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Premedication with Oral Midazolam Suppress Fentanyl- Induced Cough in Children: A Randomized Double-Blind Trial

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ABSTRACT

Background: Fentanyl administration is associated with fentanyl-induced cough (FIC), which can be distressing for both the patient and the medical team. Midazolam has a bronchodilator action on the smooth muscle of the airway.

Aim: This study aims to study the efficacy of different oral midazolam doses in controlling FIC in children.

Methods: A total of 120 children who underwent elective surgeries with orotracheal intubation (OTI) were involved in this randomized, double-blind, controlled study. Cases were randomized equally into three groups. Group C (control group) – received plain oral solution prepared by a pharmacist who did not participate in the study. Group MID 0.5 mg/kg – received 0.5 mg/kg of oral midazolam solution. Group MID 0.7 mg/kg – received 0.7 mg/kg of oral midazolam solution.

Results: Incidence of cough was 39 (97.5%) in control group, 36 (90%) in MID 0.5 mg/kg group, and 15 (6%) in MID 0.7 mg/kg group with statistically significant differences among the three groups ($p < 0.001$). The onset of cough was insignificantly different between the three groups ($p > 0.05$). Severity of cough was significantly different among the groups, with severe cases more predominant in control group followed by Group MID 0.5 while no cases suffered severe cough in Group MID 0.7 ($p < 0.001$).

Conclusions: Premedication with 0.7 mg/kg oral midazolam was superior to 0.5 mg/kg oral midazolam and placebo in suppressing FIC as evidenced by lower incidence and severity of FIC in children who underwent elective surgeries with OTI.

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1. Introduction

General anesthesia is frequently associated with certain adverse events in the sympathetic nervous system and psychological well-being [1]. A selective μ-opioid receptor agonist known as fentanyl is frequently used to induce general anesthesia due to its benefits, including fast onset with a brief duration, strong analgesia, cardiovascular safety, and low histamine secretion [2]. Nevertheless, a known adverse effect of the use of fentanyl is the occurrence of fentanyl-induced cough (FIC), which can be distressing for both the patient and the medical team [3].

In 18% to 65% of cases, bolus fentanyl injection is frequently followed by FIC [4]. In order to lessen this adverse effect, which could be accompanied by intracranial high blood pressure, cerebral or aortic aneurysms, elevated intraocular or intra-abdominal pressure, pneumothorax, or abnormal airway conditions, numerous studies have been conducted [4,5]. It had been reported that childhood is one of the most significant risk factors for the development of FIC [6,7]. Thus, finding a suitable intervention for FIC is critical in children.

Midazolam is a benzodiazepine with sedative, anxiolytic, and amnesic properties, commonly used in pediatric anesthesia [8]. It acts by enhancing the inhibition of gamma-aminobutyric acid centrally, causing sedation and anxiolysis [9]. Pretreatment with a bronchorelaxant could greatly reduce the frequency of FIC [10]. Due to its bronchorelaxant action on airway smooth muscle, midazolam is commonly utilized for the induction of anesthesia [10,11].

Maximum plasma concentrations are attained within 30 min following orally administered midazolam possessing a rapid rate of absorption [12]. Midazolam has rapid plasma elimination rate with a half-life that is nearly identical to that determined following intravenous (IV) dosing, which is 2.3 h [13]. Heizmann et al. demonstrated that due to the significant proportion of midazolam extracted by the liver,

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the oral bioavailability of midazolam varied from 31% to 72% [13].

Although the effect of IV midazolam on FIC was previously investigated [10], data are limited about the optimum dose of oral route which is the most favored method due to its benefits, including patient compliance, noninvasiveness, and simplicity of drug administration in children. Therefore, this study's objective was to compare the efficacy of different doses of premedicated oral midazolam with placebo on the incidence and severity of FIC in children.

2. Materials and methods

Such a perspective, randomized, double-blinded study involved 120 cases aged from 1 to 10 years, both sexes, and American Society of Anesthesiologists physical status classification I or II who underwent elective surgeries with orotracheal intubation (OTI). The study was done from November 2022 to October 2023. The study was carried out at Benha University Hospitals.

Each patient's guardian provided written informed consent. The research was conducted after the approval of the Ethical Committee of Benha University Hospitals (approval code: RC.40.10.2022).

