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Post-operative effects of Oral Midazolam versus Hydroxyzine on Ketamine Intravenously Sedated children

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Objectives The aim of this clinical trial was to compare the effects of oral Midazolam with oral Hydroxyzine on post sedation using IV Ketaminein children.
Methods This single blind cross over clinical trial, was conducted on 25 children aged 2-6 years of ASA I and definitely negative by Frankl behavioral scale. Participants were divided into two groups: Group I received hydroxyzine syrup premed at the first session and midazolam oral at the 2nd visit. Group II received the premed in the opposite order. Vital signs, were recorded sedation depth, recovery and discharge status and compared potential adverse effects of sedative drugs were checked and recorded including sleepiness, nausea and vomiting, vertigo at 1stand 6th hours of discharge. Collected data were analyzed using SPSS V 20 using Repeated Measures ANOVA and Mann-Whitney tests.
Results No significant differences were noticeable between two groups when vital signs, were compared in addition to response to drugs, working time, sleepiness, nausea and vomiting rates. However, there was a significant difference between groups in the incidence of vertigo one hour post operatively with higher prevalence in the Hydroxyzine group. (P=0.022)
Conclusion Under the circumstances of this study, no significant difference was found between the two regimen groups, but vertigo was appeared as being higher after the first hour in the Hydroxyzine group.
Keywords Premedication, Midazolam, Hydroxyzine, Sedation, Pediatric dentistry

Introduction

A growing number of children are suffer from sever dental decay rates with a large number of them remain untreated too. Based on several earlier community based studies it appears that neglect may be counted as one of the most frequent cause beside child dental phobia one of the most significant barriers[1]. Routine techniques for child's behaviour management have long been tried effectively in many cases, however their successfulness is mainly depend on the operator's knowledge and experience a long office time taken to respond[2]. In today' societies the use of physical restraint is no longer accepted as a choice by parents, while such approaches are not considered as appropriate for very small children[3].

Changes in expectation and life styles of families a long side opposition to any aggressive behaviours are believed to be the key to higher demands for more alternative ways to overcome the child's behaviour problems when receiving dental treatment[4]. Efficient anxiety control is a core to successful paediatric dental pharmachologic management technique is considered and used widely for many years in children. Among these, treatments conscious sedation is a technique in which the use of limited doses of sedative drugs can produce a state of depression of the central nervous system. In such circumstances verbal contact with the patient is maintained throughout the conscious sedation state while child tolerating certain dental procedures. It is important to observe a wide safety margin of drugs during conscious sedation sessions[5]. Various Premedication agents have suggested to used alone or in combination include chloral hydrate, Promethazine, Hydroxyzine, Meperidine, diazepam, Fentanyl, and Midazolam[6]. Among the routs of drug administration oral route is considered as one of the most popular as it is easier to be delivered in addition to it's low cost. However, oral sedations have limitations of use in very young children[7]. The goal is to employ the most effective method, with the least potential hazards[8].

Oral administration of the premedication agents is to decrease the anxiety prior to and during the dental treatment. The incidence of adverse effects in oral sedation is known to be quite low with minimum equipment required[8]. An ideal oral sedative agent should be able to provide reasonable immobilization, while being safe and easily accepted by child[9].

Hydroxyzine is one of the first-generation of H1-antihistamines which binds to H1-receptors and block the neurotransmitter effect of histamine on the central nervous system. Hydroxyzine has the potential to lead to depression of the central nervous system[10]. One of the drawbacks of hydroxyzine as sedative premedical is its relatively long waiting period from its administration to the time that treatment can be started[11]. Hydroxyzine has a better performance in addition to nitrous oxide or Midazolam [11, 12, 13].

Midazolam, a benzodiazepine[8] is the most commonly used sedative premedication used in both medicine and dentistry. It is mandatory to be administered while patient is under direct supervision. Major of midazolam include sits availability as an oral suspension white its short onset of action. Midazolam is commonly used for oral sedation in children before dental treatment in several earlier investigations referring to its potentials as safety, rapid onset and degrees of amnesia[14, 15]. However, incidence of adverse post-operative behaviour changes have been reported along with paradoxical reactions, and impaired cognitive functioning, has been with the use of midazolam[16]. In the other hand Ketamine is a phencyclidine derivative that antagonizes the N-methyl-D-aspartate (NMDA) receptor. The principal action of ketamine is central dissociation of the cortex from the limbic system. This will provide a desired level of sedation as well as analgesia to allow invasive procedures like dental treatment to take effect without interference. It is recommended to administer an ant sialagogue (atropine,) along with ketamine for dental sedation.[14] Shapira et al compared the effect of oral midazolam with and without hydroxyzine in the sedation of paediatric dental patients and concluded that combination of hydroxyzine with midazolam resulted in a safe and effective sedation state for dental treatment of young children. This combination's use might be more advantageous when compared to midazolam alone, resulting in less crying and movement during the first 30 minutes[11]. Minor side effects such as nausea and vomiting have been reported as the most common side effects[17].
This investigation was aimed to compare the effects of oral Midazolam and Hydroxyzine on post-operative side effects of Intravenous Ketamine Sedation in Pediatric Dentistry.

