-6.
25. da Costa LR, da Costa PS, Lima AR. A randomized double-blinded trial of chloral hydrate with or without hydroxyzine versus placebo for pediatric dental sedation.

Braz Dent J 2007; 18: 334-40.
26. Kim KH, Kim SO, Kim JS. A study on the effects of sedation and related variables for pediatric dental patients. J Korean Acad Pediatr Dent 2007; 34: 234-46.
27. Baygin O, Bodur H, Isik B. Effectiveness of premedication agents administered prior to nitrous oxide/oxygen. Eur J Anaesthesiol 2010; 27: 341-6.
28. Lenahan M, Wells M, Scarbecz M. A retrospective study of 248 pediatric oral sedations utilizing the combination of meperidine and hydroxyzine for dental treatment. J Clin Pediatr Dent 2015; 39: 481-7.
29. Kim G, Lee J, Kim H, Nam S. The effectiveness and side effects of conscious sedation using chloral hydrate, hydroxyzine, and nitrous oxide. J Korean Acad Pediatr Dent 2020; 47: 109-19.
30. Pouliquen A, Boyer E, Sixou JL, Fong SB, Marie-Cousin A, Meuric V. Oral sedation in dentistry: evaluation of professional practice of oral hydroxyzine in the University Hospital of Rennes, France. Eur Arch Paediatr Dent 2021; 22: 801-11.
31. Schneider HS. Clinical observation utilizing morphine sulfate and hydroxyzine pamoate for sedating apprehensive children for dental procedures: a nine-year report. Pediatr Dent 1986; 8: 280-4.
32. Brandt SK, Bugg JL Jr. Problems of medication with the pediatric patient. Dent Clin North Am 1984; 28: 563-79.
33. Malamed S. Sedation: A Guide to Patient Management. 5th ed. Amsterdam, Elsevier. 2009, pp 119-20.
34. Ayd FJ Jr. Chemotherapeutic management of emotional problems in children. Med Arts Sci 1957; 11: 54-8.
35. Kopel HM. The use of ataraxics in dentistry for children. J Dent Child 1959; 26: 14-24.
36. Shapira J, Holan G, Guelmann M, Cahan S. Evaluation of the effect of nitrous oxide and hydroxyzine in controlling the behavior of the pediatric dental patient. Pediatr Dent 1992; 14: 167-70.
37. Tafaro ST, Wilson S, Beiraghi S, Weaver J, Travers J. The evaluation of child behavior during dental examination and treatment using premedication and placebo. Pediatr Dent 1991; 13: 339-43.
38. Needleman HL, Joshi A, Griffith DG. Conscious sedation of pediatric dental patients using chloral hydrate, hydroxyzine and nitrous oxide-a retrospective study of 382 sedations. Pediatr Dent 1995; 17: 424-31.
39. Coté CJ, Wilson S. Guidelines for monitoring and management of pediatric patients before, during, and after sedation for diagnostic and therapeutic procedures. Pediatr 2019; 143: 1-15
40. Chicka MC, Dembo JB, Mathu-Muju KR, Nash DA, Bush HM. Adverse events during pediatric dental anesthesia and sedation: a review of closed malpractice insurance claims. Pediatr Dent 2012; 34: 231-8.
41. Shapiro BA. Oxygenation: measurement and clinical assessment. ASA refresher courses in anesthesiology. 1979; 7: 189-202.
42. Comroe JH Jr, Botelho S. The unreliability of cyanosis in the recognition of arterial anoxemia. Am J Med Sci 1947; 124: 1-6.
43. Mueller WA, Drummond JN, Pribisco TA, Kaplan RF. Pulse oximetry monitoring of sedated pediatric dental patients. Anesth Prog 1985; 32: 237-40.
44. Becker DE, Haas DA. Recognition and management of complications during moderate and deep sedation. Part 2: cardiovascular considerations. Anesth Prog 2011; 58: 126-38.
45. Dial S, Silver P, Bock K, Sagy M. Pediatric sedation for procedures titrated to a desired degree of immobility results in unpredictable depth of sedation. Pediatr Emerg Care 2001; 17: 414-20.
46. Nathan JE. Management of the difficult child: a survey of pediatric dentists' use of restraints, sedation and general anesthesia. ASDC J Dent Child 1989; 56: 293-301.
47. Smith SJ. Cardiovascular toxicity of antihistamines. Otolaryngol Head Neck Surg 1994; 111: 348-54.
48. Olasińska-Wiśniewska A, Olasiński J, Grajek S. Cardiovascular safety of antihistamines. Postepy Dermatol Alergol 2014; 31: 182-6.
49. Schlit AF, Delaunois A, Colomar A, Claudio B, Cariolato L, Boev R, et al. Risk of QT prolongation and torsade de pointes associated with exposure to hydroxyzine: re-evaluation of an established drug. Pharmacol Res Perspect 2017; 5: e00309.