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Effect of Intranasal versus Intravenous Fentanyl on the Emergence Agitation after Sevoflurane Anesthesia in Children Undergoing Bilateral Myringotomy: A Prospective Randomized Controlled Double-Blinded Study

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Abstract

Background: Bilateral myringotomy and tube insertion for pressure equalization (BMT) is a common pediatric surgical procedure that is often associated with pain-related behavior (agitation) and/or discomfort (emergence delirium) in the post-anesthesia care unit (PACU). Emergence delirium (ED) is a set of perceptual problems that mostly affect pre-school children after recovery from general anesthesia. It involves hallucinations and disorientation. The cause of ED may be due to the growing use of recent volatile agents such as sevoflurane.

Aim of Study: This randomized controlled double-blinded study is conducted to compare the effect of intranasal fentanyl in a dose of (2 μg/kg) and intravenous fentanyl in a dose of (2.5 μg/kg) on sevoflurane induced ED in children undergoing BMT and the need for adding sedatives and/or analgesics.

Patients and Methods: Forty-eight children (1-5 years), ASA physical status I and II undergoing BMT were studied. After anesthesia induction with sevoflurane and endotracheal intubation, children were classified randomly into two groups (24 children each), Group IVF (Intravenous Fentanyl Group) and Group INF (Intranasal Fentanyl Group). Group IVF children received (2.5 μg/kg) IV diluted in 5ml of normal saline volume with intranasal 1ml placebo, whereas Group INF children re-ceived (2 μg/kg) administered intranasally (1 μg/kg in each nos-tril) in a volume of 1ml of normal saline (0.5ml in each nostril) with 5ml of intravenous normal saline placebo. Anesthesia was maintained with sevoflurane at both groups and hemodynamics (heart rate, respiratory rate, O_2 saturation, mean arterial blood pressure & end-tidal CO_2) were recorded every 2 minutes. After discontinuation of sevoflurane, the emergence from anesthesia, postoperative pain, nausea and/or vomiting and time to fulfill discharge criteria from the PACU were assessed.

Results: There were insignificant changes between the two groups in hemodynamics, emergence agitation (Watcha scale), postoperative pain (objective pain scale), the incidence of post-operative complications as nausea, vomiting, respiratory depres-sion and the need of rescue analgesics but there was significant decrease in all of these parameters at each group in comparison with baseline.

Conclusion: Intranasal fentanyl at a dose of (2 μg/kg) is comparable to intravenous fentanyl at a dose of (2.5 μg/kg) in decreasing emergence agitation, postoperative pain, nausea, vomiting, respiratory depression and the need of rescue analgesics without prolonging recovery time, thus preserved the rapid recovery seen with sevoflurane anesthesia.

Key Words: *Sevoflurane – Emergence agitation – Intra-venous fentanyl – Intranasal fentanyl – Bilateral myringotomy.*

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Introduction

BILATERAL myringotomy and tube insertion for pressure equalization (BMT) is a very common pediatric surgical procedure. BMT is often associated with pain-related behavior (agitation) and/or discomfort (emergence delirium) in the post-anesthesia care unit (PACU) **[1]**.

Emergence delirium (ED) is a set of perceptual problems that most typically affect preschool children when they recover from general anesthesia. It involves hallucinations and disorientation, which can manifest as crying, restlessness, and rolling in bed **[2]**.

Contributing factors to emergence delirium are; individual risk factors (Certain age groups "preschoolers", anxiety), physiological risk factors (hypoxia, hypercapnia, sepsis, hypoglycemia, electrolyte imbalance), residual drug effects, pain and the type of surgery (e.g., ENT, ophthalmology) **[3]**.

Although ED episodes are often brief, they increase the risk of self-injury, postpone discharge,

necessitate additional nursing personnel and can increase medical care expenses [4].

Sevoflurane became the most often used inhaled anesthetic for the induction and maintenance of anesthesia in children during BMT surgical procedures. Its pleasant odor and low blood gas solubility coefficient make induction rapid and smooth [5].

Fentanyl is a short-acting opioid analgesic that has sedative effects. Fentanyl is routinely administered intravenously for anesthetic management in children who are expected to be agitated after surgery [2].

Fentanyl at a dose of (2.5 gg/kg i.v) decreases the incidence of emergence agitation in patients who have undergone adenoidectomy with or without BMT surgery using sevoflurane and/or desflurane [6].

Intranasal analgesia allows for rapid drug administration without delay. The intranasal route of opioid administration is an effective and rapid method of achieving analgesia in adults and children [7].

This study hypothesized that the use of intranasal fentanyl in a dose of (2 gg/kg) may reduce the incidence of emergence agitation after sevoflurane anesthesia in children undergoing BMT. The primary outcome was to assess the incidence of postoperative emergence agitation while the secondary outcomes were to assess the need for additional medications for sedation or analgesia and adverse effects (including laryngospasm, bronchospasm and postoperative respiratory depression, hypoxemia, trauma, self-injury and nausea or vomiting).

So, the aim of the study was to compare the effect of intranasal versus intravenous fentanyl on sevoflurane induced emergence agitation in children undergoing Bilateral Myringotomy.

Patients and Methods

This prospective double-blinded randomized controlled study was conducted from December 2019 to December 2020 at Mansoura University hospital. Forty-eight children (1-5 years), ASA physical status I and II undergoing elective bilateral myringotomy tube placement (BMT) were studied. Children's parents were interviewed the day before surgery, children were examined clinically and parents signed a written informed con-sent.

