Comparison between Buccal Midazolam versus Intranasal Dexmedetomidine Plus Oral Chloral Hydrate in Reducing Parental Separation Anxiety in Children Undergoing Inguinal Hernia Repair: A randomized Clinical Trial

Ramy Mousa Saleh[a]*, Amany Nagah Fekry[a], Mona Sobhy Emara[a]

[a]Anesthesia and Surgical ICU Department, Faculty of Medicine, Benha University, Benha 13511, Egypt.

Abstract

Background: Inguinal hernia repair is the most common surgical treatments among infants. Preoperative anxiety remains challenging concern, affecting around 50% of pediatric patients.

Objectives: The purpose of the current research was to assess whether a combination of intranasal dexmedetomidine and oral chloral hydrate induces more effective in sedation compared to buccal midazolam in children undergoing inguinal hernia repair.

Patients and methods: This randomized double blinded clinical trial included 80 children aged 2 to 7 years, both sex, American Society of Anesthesiology I and Π scheduled for inguinal hernia repair. They were allocated randomly two equal categories; group A: received buccal midazolam at 0.1 mg/ kg mixed with simple syrup, intranasal normal saline drops & oral placebo syrup, and group B: received intranasal dexmedetomidine at 2 µg/kg, oral chloral hydrate at 50 mg /kg, & buccal normal saline. All patients underwent general examination of chest, heart, abdomen and vitals as well as laboratory examinations.

Results: There was a significant difference between both groups regarding the Parental separation anxiety scale (PSAS) score (P<0.001), PSAS scores of "1 point" and "2 points" represented 82.5% of the total (33 patients) in the group A, and represented 95 % of the total (38 patients) in the group B. A Most of the children in the two groups "successfully separated from their parents."

Conclusion: In children undergoing inguinal hernia repair, combination of intranasal dexmedetomidine plus oral chloral hydrate provide significant sedation than buccal midazolam, as provided better sedation, easier parental separation and mask acceptance.

Keywords: Dexmedetomidine; Chloral Hydrate Midazolam; Inguinal hernia repair; Children ; Parental Separation Anxiety.

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***Correspondence**: ramymousa455@gmail.com

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Introduction

In early infancy, inguinal hernia surgery is among the most frequent surgical procedures **(O'Brien et al., 2021)**. Preoperative anxiety remains a challenging matter, affecting around 50% of pediatric patients **(Friedrich et al., 2022; Fronk and Billick, 2020)**. Additionally, the induction of anesthesia via inhalation is the most distressing time a kid may endure throughout the perioperative phase **(Lang et al., 2017)**. Untreated adverse clinical outcomes are most probable in children undergoing surgery who exhibit severe anxiety or have undergone a rough inhalation induction of anesthesia. These children had a high risk of developing negative clinical consequences and intraoperative long-term postoperative sleep disturbances, hemodynamic changes, anesthesia emergence delirium and abnormal cardiac excitability **(Dave, 2019)**.

Sedative medication is the prevailing approach utilized to reduce distress in pediatric patients before their admission to operation. This method enables the children to be sedated effectively**(Wang et al., 2020a)**. Premedication has been widespread with midazolam, a sedative, hypnotic, anxiolytic, and compliant amnestic drug. Its bad effects include paradoxical reactions, cognitive impairment, respiratory depression, and postoperative behavioral problems. Hence, in comparison to ketamine, dexmedetomidine, propofol, fentanyl, and midazolam has a decreased efficacy in mitigating postoperative irritability **(Amorim et al., 2017)**.

Chloral hydrate is a frequently administered sedative for young children undergoing imaging examinations due to its high success rate **(Chen et al., 2017)**. Significant post-discharge side effects of chloral hydrate sedation include vomiting, unsteadiness, hyperactivity, and tiredness for more than four hours. Within four hours following discharge, regular activity is not resumed in 54% of the children **(Lian et al., 2020)**. Dexetomidine is an alpha-2 agonist with exceptional selectivity. Similar to regular non-rapid eye movement sleep, it produces sedation while conserving respiratory effort for pediatric sedation. For the purpose of inducing anesthesia in children, sedation can be achieved via intravenous or intranasal administration at a dosage of 1-2 µg/kg. With a significantly shorter half-life than chloral hydrate, dexmedetomidine has a more favorable recovery profile **(Zhang et al., 2023)**.

