

Efficacy of Intranasal Midazolam in Cessation of Hypercyanotic Spells in Children with Tetralogy of Fallot

Kurosh Riahi¹, Babak Najibi², Mehrdad Razmara^{3*}

1. Thalassemia and Hemoglobinopathy Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
2. Department of Pediatric Cardiology, Golestan Medical Educational Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.
3. Department of Pediatrics, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran.

*Corresponding Author: Dr. Mehrdad Razmara;

Address: Department of Pediatrics, Faculty of Medicine, Ahvaz Jundishapur university of Medical Sciences, Golestan Blvd, Ahvaz, Province, 61357-15794, IR Iran.

Tel: +98 61 33113828

E-mail: razmara.m@ajums.ac.ir

mehrdad.razmara399@gmail.com

Article Info.

ABSTRACT

Article type:

Short Communication

Received: 2 May 2022

Revised: 25 July 2022

Accepted: 23 August 2022

Published: 1 March 2023

Keywords:

Cyanosis,

Heart Diseases,

Midazolam,

Nasal Absorption,

Tetralogy of Fallot

Background and Objective: Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease. Hypercyanotic spells are one of the major complications of TOF which call for a prompt intervention to resolve hypoxic conditions. The aim of this study was to evaluate the effect of intranasal midazolam on the control of spells in children with hypercyanotic TOF.

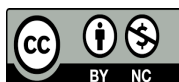
Methods: This semi-experimental study was conducted on TOF children referring to the pediatric emergency department of Golestan Hospital, Ahvaz, Iran from April 2017 to February 2018. The children were knee-chest positioned by the mother, and if the spells were not resolved, 0.2 mg intranasal midazolam was introduced into the nasal cavity. Three minutes after the child's recovery, measurement of heart rate and respiratory rate as well as pulse oximetry was done. Data were analyzed by SPSS version 17.

Findings: Of the 10 patients studied, 6 (60%) were boys and 4 (40%) were girls. The age of patients ranged from 6 months to 3.5 years. Sixty percent of the children were in recovery, 20% were crying, and 20% were fearful. Examination of before and after intervention showed that heart rate and respiratory rate were significantly reduced ($P < 0.001$). There was a significant increase in arterial blood oxygen ($P < 0.001$).

Conclusion: According to the results of this study, intranasal midazolam is effective and safe in controlling spells in patients with TOF.

Cite this article:

Riahi K, Najibi B, Razmara M. Efficacy of Intranasal Midazolam in Cessation of Hypercyanotic Spells in Children with Tetralogy of Fallot. *Caspian J Pediatr* March 2023; 9: e16.



Introduction

Tetralogy of Fallot (TOF) is the most common form of cyanotic congenital heart disease [1]. It is characterized by abnormal morphologic features including absent or rudimentary pulmonary valve leaflets, severe pulmonary valve incompetence, annular pulmonary stenosis, dilatation of the pulmonary arteries (PA) [2,3], large ventricular septal defect, biventricular origin of the aortic valve and concentric right ventricular hypertrophy. These abnormalities decrease lung blood flow, followed by hypoxia and cyanosis [1,4].

Hypercyanotic spells are one of the major complications of TOF which call for a prompt intervention to resolve hypoxic conditions [1]. The exact mechanism of cyanotic spells is not known, but possible mechanisms of these spells include hyperpnoea, peripheral vasodilatation and right ventricular mechanoreceptor stimulation [5]. Treatment of hypercyanotic spells involves calming the child down through pain and anxiety relief [6]. Various medications have been advocated to reduce anxiety and facilitate the separation of children from parents. The ideal premedicant in children should be easy to accept, fast, and reliable with minimal side effects [7,8]. One of the most common medications used to sedate children is Midazolam [9]. The aim of this study was to evaluate the efficacy of intranasal midazolam in controlling hypercyanotic spells in TOF children.

Methods

Design and participants

This semi-experimental study was conducted on 10 TOF children, referred to the Pediatric Emergency Department of Golestan Hospital, Ahvaz, southwest of Iran from November 2017 to October 2018. TOF children under 6 years of age were included in the study after informed consent was obtained from them and their parents. Patients were excluded if they had a runny nose or upper respiratory tract infection, or required emergency surgery. The study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences and was carried out in accordance with the Declaration of Helsinki.

Data collection

At the outset of admission, measurement of heart rate, respiratory rate, blood pressure as well as pulse oximetry was done by residents of pediatrics in case the child was not restless. The child was then knee-chest positioned by the mother, and if the spells were not resolved, 0.2 mg intranasal midazolam prescribed by a pediatrician was introduced into the nasal cavity. Three minutes after the child's recovery, the same measurements were repeated, and after the child's relief, an intravenous therapy line was set up. Sedation level, mood changes, reaction to separation from mother, oxygen mask acceptance, venipuncture, recovery after sedation, and side effects were assessed in all patients.