Patients were excluded from this study if one or more of these criteria were met: ASA physical status Grade more than II, children with cardiac, respiratory, psychological or neurological disorders, history of allergy to fentanyl, children with risk of airway obstruction (obstructive sleep apnea and craniofacial syndromes), nasal congestion, upper respiratory tract infection and bronchial asthma and parents who refused surgery or the study consenting.

*Preoperative preparation:*Preoperative assessment was done to all children by history taking from their parents, physical examination and basal laboratory investigations as complete blood count, coagulation profile, renal and liver function tests. Patients were not pre-medicated. On arrival of the patient to surgery room, routine anesthesia monitoring (non-invasive arterial blood pressure, pulse oximetry, electrocardiography and capnograpghy catheter attached to the port of anesthesia circuit) were applied and baseline vital signs were recorded.

Randomization: Eligible 48 children were randomly assigned into two equal groups (every group included 24 children), Group IVF (Intravenous Fentanyl Group) and Group INF (Intranasal Fentanyl Group) (Fig.1).

Children in the intravenous fentanyl group (IVF group) received i.v. injection of fentanyl at a dose of 2.5gg/kg diluted in 5ml of normal saline volume with intranasal 1ml placebo.

Children in the intranasal fentanyl group (INF group) received 2 gg/kg administered intranasally (1 gg/kg in each nostril) in a volume of 1ml of normal saline (0.5ml in each nostril) with 5ml of intravenous normal saline placebo. To ensure proper depth of anesthesia, the nasal solution was dripped gently for at least 1 minute following the induction using a 1ml insulin syringe with the child in the recumbent position and plunger was pushed, with the head inclined to the side so that the solution remains in contact with the lateral surface of the nasal cavity and does not drip into the nasopharynx.

Anesthetic technique: Anesthesia was induced via a facemask using sevoflurane then was maintained with spontaneous ventilation via a Mapleson circuit after endotracheal intubation. Peripheral I.V line was inserted and all patients received a single dose of prophylactic antibiotic after sensitivity test and acetated Ringer's 3ml/kg/hr.

Measurements: Demographic data (age, sex, BMI, ASA physical status) and hemodynamics (heart rate, respiratory rate, O_2 saturation, mean arterial blood pressure & end-tidal CO_2) were meas-ured during the surgery every 2 minutes.

Heart rate (<50b/m) was considered bradycardia, respiratory rate (<12 b/m) was defined as respiratory depression and hypotension was confirmed when mean arterial blood pressure fell >30% of baseline. Hypoxia was considered when spO_2 <95%.

At the completion of surgery, sevoflurane was discontinued and the patients were transferred to the PACU with O_2 mask. The emergence from anesthesia and recovery at PACU were assessed by Watcha scale [8] every 10 minutes for the first postoperative 1 hour (Table 1). The objective pain scale [9] was performed to evaluate the analgesic requirements every 10 minutes for the first postoperative 1 hour (Table 2). The incidence of postoperative nausea/vomiting was recorded and the time to fulfill discharge criteria from the PACU was assessed.

Statistical analysis and data interpretation:

Using the data given by J. Finkel et al., 2001 [10] and S. Demirbilek et al., 2004 [11], the sample size was done using the Power Analysis and Sample Size software application (PASS) version 15.0.5 for Windows (2017) with the incidence of postoperative emergence agitation after sevoflurane anesthesia in children undergoing BMT as the primary outcome.

Table (1): Watcha scale for emergence agitation.

Behavior	Score
Asleep	0
Calm	1
Crying, but consolable	2
Crying but unable to be consoled	3
Agitated & rolling in bed	4

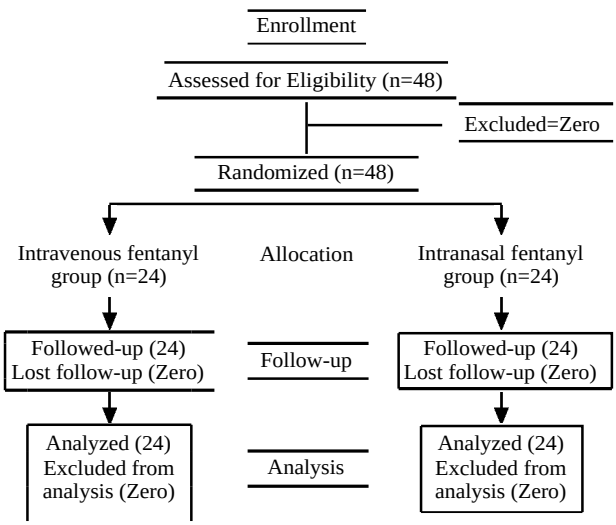

Fig. (1): Consort flow chart showing study design.

Table (2): The objective pain scale.

	Criteria	Points
Blood pressure	<20% of preoperative	0
	Between 20-30% of preoperative	1
	>30% of preoperative	2
Crying	No crying	0
	Responds to loving care	1
	Doesn't respond to loving care	2
Movements	No movement	0
	Rest lessness	1
	Trashes around and rolls in bed	2
Agitation	Clam or asleep	0
	Mildly agitated	1
	Hysterical	2
Pain complaints	Asleep/states no pain	0
	Can't localize	1
	Localizes pain	2

J. Finkel et al., reported higher incidence of postoperative emergence agitation 14.58% for the patients who received intra-nasal fentanyl than S. Demirbilek et al., who reported agitation incidence of 7% for those who received intra-venous fentanyl. The null hypothesis was considered as the absence of difference between the incidence of postoperative emergence agitation after sevoflurane anesthesia between both treatment modalities.