Materials and Methods

This prospective, single-blind, crossover clinical trial was conducted on25 young uncooperative children aged 24 to 72 months (7 males and 18 females). Children were selected from those references to Pediatric Dental Clinic at Shahid Beheshti University for treatment during 2016. Those scored 1 or 2 according to Frankl behaviour scale were included who were at ASA 1, in need of at least 2 similar dental treatment visits in a simple sampling manner. An informed consent was signed by parents. Pulpotomy and restoration were the two options for including teeth in this study with attempts being made to match the two visits. An experienced specialist (Fellow Candidate) operated the cases of this investigation at follow clinic of Shahid Beheshti dental school during 2016. All procedures performed in this investigation were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This randomized clinical trial was registered under #IRCT (201602291882N8).Parents received verbal and printed discharge instructions in order to be able to observe their child's post-operative reactions. They were requested to report any reaction including: dizziness, prolonged sleep, nausea and vomiting. Children were instructed to observe an at least -6hours NPO prior to sedation based on child's individual age. Subjects were randomly assigned to one of the two groups in order to receive either oral midazolam (0.5 mg/kg with atropine (0.25mg) or Hydroxyzine (1 mg/kg) (Poorsina Co., Iran) and Atropin (0.25 mg) (Alborz Daru, Iran) in their first visit. The other combination was given at their second visit. Patients in both groups received an intravenous ketamine (1-2mg/kg) (Bremer Farma GMBH, Germany) and midazolam (0.1mg/kg) (Caspian Tamin Co. Iran) as main sedation course, 30 minutes after the initial premedication was administered. All subjects were placed under oxygen (2lit/min). The child's behaviours scale was scored using Houpt scale in every 15 minutes by an experienced independent pediatric dentist. Patient's vital signs were recorded using a medical monitoring machine (Saadat, Tehran, Iran).Children were put under direct observation of anaesthesiologist in charge. Any adverse effect was recorded by the operator at the first hour in recovery and at discharge. A telephone call was conducted by the operator at 6 hour after discharge. Data calculation was carried out using Repeated Measures ANOVA, Wilcoxon and Mann-Whitney tests.

Results

The mean patient's age was 38.08 months and their weight ranged between 10-20kg. The carry over and period effect was not significant for all the dependent variables ($p>0.05$). There were no significant difference between the two drugs for their adverse effects with a slightly higher rate of vertigo in hydroxyzine group during the first hour of recovery using Wilcoxon test ($p=0.022$) (Tables 1, 2, 3) Moreover, these drugs had a similar effect on vital signs alteration level using repeated measure ANOVA. Houpt scale recordings were compared between the two groups as well as discharge time both showing no significant difference using Mann-Witney and Wilcoxon tests ($p>0.05$).

Table 1- Comparison of the differences of the drugs in terms of sleepiness

Time	Wilcoxon	Mann-Whitney U	Z statistic	Sig.
The 1st hour	6000.000	275.000	-0.843	0.399
The 2nd hour	6000.000	275.000	-1.014	0.311
Six hours after discharge	620.000	295.000	-0.345	0.730

Table 2- Comparison of the differences of the drugs in terms of nausea and vomiting

Time	Wilcoxon	Mann-Whitney U	Z statistic	Sig.
The 1st hour	6000.000	275.000	-1.400	0.162
The 2nd hour	6000.000	275.000	-1.093	0.274
Six hours after discharge	612.500	287.000	-0.862	0.389

Table 3- Comparison of the differences of the drugs in terms of

vertigo

Time	Wilcoxon	Mann-Whitney U	Z statistic	Sig.
The 1st hour	562.500	237.500	-2.291	0.022*
The 2nd hour	612.500	287.500	-0.600	0.548
Six hours after discharge	637.500	312.500	-0.000	1.000

*Significant

Discussion

There remain to be a debate on the effectiveness and safety of drugs used for dental sedation and their relative premedication in this line few on go in research are to identify a desired and widely accepted premedication for children[18]. Besides, as there is underway at this dental school while several recently published materials also indicate the existing gap in literature, limited information to support the effects of Hydoxyzine to sedate children the use of this medication worth looking at[19]. Result of the current investigation revealed that the incidence of post-operative adverse events of hydroxyzine oral administration is similar to that of midazolam following dental IV ketamine sedation in children.

There was no significant difference between the two groups of drugs tested when their adverse effects were texted following discharge small exception of vertigo was noted during the first hour in Hydroxyzine group. This could be explained by its oral administration with late onset and long half-life of about 3 hours, encountering vertigo. Vertigo was one of the hydroxyzine's specific side effects[20] confirmed by Ritwik[19], Dallman[21], and Songarj[22] while Martinez stated high levels of sleepiness using hydroxyzine[23].

Measuring children by Houpt scale showed no significant difference between the two visits. These findings were different from the results reported by Shapira[11] and Al-Taher[5] indicating clear difference between hydroxyzine and Midazolam sedation effects.

Vital signs were compared with their baseline and minimum alteration including difference within and between groups were noted. Shapira[11], Cathers[4] and Fallahinejadghajari[24] reported similar findings with significant differences in their earlier studies. On the other hand, HR and blood pressure may decrease following the administration of midazolam, triclofos and hydroxyzine combination in certain cases[18].

As pre sedation medication is an assisting step towards better acceptance of the main sedation course prior to the dental treatment, its effectiveness and use can encourage both the operator and patient to practice in with confidence. It is of note that conscious sedation is not only used in dentistry but also is highly popular for use in diagnostic medicines and therefore many studies have been performed on the medications and routes in order to evidently indicate the best choice[25].

Conclusion

Under the condition of this study, no significant differences were found between hydroxyzine and midazolam premedication when used as oral premedication for dental treatment and their effect on post sedation adverse effects. This indicates that hydroxyzine cannot be considered any superior to already approved readily available Midazolam oral required with similar or bigger size samples and further sedative agents.

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Conflict of Interests

None Declared ■

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