Statistical analysis

Data were analyzed by SPSS 17. The data were reported using descriptive statistics including mean, standard deviation, frequency, and frequency percentage. Paired t-test was used to analyze the data. Wilcoxon test was used if the variable conversion did not result in normalization of the data.

Results

Of the 10 patients studied, 6 (60%) were boys and 4 (40%) were girls. The age of patients ranged from 6 months to 3.5 years with a mean age of 1.66 ± 0.98 years (Table 1). Sixty percent of the children were in recovery, 20% were crying, and 20% were fearful. At the time of separation from their mothers, 70% were calm and 30% were crying. While receiving the mask, 70% were calm and 30% were crying. In terms of sedation level, 80% were calm and 20% were agitated. The mean heart rate was 137/min before the intervention, and 110.5/min after the intervention, which decreased significantly by 26.5 units ($P < 0.001$). The mean respiratory rate before and after the intervention was 68.5 and 48.5 minutes, respectively, which was significantly reduced by 20 units ($P < 0.001$). Mean arterial blood oxygen content was 45% and 61.5% before and after the intervention, respectively, indicating a significant increase of 16.5 units ($P < 0.001$) (Table 2). No side effects were observed.

Table 1. Demographic information of the studied patients

Variable	N (%)±SD
Age (y)	1.66±0.98
Male/Female	6 (60)/4(40)
Duration of masking (min)	9.6±2.87
Duration of recovery (min)	45.5±9.55

Table 2. Clinical findings before and after intervention

Variable	Before (mean ± SD)	After (mean ± SD)	P- value
Heart Rate (per min)	137±18.28	110.5±17.39	<0.001*
Respiratory Rate (per min)	68.5±8.51	48.5±11.55	<0.001
Arterial Blood Oxygen (%)	45±8.16	61.5±9.73	<0.001

* Paired t-test

Discussion

This study showed intranasal midazolam is effective and safe in controlling spells in patients with TOF. Hypercyanotic spell is a pediatric cardiac emergency [10]. Patients suffering from TOF usually develop the spells prior to going to the hospital and require prompt intervention. In addition, venipuncture in these patients is difficult and may worsen the spells. Therefore, the aim of this study was to evaluate the effect of intranasal midazolam on controlling spells in children with hypercyanotic TOF. The reason why midazolam was used in the current study was twofold. First, midazolam is usually available and easy to administer. Second, it has a greater anxiolytic effect and a faster reaction speed compared to other benzodiazepines [11, 12]. Because of its rapid effectiveness and improved cardiopulmonary function, this drug is also applied in cardiac operations, and it is one of the most common medications used to sedate children.

In the present study, midazolam was used intranasally. In this way, midazolam rapidly passes through the nasal mucosa and blood-brain barrier, increasing the concentration of this drug in plasma and cerebrospinal fluid [13]. In studies, both nasal drops and nasal spray have been used to penetrate nasal mucus, but nasal spray covers a larger area of the nasal mucosa, penetrates better through the nasal mucosa, and has a better sedative effect [9, 14]. Intranasal midazolam is used in a wide range of surgeries and for inducing sleep in seizure patients whose peripheral veins are inaccessible.

According to the results of the ongoing study, intranasal midazolam administration in children with TOF spells significantly reduced heart rate and respiratory rate. Further, it increased the children's arterial blood oxygen level and their acceptance of the mask. A number of studies have examined the effect of midazolam on TOF spells. Montero et al., for example, evaluated the efficacy of intranasal midazolam in controlling spells in a 2-month-old baby with TOF and concluded that the drug increased concomitant systemic hypertension and possibly decreased systemic vascular tone by providing appropriate sedation in the patient and by increasing pulmonary flow [11]. Other studies investigated and compared the effect of intranasal midazolam and ketamine [8, 15]. Some researchers reported no significant difference between the midazolam+ketamine group and intranasal midazolam group in terms of heart rate, respiratory rate, and blood oxygen concentration. They argued that although the two parameters of sedation and calmness were significantly better in the midazolam+ketamine group, intranasal midazolam, like midazolam and ketamine combined, produced a good level of sedation, causing the children to calm down [15]. Others have generally considered ketamine as a better alternative to midazolam, reporting good sedation for midazolam and excellent sedation for ketamine [8]. Thus, these studies, like ours, confirm the establishment of a good sedation level by intranasal midazolam in TOF patients. Therefore, intranasal midazolam ampoule

can be useful in controlling spells in patients with TOF. The present study focused only on intranasal midazolam, so further studies are needed to compare the effects of midazolam and ketamine.

According to the results of the current study, intranasal midazolam was not associated with adverse events. Other studies have also reported no adverse effects of nasal spray, and the most common side effect of intranasal midazolam has been its bitter taste for 30 to 45 seconds. Overall, many studies have shown that midazolam is a safe compound. It has no adverse effects on the cardiovascular system and does not suppress the respiratory system. It enters the cerebrospinal fluid and does not pass through the liver [7, 8, 16, 17].