Data analysis:

IBM's SPSS statistics (Statistical Package for the Social Sciences) for Windows (version 25) will be utilized for statistical analysis of the obtained data. The Shapiro-Wilk test will be used to determine the normality of the data distribution.

Normally distributed continuous variables will be expressed as mean ± SD, while categorical variables and the abnormally distributed continuous ones will be expressed as median and inter-quartile range or number and percentage (as appropriate). For normally & abnormally distributed continuous data, Student *t*-test and Mann-Whitney will be used respectively.

For categorical data, Chi-square test will be used using the cross-tabs function. All tests will be carried out with a 95% confidence interval. If needed, bivariate correlations will be assessed using Pearson's or Spearman's correlation coefficient depending on the nature of data. Statistical significance is determined when p (probability) value is <0.05.

Results

This double-blinded prospective randomized study was done on 48 children (1-5 years), ASA physical status I and II of both sexes that were

assessed for eligibility and underwent elective Bilateral Myringotomy tube placement (BMT). There was no significant difference among the three groups as regards demographic data (age, sex, BMI, ASA physical status and duration of surgery). (Table 3).

Table (3): Patient's characteristics of the studied groups (data expressed as mean ± SD or number %).

	Group INF N=24	Group IVF N=24	Test of significance
Age (years)	4.78±0.693	5.18±0.737	*p*=0.064
BMI (Kg/m^2)	24.87±1.393	24.78±1.097	*p*=0.801
Gender:			
Male	66.7% (16)	62.5% (15)	*p*=0.763
Female	33.3% (8)	37.5% (9)	
ASA:			
I	83.3% (20)	87.5% (21)	*p*=0.35
II	16.7% (4)	12.5% (3)	*p*=0.683
Duration surgery (minutes)	29.96±1.197	29.96±0.859	*p*=1

Group INF: Intranasal Fentanyl group. N : Number.
Group IVF: Intravenous Fentanyl group. *p* : Probability value.

According to heart rate: There was no statistically significant difference between both groups as regards the basal and follow-up values of heart rate (p>0.05) (Fig. 2), whereas the follow-up values are significantly lower than the basal values with (P?0.05) (Table 4).

According to respiratory rate: There was no sta-tistically significant difference between both groups as regards the basal and follow-up values of respiratory rate (p>0.05) (Fig. 3), while the follow-up values are significantly lower than the basal values with (p<0.001) (Table 5).

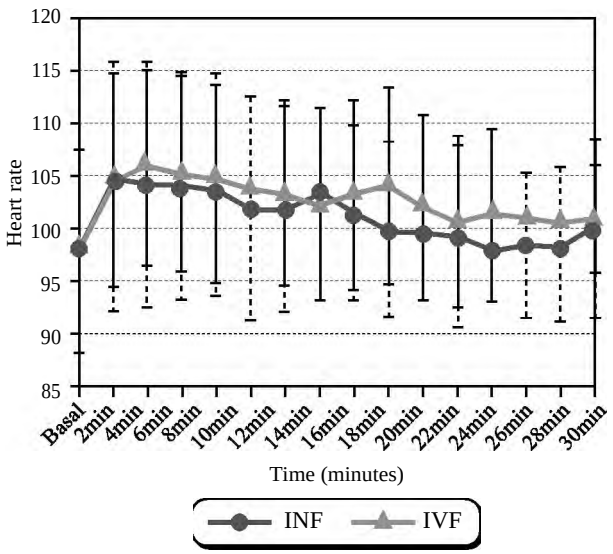

Fig. (2): Comparison between both groups as regards heart rate.

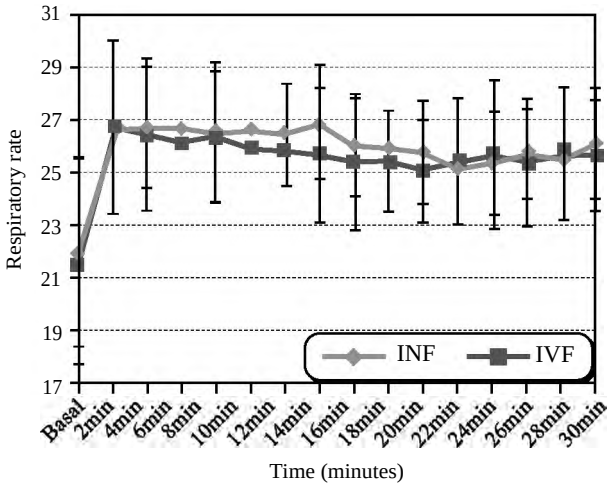

Fig. (3): Comparison between both groups as regards respiratory rate.

Table (4): Within-group comparison of heart rate in the studied groups.