The hypothesis of this paper is to compare between combination of intranasal dexmedetomidine and oral chloral hydrate than buccal midazolam induces more effective sedation in pediatric patients undergoing inguinal hernia surgery.

Patients and methods

This pilot randomized double blinded clinical trial was carried out on eighty children aged 2 to 7 years, of both sex, American Society of Anesthesiology (ASA) I and Π scheduled for inguinal hernia repair. The patients' parents provided informed written consent before participating in the study. The research was conducted after the approval guidelines of the Institutional Ethical Committee of Benha University Hospitals (Approval code: RC 29-11-2023) and registered on clinical trials (NCT06389318) in the duration from March 26, 2023 to April 24, 2024. This manuscript adheres to the CONSORT guidelines.

Children diagnosed with the subsequent conditions may be excluded from the study: refusal to participate, sensitivity to dexmedetomidine or midazolam, upper respiratory tract infection, severe liver or kidney disease, organ dysfunction, congenital heart disease or cardiac arrhythmia, and mental retardation.

Randomization and blindness: Eighty children were allocated randomly by

a computer-generated sequence through sealed opaque envelopes into two equal categories. Both supervisor and the care-provider in this trial were blinded.

Group A (40 patients): A placebo syrup was administered orally to the children, intranasal 0.03 ml/kg of 0.9% normal saline, and buccal midazolam 0.1 mg/kg combined with simple syrup. For buccal administration, buccal midazolam was dripped in both sides of buccal mucosa by tuberculin syringe. Since The syrup used was very sticky, the drug tended to adhere and remain in mucosa. The final volume of buccal medication was 0.05 mL/ kg.

The intravenous formulation of midazolam (Midathetic, 5mg/ml ,1ml ampoule, Amoun company, Egypt) 5 mg /mL was mixed with 0.1-0.4 mL of simple syrup.

Group B (40 patients): Children were administrated oral chloral hydrate (Chloral Hydrate mixture, at a dosage 0.5gm/5ml, 250 ml bottle, prepared at abo Elreesh pharmacy, Elmoneerah, Egypt) at 50 mg /kg, additionally the were administrated intranasal dexmedetomidine at 2 μg/kg and buccal normal saline. A concentration of 100 μg/mL of dexmedetomidine used was as preservative-free dexmedetomidine (Precedex, 2ml ampoule,100 ug /ml, Hospira, Inc, Rocky Mount, USA). The children were administered the drug intranasal, while lying in a recumbent position. It was recommended that the youngster sustain this posture for a duration of 1.2 minutes to maximize the penetration of the drug.

Each patient underwent a preoperative evaluation including medical history and performing a thorough clinical assessment general as examination of the patient's abdomen, chest, heart, and vital signs, and laboratory investigations included complete blood counts and kidney function tests, as well as a. Children fasted for at least 2 h for clear fluid, 4h for unclear fluid and 6h for solid prior to anesthesia. The parents are present in the preoperative holding area 30 min before surgery children had premedication. The infant was placed in the recumbent position as a 1/mL of tuberculin syringe was administrated intranasally into both nostrils.

Ramsay sedation score (RSS): The evaluation of criteria was scored according to the following: (1) signs of anxiety and restlessness on patient; (2) cooperation, orientation, and quietness ere exhibited by the patient; (3) the patient complied with instructions; (4) somnolence was accompanied by responsiveness to loud auditory stimuli or glabellar tapping; (5) somnolence was accompanied by no responsiveness to loud auditory stimuli or glabellar tapping; and (6) somnolence was accompanied by no responsiveness response. RSSs were recorded immediately prior to dosing as well as 10, 20, and 30 minutes after dosing **(Rasheed et al., 2019)**. Parents were granted the privilege of remaining with their children at all times. Upon determining that a child had been sufficiently sedated using the parental separation anxiety scale, the youngster would be moved to the surgery room.