Exclusion criteria were hypersensitivity to medication, atrioventricular block, arrhythmias, heart failure, renal failure, and expected difficult OTI.

3. Randomization and blindness

Random numbers generated by a computer system were applied to randomly allocate 120 cases equally into three groups. Group C (control group) – received plain oral solution with the same content of Epistatus® but free from any medication prepared by a pharmacist who did not participate in the study. Group MID 0.5 mg/kg – received 0.5 mg/kg of midazolam oral solution (Epistatus®). Group MID 0.7 mg/kg – received 0.7 mg/kg of midazolam oral solution (Epistatus®). Sealed envelopes were used to ensure random allocation by a nurse who did not take part in the study. Patient's guardians and outcome assessors were blinded to the experimental medication. Drugs were prepared by an additional pharmacist who did not join in the remaining phases of trial. All syringes containing oral solution were sealed by aluminum foils that are identical in appearance.

4. Interventions

Thirty minutes before induction of anesthesia, patients received the study intervention, either plain oral solution or 0.5 mg/kg or 0.7 mg/kg midazolam oral solution according to the allocation group. All patients received IV fentanyl at the dose of 2 mic/kg inside the operating room.

5. Outcomes

The incidence of cough was chosen as the primary outcome for the studied groups. Secondary outcomes were cough onset and severity. There were three classifications of cough severity [14], depending on the number of produced coughs (mild, 1–2; moderate, 3–4; and severe, ≥5). The severity of cough was documented for 2 min after fentanyl injection.

After fentanyl administration, assisted mask with oxygen was administered to patients with SpO_2 below 95%, apnea, and/or muscular stiffness. A 15-s or longer stoppage in breathing is the definition of apnea. Muscle rigidity was understood to be a muscle tone that made breathing difficult or impossible. Lastly, propofol 2 µg/kg and atracurium 0.5 mg/kg were administered to induce anesthesia, and isoflurane 1.3% and a combination of oxygen and air (50% for each) were applied for anesthesia maintenance.

6. Sample size calculation

The sample size determination was done using G*Power 3.1.9.2 (Universitat Kiel, Germany). Based on a previous study [14], the incidence of FIC in placebo group was 54.5%. Assuming that 0.5 mg/kg oral midazolam will decrease the incidence of FIC to 26%, the estimated sample size should be $N > 36$. To overcome dropouts, four patients were added to each group; hence, we enrolled 40 cases in each group.

7. Statistical analysis

SPSS v28 (IBM©, Armonk, NY, USA) was used for statistical analysis. Using the Shapiro–Wilk test and histograms, the data normality distribution was tested. As mean and standard deviation (SD), quantitative parametric data were expressed and were analyzed by ANOVA test among the three groups with post hoc (Tukey) test to compare each two groups. Qualitative variables were presented as frequency and percentage (%) and analyzed by chi-square or Fisher's exact test when applicable. A two-tailed P value <0.05 was judged to be statistically significant.

8. Results

In this trial, 153 cases were evaluated for eligibility; 24 cases did not match the criteria and nine cases refused to join the trial. The residual 120 cases were allocated randomly into three groups in a parallel manner and allocation ratio of 1:1 (40 cases in each). All allocated cases were monitored and statistically analyzed (Figure 1).

Age, sex, weight, baseline heart rate, and SpO_2 were matched among the three studied groups (Table 1).

Incidence of cough was 39 (97.5%) in control group, 36 (90%) in MID 0.5 mg/kg group, and 15 (6%%) in MID