Heart rate	Group INF N=24		Group IVF N=24	
Basal	97.46±12.014	*p*	97.95±9.647	*p*
2 minutes	104.00±11.814	<0.001*	104.54±10.24	<0.001*
4 minutes	104.17±11.709	<0.001*	105.75±9.419	<0.001*
6 minutes	103.96±10.728	<0.001*	105.17±9.342	<0.001*
8 minutes	103.50±10.104	0.002*	104.67±9.981	<0.001*
10 minutes	101.88±10.670	0.012*	103.67±9.192	<0.001*
12 minutes	101.83±9.845	0.024*	103.33±8.820	<0.001*
14 minutes	103.08±8.005	0.001*	102.17±9.130	<0.001*
16 minutes	101.42±8.319	0.011*	103.08±9.031	<0.001*
18 minutes	99.88±8.279	0.176	104.00±9.381	0.001*
20 minutes	99.67±8.616	0.127	101.96±8.785	0.005*
22 minutes	99.21±8.698	0.208	100.54±8.177	0.036*
24 minutes	98.08±8.309	0.662	101.25±8.248	0.004*
26 minutes	98.29±6.937	0.631	100.79±8.299	0.007*
28 minutes	98.42±7.312	0.509	100.46±6.311	0.037*
30 minutes	99.95±8.475	0.554	100.86±5.176	0.103

All parameters described as mean ± SD.
*Statistically significant (if p<0.05).
- p-value is generated by comparing each reading to its respective basal value.

Table (5): Within-group comparison of respiratory rate in the studied groups.

Respiratory rate	Group INF N=24		Group IVF N=24	
Basal	21.96±3.605	*p*	21.63±3.965	*p*
2 minutes	26.79±2.359	<0.001*	26.75±3.300	<0.001*
4 minutes	26.71±2.274	<0.001*	26.50±2.978	<0.001*
6 minutes	26.75±2.231	<0.001*	26.21±3.064	<0.001*
8 minutes	26.54±2.734	<0.001*	26.42±2.552	<0.001*
10 minutes	26.67±1.926	<0.001*	26.00±2.359	<0.001*
12 minutes	26.46±2.000	<0.001*	25.88±2.092	<0.001*
14 minutes	26.92±2.205	<0.001*	25.71±2.562	<0.001*
16 minutes	26.04±1.853	<0.001*	25.42±2.620	<0.001*
18 minutes	25.96±1.805	<0.001*	25.46±1.933	<0.001*
20 minutes	25.79±1.978	<0.001*	25.13±1.963	<0.001*
22 minutes	25.13±2.133	0.001*	25.42±2.448	<0.001*
24 minutes	25.38±1.952	<0.001*	25.71±2.866	<0.001*
26 minutes	25.75±1.751	<0.001*	25.42±2.448	<0.001*
28 minutes	25.58±2.145	<0.001*	25.75±2.524	<0.001*
30 minutes	26.16±2.167	<0.001*	25.68±2.169	<0.001*

All parameters described as mean ± SD.
*Statistically significant (if p<0.05).
- p-value is generated by comparing each reading to its respective basal value.

According to O_2 saturation: There was no statistically significant difference between both groups as regards the basal and follow-up values of O_2 saturation (p>0.05) (Fig. 4), while the follow-up values are significantly higher than the basal values with (p<0.05). (Table 6).

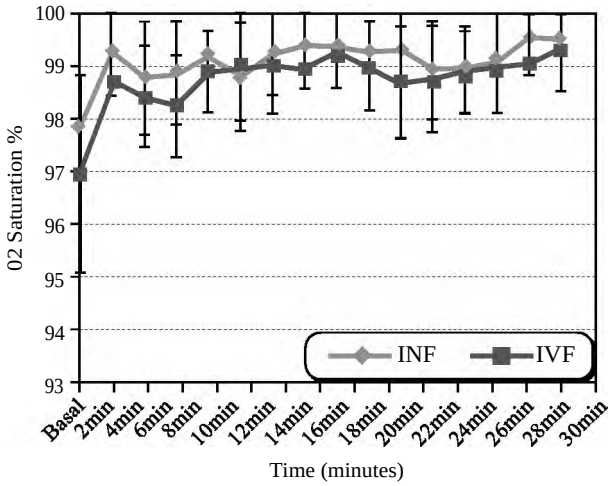

Fig. (4): Comparison between both groups as regards O_2 saturation.

Table (6): Within-group comparison of O_2 saturation in the studied groups.

Heart rate	Group INF N=24		Group IVF N=24	
Basal	98.42±1.349	*p*	97.95±9.647	*p*
2 minutes	99.50±0.659	<0.001 *	99.08±0.504	<0.001 *
4 minutes	99.08±0.776	0.008*	98.83±0.702	0.001 *
6 minutes	99.17±0.702	0.001 *	98.71±0.690	0.007*
8 minutes	99.42±0.504	0.001 *	99.17±0.565	<0.001 *
10 minutes	99.13±0.704	0.018*	99.25±0.737	<0.001 *
12 minutes	99.46±0.588	<0.001 *	99.29±0.690	<0.001 *
14 minutes	99.54±0.588	<0.001 *	99.21±0.779	<0.001 *
16 minutes	99.54±0.588	0.002*	99.46±0.588	<0.001 *
18 minutes	99.46±0.779	0.002*	99.25±0.608	<0.001 *
20 minutes	99.50±0.590	0.001 *	99.04±0.751	<0.001 *
22 minutes	99.21±0.658	0.010*	99.08±0.717	<0.001 *
24 minutes	98.21±0.588	0.015*	99.17±0.565	<0.001 *
26 minutes	99.33±0.702	0.006*	99.25±0.737	<0.001 *
28 minutes	99.63±0.495	<0.001 *	99.29±0.464	<0.001 *
30 minutes	99.63±0.597	<0.001 *	99.52±0.593	<0.001 *

All parameters described as mean ± SD.
*Statistically significant (if p<0.05).
- p-value is generated by comparing each reading to its respective basal value.