Parental separation anxiety scale (PSAS): Anxiety score was determined when the child was separated from the parents according to four levels: (1) crying loudly and holding the parents and not willing to let them go easy to separate; (2) crying loudly and difficult to stop but still holding the parents and not letting them go (3) sobbing easily ceasing; and (4) PSAS scores of 1 and 2 were considered “successful separation from parents (**Anupriya and Kurhekar, 2020**). In both groups, the count of children who achieved "successful separation from their parents" was documented. After 30 minutes after administering study medicines, all the

children were taken to the operation room, where they were all connected with pulse oximetry, ECG, and non-invasive blood pressure monitors. Induction of anesthesia intravenously was achieved using 0.5 mg/kg propofol and 1.0 mg/kg atracurium. Following the insertion of a cannula, sevoflurane and 100 percent oxygen were achieved to induce anesthesia via inhalation. All patients received fentanyl 1ug/kg intraoperative. The airway was maintained with endotracheal tube throughout the operation. Sevoflurane and 60% nitrous oxide in oxygen were used to maintain anesthesia; intermittent atracurium was administered to maintain muscle relaxation. Following the initiation of anesthetic administration, the surgical procedure was carried out as planned. At the end of the operation, all patients underwent extubation, muscle relaxant reversal, and were transferred to the PACU.

Mask acceptance scale (MAS): On four scales, the anesthesiologist's presentation of MAS was evaluated: Very good (1 point) **(**not afraid, cooperative, easy to accept the mask)**;** good (2 points) (slight fear of mask, comfortable); moderate (3 points) (moderate fear of mask, difficult to calm through comfort); and poor (4 points) (afraid, crying or struggling) **(Qiao et al., 2022)**. Satisfactory mask reception behavior was defined as both "score 1" and "score 2" in this study; Selected individual for each group was the number of children who obtained "satisfactory" scores. Patients were extubated after surgery. Following administration of the reversal medication (atropine plus neostigmine), the children were transferred to the PACU while in the recovery posture. The duration of time required to be discharged from the PACU was documented.

Outcomes to be measured: The primary endpoint was PSAS during anesthetic induction. The secondary endpoints were Mean arterial blood pressure (MAP), heart rate (HR), and arterial oxygen saturation (SpO2) were measured at 15 minutes, 30 minutes, and 45 minutes at perinduction and end of operation. The time to discharge from the PACU, the RAS score, the MAS, and adverse effects of the medications under study were all assessed.

Sample size: The G*Power 3.1.9.2 software package was utilized for determination of sample size (Universitat Kiel, Germany). As anticipated, we conducted a pilot study (10 cases in each group) to determine whether Dexmedetomidine was more effective than chloral hydrate at achieving successful parental separation (60 percent versus 90%). The proportion of the sample was determined by the following factors: The study's power was 80%, the effect size was 0.99%, the confidence interval was 95%, the group ratio was 1:1, and eight cases were added to each group in order to account for attrition. As a result, forty patients were recruited for each group.

Statistical analysis

We used SPSS v28 to examine the data (IBM Inc., Armonk, NY, USA). Unpaired Student's t-test was used to analyze the quantitative variables which were represented by means ± SD. To examine the qualitative variables, which were given as percentages or frequencies, Chi-square test or Fisher's exact test “when appropriate” was employed. A paired sample t-test was utilized for comparison between the means of two correlated samples. When the two-tailed P value was less than 0.05, it was considered statistically significant.

Results

In this study, 117 patients were evaluated for eligibility, 14 patients refused to participate and 23 patients did not meet the criteria. The remaining 80 patients were randomly allocated into 2 equal groups. All allocated