Limitations of the study

Since there were no other groups in our study that received another drug for comparison, it is better to design a study with a larger sample size comparing the efficacy of intranasal midazolam ampoule with another drug in controlling the spells in patients with TOF.

Conclusion

According to the results of this study, administration of intranasal midazolam to children with TOF spells resulted in significant relaxation, reduction in heart rate, improvement in arterial blood oxygenation, and increased acceptance of the mask by the children. It was also not associated with side effects. Therefore, intranasal midazolam can be considered an effective and safe drug for controlling spells in patients with TOF.

Acknowledgments:

This paper was excerpted from the dissertation of a pediatric resident. This manuscript was financially supported by a grant (U-96089) from the Vice Chancellor for Research Affairs, Ahvaz Jundishapur University of Medical Sciences.

Ethical approval

Ethical approval was obtained from the Research Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (IR.AJUMS.REC.1396.500).

Funding

This paper was financially supported by a grant (U-96089) from Ahvaz Jundishapur University of Medical Sciences.

Conflict of interest

There is no conflict of interest.

References

- Hayes-Lattin M, Salmi D. Educational Case: Tetralogy of Fallot and a review of the most common forms of congenital heart disease. *Acad Patho* 2020; 3: 7: 2374289520934094.
- Verma M, Pandey NN, Ojha V, et al. Evaluation of cardiovascular morphology and airway-related abnormalities in tetralogy of fallot with absent pulmonary valve syndrome on multidetector computed tomography angiography. *J Card Surg* 2021; 36(8): 2697-704.
- Escalon JG, Browne LP, Bang TJ, et al. Congenital anomalies of the pulmonary arteries: an imaging overview. *Br J Radiol* 2019; 92(1093): 20180185.
- Song MS, Hu A, Dyamenahalli U, et al. Extracardiac lesions and chromosomal abnormalities associated with major fetal heart defects: comparison of intrauterine, postnatal and postmortem diagnoses. *Ultrasound Obstet Gynecol* 2009; 33(5): 552-9.
- Duro RP, Moura C, Leite-Moreira A. Anatomophysiologic basis of tetralogy of Fallot and its clinical implications. *Rev Port Cardiol* 2010; 29(4): 591-630.
- Park MK. *Pediatric Cardiology for Practitioners*. 5th ed. Philadelphia, PA: Elsevier. PLoS One. 2007; pp: 235-48.
- Audenaert SM, Wagner Y, Montgomery CL, et al. Cardiorespiratory effects of premedication for children. *Anesth Analg* 1995; 80(3): 506-10.
- Gharde P, Chauhan S, Kiran U. Evaluation of efficacy of intranasal midazolam, ketamine and their mixture as premedication and its relation with bispectral index in children with tetralogy of fallot undergoing intracardiac repair. *Ann Card Anaesth* 2006; 9(1): 25-30.
- Lane RD, Schunk JE. Atomized intranasal midazolam use for minor procedures in the pediatric emergency department. *Pediatr Emerg Care* 2008; 24(5): 300-3.

10. Yates MC, Rao PS. Pediatric cardiac emergencies. *Emerg Med* 2013; 3: 164.
11. Montero JV, Nieto EM, Vallejo IR, Montero SV. Intranasal midazolam for the emergency management of hypercyanotic spells in tetralogy of Fallot. *Pediatr Emerg Care* 2015; 31(4): 269-71.
12. Hardmeier M, Zimmermann R, Ruegg S, et al. Intranasal midazolam: pharmacokinetics and pharmacodynamics assessed by quantitative EEG in healthy volunteers. *Clin Pharmacol Ther* 2012; 91(5): 856-62.
13. Wermeling DP, Record KA, Kelly TH, et al. Pharmacokinetics and pharmacodynamics of a new intranasal midazolam formulation in healthy volunteers. *Anesth Analg* 2006; 103(2): 344-9.
14. Senzaki H, Ishido H, Iwamoto Y, et al. Sedation of hypercyanotic spells in a neonate with tetralogy of Fallot using dexmedetomidine. *J Pediatr (Rio J)* 2008; 84(4): 377-80.
15. Khatavkar SS, Bakhshi RG. Comparison of nasal Midazolam with Ketamine versus nasal Midazolam as a premedication in children. *Saudi J Anaesth* 2014; 8(1): 17-21.
16. Holsti M, Sill BL, Firth SD, et al. Prehospital intranasal midazolam for the treatment of pediatric seizures. *Pediatr Emerg Care* 2007; 23(3): 148-53.
17. Whitfield D, Bosson N, Kaji AH, Gausche-Hill M. The Effectiveness of Intranasal Midazolam for the Treatment of Prehospital Pediatric Seizures: A Non-inferiority Study. *Prehosp Emerg Care* 2022; 26(3): 339-47.