According to mean arterial blood pressure (MAP): There was no statistically significant difference between both groups as regards the basal and follow-up values of MAP (p>0.05) (Fig. 5), while the follow-up values are significantly lower than the basal values with (p<0.001). (Table 7).

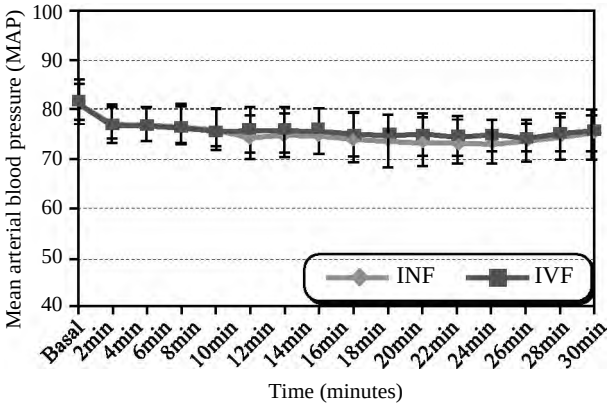

Fig. (5): Comparison between both groups as regards MAP.

Table (7): Within-group comparison of MAP in the studied groups.

MAP	Group INF N=24		Group IVF N=24	
Basal	81.71±4.369	*p*	82.00±3.514	*p*
2 minutes	77.42±3.798	<0.001 *	77.42±3.348	<0.001 *
4 minutes	77.00±3.575	<0.001 *	77.08±3.525	<0.001 *
6 minutes	77.08±4.242	<0.001 *	76.88±3.893	<0.001 *
8 minutes	76.42±3.900	<0.001 *	76.08±3.988	<0.001 *
10 minutes	74.50±4.324	<0.001 *	76.04±4.777	<0.001 *
12 minutes	75.17±4.459	<0.001 *	76.00±4.727	<0.001 *
14 minutes	74.92±4.699	<0.001 *	75.75±4.656	<0.001 *
16 minutes	74.46±5.004	<0.001 *	75.04±4.486	<0.001 *
18 minutes	73.88±5.269	<0.001 *	75.21±4.324	<0.001 *
20 minutes	73.58±5.064	<0.001 *	75.29±3.928	<0.001 *
22 minutes	73.71±4.573	<0.001 *	74.71±4.016	<0.001 *
24 minutes	73.46±4.433	<0.001 *	75.00±3.148	<0.001 *
26 minutes	73.79±4.242	<0.001 *	74.33±2.808	<0.001 *
28 minutes	74.63±4.509	<0.001 *	75.21±3.388	<0.001 *
30 minutes	75.21±5.073	<0.001 *	75.59±3.912	<0.001 *

All parameters described as mean ± SD.
*Statistically significant (if p<0.05).
- p-value is generated by comparing each reading to its respective basal value.

According to capnogram (End-tidal CO_2): There was no statistically significant difference between both groups as regards the basal and follow-up values of End-tidal CO_2 (p>0.05) (Fig.6), while the follow-up values are significantly lower than the basal values with (p<0.05). (Table 8).

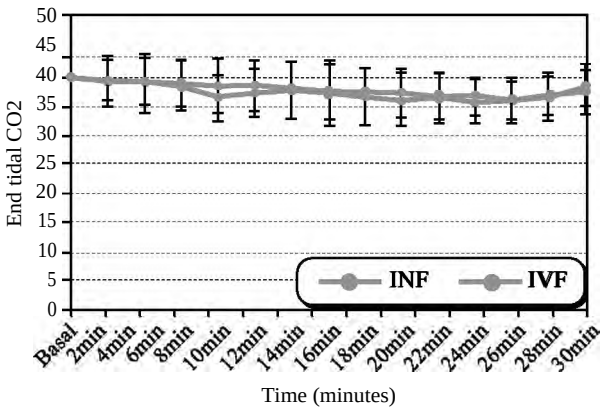

Fig. (6): Comparison between both groups as regards End-tidal CO_2.

Table (8): Within-group comparison of End-tidal CO_2 in the studied groups.

End-tidal CO2	Group INF N=24		Group IVF N=24	
2 minutes	39.88±4.446	*p*	39.75±3.698	*p*
4 minutes	39.17±4.361	0.074	39.29±3.381	0.118
6 minutes	38.96±5.052	0.158	39.21±4.242	0.220
8 minutes	38.46±4.075	0.010*	38.75±3.948	0.015 *
10 minutes	36.46±4.064	<0.001 *	3 8.42±4.662	0.012*
12 minutes	37.17±4.260	<0.001 *	3 8.46±4.263	0.018*
14 minutes	37.67±5.027	0.001 *	37.96±4.787	0.004*
16 minutes	37.17±5.498	<0.001 *	37.33±4.815	0.002*
18 minutes	36.54±4.978	<0.001 *	37.33±4.498	<0.001 *
20 minutes	35.96±4.601	<0.001 *	37.29±4.217	<0.001 *
22 minutes	36.29±4.359	<0.001 *	36.71±4.048	<0.001 *
24 minutes	35.58±3.955	<0.001 *	36.71±3.057	<0.001 *
26 minutes	35.92±4.021	<0.001 *	35.83±3.332	<0.001 *
28 minutes	36.50±3.901	<0.001 *	36.92±3.844	<0.001 *
30 minutes	37.89±4.370	0.005*	37.50±4.021	0.001 *

All parameters described as mean ± SD.
*Statistically significant (if $p<0.05$).
- *p*-value is generated by comparing each reading to its respective basal value.