patients were followed-up and statistically analyzed, **(Fig.1).**

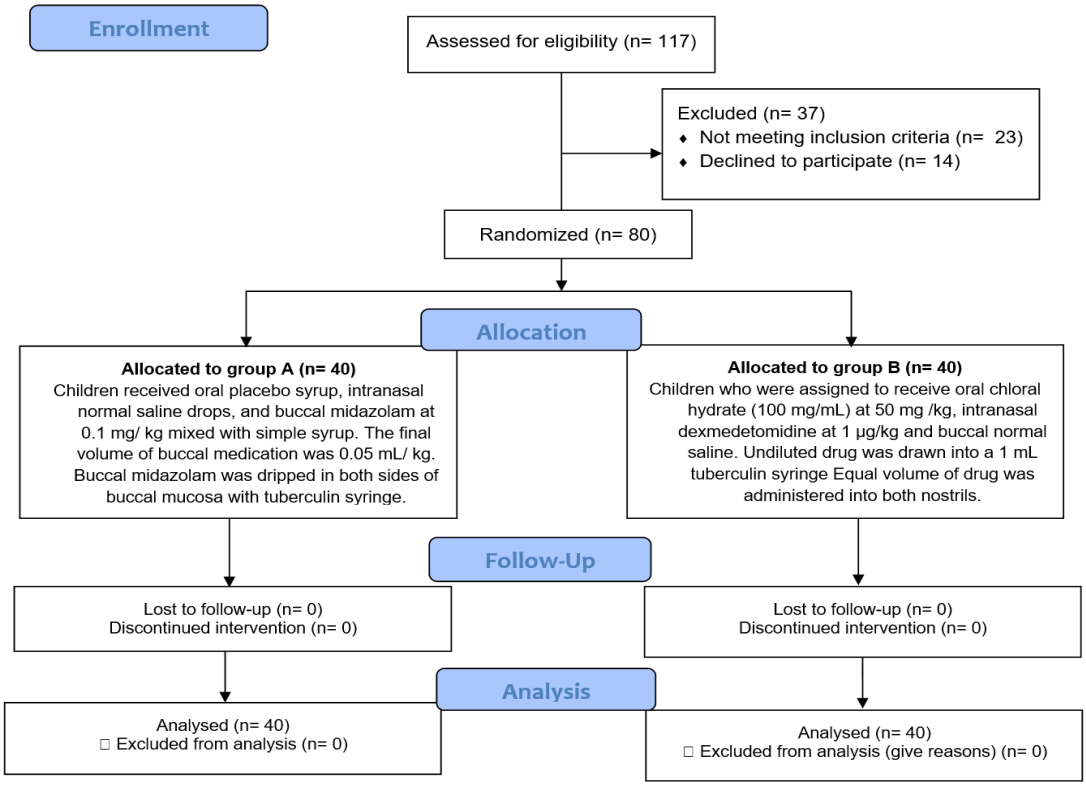

Fig. 1. CONSORT flowchart of the enrolled patients

There was an insignificant difference between both groups regarding the baseline characteristics and duration of surgery, **(Table.1).** Group B showed a significantly lower HR and MAP at 15, 30, 45 min and at the end of surgery compared to group A ($P<0.05$), while premedication HR and MAP were comparable between both groups, **(Table. 2).**

Table 1. Baseline characteristics and duration of surgery of the studied groups

Variables		Group A (n=40)	Group B (n=40)	P value
Age (years)		4.2 ± 1.65	4.3 ± 1.85	0.849
Sex	**Male**	22 (55%)	15 (37.5%)	0.178
	Female	18 (45%)	25 (62.5%)	
Weight (Kg)		22.8 ± 4.62	22.9 ± 4.28	0.980
Height (m)		1.3 ± 0.1	1.3 ± 0.11	0.584
BMI (Kg/m^2)		14.5 ± 3.31	14.98 ± 3.98	0.536
Duration of surgery (min)		46.1 ± 8.2	44.25 ± 8.1	0.314

Data presented as mean ± SD or frequency (%), BMI: body mass index.