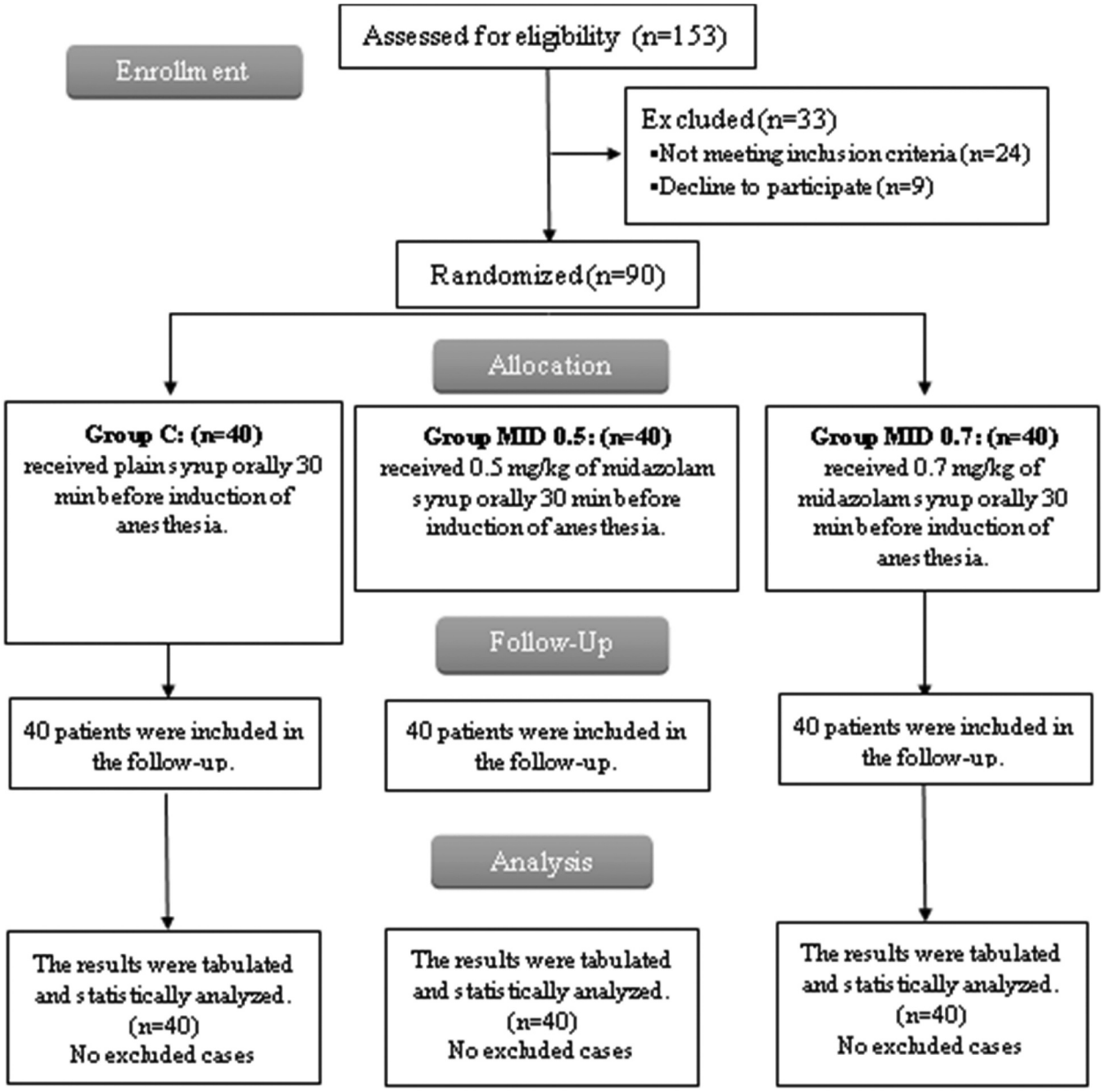

Figure 1. CONSORT flowchart of the enrolled patients.

Table 1. Demographic data and baseline data of the studied groups.

		Group C ($n = 40$)	Group MID 0.5 ($n = 40$)	Group MID 0.7 ($n = 40$)	P value
Age (years)		4.39 ± 2.99	4.38 ± 2.67	5.00 ± 3.41	0.63
Sex	Male	17 (56.67%)	17 (56.67%)	16 (53.33%)	0.956
	Female	13 (43.33%)	13 (43.33%)	14 (46.67%)	
Weight (kg)		18.84 ± 7.96	20.53 ± 1.27	18.35 ± 7.11	0.47
Heart rate		123.78 ± 20.27	121.79 ± 9.15	124.24 ± 16.93	0.803
SpO_2		97.27 ± 1.52	124.32 ± 5.2	97.60 ± 1.72	0.07

Data are presented as mean ± SD or frequency (%), SpO_2: oxygen saturation.

0.7 mg/kg group, with significant difference among the groups ($p < 0.001$). The onset of cough was insignificantly different among the three groups ($p > 0.05$). The severity of cough was significantly different among the groups, with severe cases and more predominant in control group followed by Group MID 0.5, while no cases suffered severe cough in Group MID 0.7 ($p < 0.001$) (Table 2).