According to emergence agitation and pain: There was no statistically significant difference between the two groups as regards the emergence agitation score or the objective pain scale ($p>0.05$). (Fig. 7) and (Table 9).

Table (9): Emergence agitation score (Watcha Scale) and Objective Pain Scale of the studied groups.

	Group INF N=24	Group IVF N=24	Test of significance
Emergence agitation score (Watcha Scale)	1.92±1.018	2.13±0.900	*p*=0.456
Objective pain scale	2.29±0.955	2.29±1.122	*p=1*

All parameters described as mean ± SD.
p Is statistically significant when (<0.05).

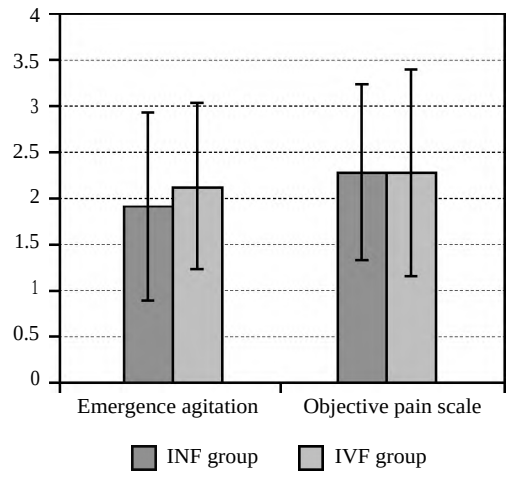

Fig. (7): Emergence agitation score (Watcha Scale) and Objective Pain Scale of the studied groups.

According to postoperative complications and the need for rescue medications: There was no statistically significant difference between the two groups in the incidence of postoperative complications as nausea, vomiting, respiratory depression and the need of analgesic drugs ($p>0.05$). (Table 10).

Table (10): Emergence agitation score (Watcha Scale) and Objective Pain Scale of the studied groups.

	Group INF N=24	Group IVF N=24	Test of significance
Postoperative paracetamol analgesia requirement	25.0% (6)	29.2% (7)	*p*=0.745
Postoperative nausea and vomiting:			
Absent	91.7% (22)	91.7% (22)	*p*=0.513
Nausea	0.0% (0)	4.2% (1)	
Vomiting	8.3% (2)	4.2% (1)	
Postoperative metoclopramide	8.3% (2)	8.3% (2)	*p*=1

All parameters described as number and %.
p Is statistically significant when (<0.05).

Discussion

Emergence delirium (ED) is defined as a condition of mild restlessness, anxiety and emotional dis-tress that arises as a result of a variety of factors including recovery in an unfamiliar environment, pain from surgical wounds, agitation during induction, obstruction of the airway, prolonged anesthesia duration, inhaled and intravenous anesthetics and the anesthetic technique used **[12]**. Certain age groups (preschoolers) and type of surgery (e.g., ENT, ophthalmology) are mostly associated with a higher incidence of ED. The growing use of recent volatile agents such as sevoflurane is associated with high incidence of ED due to low blood solu-bility, which leads to quick awakening **[13]**.

Fentanyl and other opioids are usually used for ED prevention due to their sedative and analgesic effects and it was assumed that uncontrolled pain can cause ED. Intravenous route is the traditional route of administration of fentanyl and other opioids for management of agitation in children after surgery as it rapidly reaches the central blood stream before crossing the blood brain barrier to produce CNS effects. Intranasal method also delivers the opioid directly to the CNS site of action. The olfactory & trigeminal nerves, the vasculature, the cerebrospinal fluid, and the lymphatic system are all thought to be possible routes for direct CNS access **[14]**.

This study was conducted to prove that intranasal fentanyl at a dose of (2γg/kg) is comparable to intravenous fentanyl at a dose of (2.5 γg/kg) as regards ED incidence, its degree and the need for adding sedatives and analgesics after anesthesia with sevoflurane in children undergoing BMT. The primary outcome was to compare the incidence of post-operative ED between the two groups. The secondary outcome was comparing the intraoperative hemodynamic changes, respiratory effects and postoperative need of additional medications for sedation and adverse effects (including laryngospasm, bronchospasm and postoperative respiratory depression, hypoxemia, trauma, self-injury and nausea or vomiting).

Emergence agitation incidence: This study revealed that administration of either intranasal fentanyl (2γg/kg) or intravenous fentanyl (2.5γg/kg) at the end of anesthesia with sevoflurane was comparable in reducing ED which was evaluated by Watcha scale.

These results are correlated with the meta-analy-sis of randomized controlled studies conducted by Wang X et al., 2016 **[15]** and the meta-analysis conducted by Shi F et al., 2015 **[16]** which revealed that fentanyl minimizes the risk of ED in children under anesthesia with sevoflurane and reduces postoperative pain. The meta-analysis conducted by Shi F et al., observed that both intranasal and intravenous fentanyl showed to be effective and can reduce the risk of ED. Whereas, the meta-analysis by Song J. et al., 2021 **[17]** showed that intravenous fentanyl did not prevent ED. This difference may be attributed to the fact that just two studies were included in the meta-analysis by Song J. et al.