Table 2. Heart rate and mean arterial pressure of the studied groups

Variables		Group A (n=40)	Group B (n=40)	P value
HR (beats/ min)	Premedication	88.7 ± 4.44	87.6 ± 5.02	0.292
	At 15 min	87.8 ± 9.64	84.1 ± 5.19	**0.035***
	At 30 min	82.1 ± 8.69	78.6 ± 5.35	**0.037***
	At 45 min	84.9 ± 4.3	80.7 ± 5.05	**<0.001***
	End of surgery	86.5 ± 4.6	83.9 ± 5.16	**0.018***
MAP (mmHg)	Premedication	73.98 ± 3.96	73.2 ± 3.37	0.349
	At 15 min	75.2 ± 4.88	71.9 ± 3.28	**0.001***
	At 30 min	73.98 ± 5.13	70.5 ± 2.41	**<0.001***
	At 45 min	75.13 ± 4.69	71.9 ± 3.58	**0.001***
	End of surgery	74.55 ± 5.29	71.6 ± 3.11	**0.003***

Data presented as mean ± SD, HR: heart rate, MAP: mean arterial pressure, *: statistically significant as P value <0.05.

(Table.3) shows that SPO_2 at all-time measurements (premedication, at 15, 30, 45 min and at the end of surgery) was insignificantly different between both groups.

Table 3.SPO_2 of the studied groups

Variables	Group A (n=40)	Group B (n=40)	P value
Premedication	97.5 ± 1.15	97.5 ± 1.13	0.922
At 15 min	97.65 ± 1.23	97.5 ± 1.06	0.439
At 30 min	97.6 ± 1.17	97.7 ± 1.1	0.768
At 45 min	97.63 ± 1.1	97.5 ± 1.24	0.704
End of surgery	97.55 ± 1.15	97.6 ± 1.05	0.762

Data presented as mean ± SD, SPO_2: oxygen saturation.

Regarding sedation, in both groups the vast majority of children were "successfully separated from their parents". There was a significant difference between both groups regarding the PSAS score (P<0.001), PSAS scores of "1 point" and "2 points" represented 82.5% of the total (33 patients) in the group A, and represented 95 % of the total (38 patients) in the group B. Moreover, group B showed a significantly better RSS than group A (P<0.001). Additionally, MAS was significantly better in group B compared to group A (P<0.001), showing higher satisfaction as MAS of "1" and "2" were considered "satisfactory" (90% in group B vs. 80.0% in group A), (**Table. 4).**

Table 4. Assessment of sedation of the studied groups by different scores

Variables		Group A (n=40)	Group B (n=40)	P value
PSAS score	1	3 (7.5%)	29 (72.5%)	**<0.001***
	2	30 (75%)	9 (22.5%)	
	3	5 (12.5%)	2 (2.5%)	
	4	2 (5%)	0 (0%)	
RSS	2	10 (25%)	2 (5%)	**<0.001***
	3	14 (35%)	2 (5%)	
	4	10 (25%)	12 (30%)	
	5	5 (12.5%)	11 (27.5%)	

	6	1 (2.5%)	13 (32.5%)	
Mask acceptance scale	**1**	6 (15%)	23 (57.5%)	**<0.001***
	2	26 (65%)	13 (32.5%)	
	3	4 (10%)	2 (5%)	
	4	4 (10%)	2 (5%)	

Data presented as number (%), PSAS: Parental separation anxiety scale, RSS: Ramsay sedation score, *: statistically significant as P value <0.05.

Regarding the adverse effects, bradycardia occurred in 1 (2.5%) case in group A and 3 (7.5%) cases in group B nausea and vomiting occurred in 2 (5%) cases in group A and in 5 (12.5%) cases in group B, and hypotension occurred only in 2 (5%) cases in group B. The adverse effects (nausea and vomiting, bradycardia, and hypotension) were comparable between both groups,(**Table. 5).**

Table 5.Adverse effects of the studied groups

Variables	Group A (n=40)	Group B (n=40)	P value
Nausea and vomiting	2 (5%)	5 (12.5%)	0.431
Bradycardia	1 (2.5%)	3 (7.5%)	0.615
Hypotension	0 (0%)	2 (5%)	0.494

Data presented as number (%), *: statistically significant as P value <0.05.

Discussion

Children may experience anxiety prior to surgery due to a variety of circumstances (e.g., A fear of physicians and syringe needles, parental separation, and unfamiliar environments), which may subsequently lead to suboptimal adherence to anesthetic induction **(Lööf et al., 2019)**. Hence, the tasks of pediatric anesthesiologists are to reduce the fear of children and enhance their adherence to anesthetic induction prior to operation **(Cai et al., 2021)**.