9. Discussion

FIC is commonly caused by fentanyl during the induction of general anesthesia, especially in pediatrics [14]. Fentanyl was classified as a cough-suppressant medicine due to its antagonistic effect on the mu receptor in the lung's periphery and inhibition of the cough center in the medulla oblongata's central region [15]. However,

Table 2. Incidence, onset, and severity of FIC in the studied groups.

		Group C ($n = 40$)	Group MID 0.5 ($n = 40$)	Group MID 0.7 ($n = 40$)	P value
Incidence of FIC		39 (97.5%)	36 (90%)	15 (6%)	0.001
Onset (seconds)		5.57 ± 2.87	6.9 ± 2.07	6.94 ± 2.95	0.99
Severity	Mild	10 (25%)	30 (75%)	38 (95%)	0.001
	Moderate	2 (5%)	8 (20%)	2 (5%)	
	Severe	28 (70%)	2 (5%)	0%	

Data are presented as mean ± SD or frequency (%).

paradoxically, it commonly induces coughing shortly after its administration [3]. FIC's precise mechanisms have not been exactly elucidated. However, there are several suggested mechanisms, including pulmonary chemoreflex: FIC may be regulated by irritant receptors or vagal C-fiber receptors (juxta-capillary receptors). These receptors may trigger a cough reflex when stimulated [16]. Also, fentanyl-induced constriction of the tracheal smooth muscle leads to triggering of pulmonary mucosal irritant receptors and cough induction [3]. Also, fentanyl may cause the production of histamine by the mast cells in the lungs, which can induce cough [17]. In addition, muscle rigidity generated by fentanyl can cause abrupt adduction of the vocal cords or supraglottic blockage by soft tissue, resulting in cough [18].

Our study evaluated for the first time the effect of different doses of premedication with oral midazolam on FIC in children. Our results revealed that the incidence and severity of FIC were dose dependent as 0.7 mg/kg of oral midazolam exhibited the least incidence of cough and lowest frequency of cases suffered from severe cough compared to 0.5 mg/kg and control groups.

The appropriate mechanism through which midazolam could prevent cough is not well recognized but may be attributed to the fact that midazolam has a bronchorelaxant effect on airway smooth muscles [10]. Midazolam may indirectly help alleviate cough by promoting relaxation and sedation. Also, during medical procedures, midazolam is often used to induce sedation and amnesia. By reducing the patient's awareness and memory of the procedure, midazolam may help prevent the anticipatory anxiety and cough reflex triggered by medical interventions [19]. Also, midazolam is known for its anxiolytic properties, which help reduce anxiety and promote relaxation and thus may indirectly contribute to cough prevention [20].

Our results are supported by Biro et al. [21], who examined the psychological impacts, well-being, and adverse consequences of various oral midazolam dosages and reported that sedation and amnesia were dose dependent. The suggested oral dosage of midazolam for emergency procedures is 0.5–0.7 mg/kg [22].

The pharmacokinetic findings of midazolam indicated a high bioavailability and consistent plasma concentrations, with the maximum plasma concentration occurring 30 min after buccal administration [12]; thus, we administered drugs 30 min before induction.

Oral midazolam was reported to give a better effect in preoperative sedation than oral diazepam [23]. Our study gave consistent results with Gecaj-Gashi et al. [16] who concluded that IV lidocaine can control FIC in children. Lidocaine is also used for sedation, analgesia, and the suppression of hyperalgesia [24], which supports the FIC suppression by midazolam. We also agree with Yu et al. [10] as they concluded that FIC could be totally suppressed by IV dexmedetomidine–midazolam.

Limitations: The trial was conducted in a single center with a relatively short follow-up period. Thus, further large-scale multicenter collaboration studies and longer monitoring duration are necessary to validate our findings.

10. Conclusions

It is concluded that premedication with 0.7 mg/kg oral midazolam was superior to 0.5 mg/kg oral midazolam and placebo in suppressing FIC as evidenced by lower incidence and severity of FIC in children who underwent elective surgeries with OTI.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Author contributions

All authors participated in preparing this clinical trial and approved of the work as it is being submitted. All authors read and approved the final manuscript.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

This study was performed in line with the principles of the Declaration of Helsinki. Each patient provided written informed consent. The research was performed after the approval of the Ethical Committee of Benha University Hospitals (approval code: RC.40.10.2022).

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