In a study conducted by Menser C et al., 2020 **[18]**, it was revealed that in children undergoing ad-enoidectomy under sevoflurane anesthesia, a dose of 2.5γg/kg i.v. fentanyl decreases the incidence of ED. On the other hand, a study conducted by Demirbilek S et al., 2004 **[11]** revealed that after midazolam premedication, intravenous fentanyl 2.5γg/kg did not provide any clinically significant benefit on ED in children who received sevoflurane anesthesia. Intranasal fentanyl administration during sevoflurane anesthesia has been reported to be associated with decreased ED. Elitsur R et al., 2019 **[19]**. Other study conducted by Robinson H et al., 2017 **[20]** revealed that intranasal fentanyl is effective in controlling postoperative pain and ED in children undergoing BMT under anesthesia with sevoflurane. Intranasal fentanyl was documented by Kaushal S et al., 2020 **[21]** to be equivalent or superior to morphine and equivalent to intravenous fentanyl in reducing pain in children undergoing pain-ful procedures. Lower intranasal fentanyl doses were not effective in reducing emergence agitation which was documented by McHale B et al., 2018 **[22]**. Intranasal fentanyl 1 γg/kg, when compared to 2γg/kg revealed a significant reduction in the agitation score in the 2γg/kg group. The drawback of intranasal route, especially in patients requiring BMT is that ongoing respiratory issues including chronic rhinitis may interfere with absorption and could theoretically alter efficacy as revealed by Ku-mar L et al., 2017 **[23]**.

Hemodynamic changes: In this study, there was no significant difference in the intraoperative heart rate, respiratory rate, O_2 saturation, MAP & end-tidal CO_2 between the two groups. While, there was a noticeable difference between basal and follow-up values within each group with significant de-crease in heart rate, MAP & end-tidal CO_2 at almost all measurement times.

These results are correlated with the study conducted by Thippeswamy RR et al., 2018 **[24]** that revealed that after the induction of anesthesia, MAP and heart rate decreased in the groups pre-treated with fentanyl. While Chatrath V et al., 2018 **[25]** reported that there wasn't noticeable difference in intraoperative heart rate or MAP in patients received intranasal fentanyl.

Respiratory depression: In our study, there were no incidences of upper airway obstruction, respiratory depression, apnea or laryngospasm.

These results are correlated with the study conducted by Chatrath V et al., 2018 **[25]** that revealed that there was no significant difference in the res-piratory rate in children receiving intranasal fentanyl at a dose of (2 γg/kg) at all time intervals. No adverse events such as laryngospasm or postoperative respiratory depression were noted after intranasal fentanyl administration in a study conducted by Elitsur R et al., 2019 **[19]**. A supporting study by Menser C et al., 2020 **[18]** clarified that in children receiving intravenous fentanyl at doses up to 2.5 γg/kg, there were no cases of upper airway obstruction or apnea.

While the results of three studies in a meta-analysis conducted by Kim N et al., 2017 [26] showed that a small number of children who received intra-venous fentanyl, presented with laryngospasm, de-saturation and airway obstruction. A study conducted by Fallah R et al., 2016 **[27]**, also revealed that intravenous fentanyl may cause skeletal muscle and/or chest wall rigidity with even

low analgesic doses, especially in small infants, and this might compromise ventilation.

Postoperative Nausea & Vomiting (PONV): In the present study, PONV incidence was similar in both groups and occurred in a small number of patients (only 2 patients in each group). These patients were treated with 0.15mg/kg i.v. metoclopramide.

These results are correlated with the study conducted by McHale B et al., 2018 **[22]** that showed that no children receiving intranasal fentanyl at a dose of (2 µg/kg), experienced PONV. The study claimed that PONV is a rare adverse effect at this low dose. Children with PONV can be treated with appropriate anti-emetics, thus this is not a reason to avoid intranasal fentanyl.

In a meta-analysis conducted by Shi F et al., 2015 **[16]**, the results of 9 studies showed that intravenous fentanyl significantly increased the incidence of PONV in children under anesthesia with sevoflurane.

Pain incidence and need for rescue analgesics: In the present study, there was no significant difference between the two groups as regards postoperative pain assessment using the objective pain scale with overall small incidence. Postoperative consumption of rescue analgesics also was similar in both groups. Only 6 patients in INF group and 7 pa-tients in IVF group received 10-15mg/kg i.v. paracetamol.

These results are correlated with the results of 5 studies included in the meta-analysis conducted by Shi F et al., 2015 **[16]** which revealed that intrave-nous fentanyl dramatically reduced the incidence of pain in children in the PACU. (p=0.004). Other study conducted by Yenigun A et al., 2018 **[28]** revealed that intranasal fentanyl had an effective anal-gesia in pediatric patients undergoing tonsillectomy.

In a study conducted by Triarico S et al., 2019 **[29]** showed that absorption may be reduced due to anatomical and physiological and consequently re-duces its bioavailability. These factors include:

- A septal deviation or turbinate hypertrophy can partially block the nasal cavity, preventing drug deposition on the respiratory zone and reducing intranasal fentanyl absorption.
- Epistaxis, chronic rhinitis, and nasal polyposis can all lower the nasal surface area available for IN medication absorption.
- IN drug absorption may be affected in response to factors that reduce nasal blood flow such as vasoconstrictive drugs including a-1 adrenergic receptor agonists as phenylephrine & oxymetazoline.
- Mucociliary clearance may also impair IN medication absorption. It has been shown that around 50% of the dose is removed by the ciliated cells of the respiratory zone 30 minutes after administration.

Conclusion:

Intranasal fentanyl at a dose of (2 µg/kg) is com-parable to intravenous fentanyl at a dose of (2.5 µg/kg) in decreasing emergence agitation, postoperative pain, nausea, vomiting, respiratory depression and the need of rescue analgesics without prolonging recovery time, thus preserved the rapid recovery seen with sevoflurane anesthesia.