Dexmedetomidine, an alpha-2 adrenoceptor agonist known for its great selectivity, exerts its analgesic and anti-anxiety effects by Adrenergic receptor stimulation in the locus coeruleus. This action induces a condition of natural sleep **(Jannu et al., 2016; Feng et al., 2017)**. Intranasal dexmedetomidine has gained popularity due to its improved bioavailability and sedative properties **(Miller et al., 2018)**.

Numerous investigations have examined the administration and route of DEX. However, DEX route and dosage optimization research is ongoing still unknown. Yuen *et al.* demonstrated that 1 μg/kg dexmedetomidine nose drops before surgery induce a good sedative effect in 62% of children undergoing the operation **(Yuen et al., 2012)**. Li *et al.* he found that 0.2 mg/kg of midazolam nasal drops produced the same effect as 1.0 μg/kg of dexmedetomidine nasal drops 45 to 60 minutes prior to inducing paediatric anaesthesia **(Li et al., 2018a)**. Before operation, 2.0 μg/kg of dexmedetomidine was administered for sedation **(Talon et al., 2009)**.

Li *et al.* declared that It is recommended to administer dexmedetomidine nasal drops containing 2.0 μg/kg to children aged 5–8 years prior to induction of pediatric anesthesia. The increased sedative efficacy of the nasal drops was not accompanied by an increased prevalence of adverse effects **(Li et al., 2018b)**.

Regarding sedation, in both groups the vast majority of children were "successfully separated from their parents". There was a significant difference between both groups regarding the PSAS score (P<0.001), PSAS scores of "1 point" and "2 points" represented 82.5% of the total (33 patients) in the group A, and represented 95 % of the total (38 patients) in the group B. Moreover, group B showed a

significantly better RSS than group A (P<0.001). Additionally, MAS was significantly better in group B compared to group A (P<0.001), showing higher satisfaction as MAS of "1" and "2" were considered "satisfactory" (90% in group B vs. 80.0% in group A).

A randomized controlled trial by Li *et al.* analyzed one hundred sixty-two pediatric patients comparing oral chloral hydrate to intranasal dexmedetomidine plus buccal midazolam for auditory brainstem response testing. The findings indicated that 67 out of 82 children (69.5%) were sedated successfully with chloral hydrate, while 70 out of 78 children (89.7%) were sedated successfully using a combination of buccal midazolam and intranasal dexmedetomidine. The odd ratio (95%) estimated to be 3.84 (1.61-9.16), P= 0.002. Also, significantly, the combination of dexmedetomidine and midazolam resulted in a greater proportion of children attaining Narcotrend stage E (general anesthesia with deep hypnosis) than chloral hydrate (10 out of 37 [21.3%]; odd ratio (95% CI) of 2.50 (1.07–5.86), P = 0.035) **(Li et al., 2018b)**.

Yuen *et al.* compared between the premedication effects of oral midazolam and intranasal dexmedetomidine in the context of pediatric anesthesia research. The results indicated that children premedicated with 1 ug/kg of intranasal dexmedetomidine achieved more significant and satisfactory sedation during parental separation and anesthesia induction, in contrast to the patients who were administered oral midazolam. While children premedicated with 0.5 μg/kg dexmedetomidine were initially efficiently sedated, external stimulation was induced greater arousal in the children. Thus, it is possible that the 0.5 μg/kg dose is insufficient for children. Subgroup analysis found that intranasal dexmedetomidine appeared to induce greater sedation in children aged 2 to 5 years. Nevertheless, the absence of a significant sedative effect observed with intranasal dexmedetomidine in the age ranges of 6–9 and 10–12 may be attributed to an insufficient sample size. Therefore, they investigated the dose of 2 μg/kg of intranasal dexmedetomidine. The effects of 2 g/kg intranasal dexmedetomidine were examined. According to their behavior scale, the outcomes of this study indicate that children who were administered intranasal dexmedetomidine and oral midazolam exhibited comparable behavior upon separation from their parents and induction of anesthesia. While the administration of oral midazolam did not induce significant drowsiness in the participants, it might have had significant anxiolytic and/or amnesic effects. Furthermore, the potential anxiolytic effect of intranasal dexmedetomidine associated with sedation remains unknown **(Yuen et al., 2008)**.

By using established anxiety instruments, such as the modified Yale Preoperative Anxiety Scale, it becomes possible to evaluate the impact of premedication on anxiety levels in children and distinguish between sedative and anxiolytic effects **(Kühlmann et al., 2019)**.

In contrast to other sedatives, dexmedetomidine induces sedation in which children may experience increased arousal and cooperation. Although these children were heavily sedated at the time of parental separation, several of them became disturbed when aroused at the induction of anesthesia after being premedicated with dexmedetomidine. It may be necessary to modify the anesthetic technique to provide optimal conditions for induction in children who are sedated with dexmedetomidine. **(Leister et al., 2022)**.

Wang *et al.* By Applying RSS to determine the ideal level of sedation in children, we discovered that with an RSS of two or three, the children are able to

maintain their cooperation, consciousness, orientation, and silence **(Wang et al., 2020a)**. Jun *et al.* It was that 30 minutes prior to surgery, oral injections of 0.5 mg/kg midazolam and 2 μg/kg dexmedetomidine resulted in satisfactory acceptance of the mask and allowed for the child to be separated from their parents **(Jun et al., 2017)**.

Wang *et al.* study agreed with the results of the study by Jun *et al.* **(Wang et al., 2020a; Jun et al., 2017)**. In both groups, RSSs exhibiting sedation levels ranging from 2 to 3 demonstrated suitable outcomes with regard to parental separation and mask acceptability.

Faritus *et al.* found that during congenital heart disease surgery, it was observed that children who received preoperative oral administration of 0.5 mg/kg midazolam or 2 μg/kg dexmedetomidine were able to be separated from their parents without experiencing significant hemodynamic changes, thus enabling them to receive an anesthesia mask. A moderate reduction in both heart rate and blood pressure is induced by 2-agonists **(Faritus et al., 2015)**.

Yuen *et al.* shown that SBP differed significantly from baseline declined with time, and at 30 minutes ($P < 0.003$), 45 minutes ($P < 0.001$), and 60 minutes ($P < 0.001$) after medication administration in group D1. Furthermore, group D1 exhibited a significantly lower SBP in comparison to group M. ($P=0.004$). Sixty minutes later, the SBP in group D1 decreased by 14.1%. Post hoc analysis showed that HR decreased significantly with time in group D0.5 ($P < 0.001$) and group D1 ($P < 0.001$). There was also a significant time effect and group time interaction ($P < 0.001$) on HR ($P < 0.001$). The group effect on HR was not significant ($P=0.102$) **(Yuen et al., 2008)**.

Wang *et al.* reported that their analysis revealed no statistically significant differences in changes of HR and blood pressure between the two groups. In addition, intranasal dexmedetomidine or midazolam administered before to surgery HR, respiration, or finger SpO_2 of the infant were not significantly affected. Possibly the result of an alternative operation. According to administration route and dosage the incidence of hypotension, bradycardia, and hypoxia. Although a significant reduction in heart rate was detected 30 minutes after dexmedetomidine administration, The HR change remained within the expected range and did not exhibit a statistically significant difference from the HR change observed in the midazolam group throughout their study **(Wang et al., 2020b)**.

Limitations: despite increasing clinical evidence supporting the safety of DEX for Regarding pediatric anesthesia, relevant authorities in various countries, including the FDA, have yet to grant approval for its application in pediatric anesthesia. Thus, it remains to be classified as an off-label medication. Studies with substantial sample sizes are necessary, notwithstanding these constraints. It is crucial to ensure the safety and effectiveness of DEX in pediatric patients by determining the correct dosages.

Conclusion

The mixture usage of oral chloral hydrate and intranasal dexmedetomidine induces significant sedation in pediatric patients undergoing inguinal hernia surgery, since it offers superior sedation, facilitates parental separation, and promotes mask acceptance in comparison to buccal midazolam.

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