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تأثير حقن دواء الفنتانيل عن طريق الأنف مقابل حقنة عن طريق الوريد على ظهور الانفعالات بعد التخدير بسيفوفلورين فى الأطفال الذين يخضعون لفتح طبلة الأذن على الجانبين: دراسة مستقبلية عشوائية مزدوجة التعمية

المقدمة: شق طبلة الأذن على الجانبين وإدخال أنابيب معادلة الضغط هو إجراء جراحى شائع للأطفال الذين يظهرون سلوكاً مرتبطاً بالألم أو عدم الراحة (ظهور الهذيان) فى وحدة رعاية ما بعد التخدير ويساعد على ذلك التخدير بسيفوفلوران.

الفنتانيل هو مسكن أفيونى قصير المفعول له تأثيرات مهدئة. كثيراً ما يستخدم الفنتانيل عن طريق الوريد أثناء تخدير الأطفال الذين من المتو قع أن يتعرضوا للانفعالات بعد العملية الجراحية. حقن الفنتانيل أيضاً عن طريق الأنف هو وسيلة فعالة وسريعة لتحقيق تسكين فى البالغين والأطفال عندما لا يكون القسطرة الوريدية متاحة.

الهدف من الدراسة: هو إجراء دراسة مستقبلية عشوائية لمقارنة تأثير الفنتانيل عن طريق الأنف بجرعة ٢ ميكروغرام / كيلو غرام والفنتانيل عن طريق الوريد بجرعة ٢.٥ميكروغرام للوقاية من ظهور الانفعالات بعد التخدير بسيفوفلوران، فى الأطفال الذين يخضعون لفتح طبلة الأذن على الجانبين.

المرضى وطريقة البحث: لقد تم تنفيذ هذه الدراسة العشوائية على ٤٨ من المرضى الذين خضعوا لجراحة فتح طبلة الأذن على الجانبين وإدخال أنابيب معادلة الضغط. لقد تم تصنيف المرضى بشكل عشوائى إلى مجموعتين ٢٤ مريض لكل مجموعة منهما .

مجموعة INF: تلقى المريض جرعة من الفنتانيل عن طريق الأنف (٢ ميكروغرام / كيلو غرام) بعد التخدير باستخدام سيفوفلوران.

مجموعة IVF: تلقى المريض جرعة من الفنتانيل عن طريق الوريد (٢.٥ ميكروغرام / كيلو غرام) بعد التخدير باستخدام سيفوفلوران.

طريقة التخدير:

- لقد تم التخدير باستخدام سيفوفلوران عبر قناع للوجه ثم وضع قسطرة وريدية ومتابعة العلامات الحيوية للمريض أثناء العملية وتسجيل معدل ضربات القلب وضغط الدم.
- تلقى المرضى فى مجموعة الفنتانيل عن طريق الأنف (٢ ميكروغرام / كيلو غرام) ميكروغرام / كيلو غرام فى كل منخر. تتم تقطير محلول الأنف ببطء على الأقل بعد دقيقة من التخدير لضمان عمق كافٍ للتخدير باستخدام حقنة ١ مل. وتم وضع المريض فى وضع الاستلقاء، مع تحول الرأس إلى الجانب بحيث يبقى السائل على اتصال مع السطح الجانبى للتجويف الأنفى ولا يقطر فى البلعوم الأنفى. المرضى الذين يعانون من احتقان الأنف تم شفط أنفهم قبل إعطاء الفنتانيل عن طريق الأنف.
- تلقى المرضى فى مجموعة الفنتانيل عن طريق الوريد جرعة ٢.٥ ميكروغرام / كيلو غرام.
- عند الانتهاء من الجراحة، تم إيقاف التخدير، وتم نقل المرضى إلى غرفة ما بعد الجراحة.
- لقد تم تقييم ظهور الانفعالات باستخدام مقياس وأنشأ المكون من ٤ نقاط.
- ولقد تم أيضاً استخدام مقياس الألم الموضوعى لتقييم الحاجة إلى تسكين الألم، وتسجيل وجود أو عدم وجود غثيان قئ.
- لقد تم تقييم الو قت اللازم للوفاء بمعايير الخروج من غرفة ما بعد الجراحة.

النتائج: لقد أسفرت هذه الدراسة عن عدم وجود تغييرات كبيرة فى البيانات الديمغرافية للمرضى أو فى مدة الجراحة بين مجموعتى الدراسة. وقد أسفرت الدراسة أيضاً عن عدم وجود فرق كبير بين المجموعتين فيما يتعلق بالوظائف الحيوية كمعدل ضربات القلب، معدل التنفس، تشبع الأكسجين متوسط ضغط الدم الشريانى وتركيز ثانى أكسيد الكربون فى نهاية دورة التنفس. لم يكن هناك أيضاً فرق واضح فى الانفعالات عن طريق مقياس واتشا أو فى مقياس الألم الموضوعى بين المجموعات المدروسة، كما لم يكن هناك فرق كبير فى معدل حدوث مضاعفات ما بعد الجراحة مثل الغثيان والقئ وتثبيط الجهاز التنفسى والحاجة إلى المسكنات الإنقاذية فى المجموعات المدروسة.

الخلاصة: تُظهر هذه الدراسة أنه فى الأطفال الذين تتراوح أعمارهم بين ١ إلى ٤ سنوات والذين يخضعون لـ BMT، الفنتانيل داخل الأنف بجرعة (٢ مجم / كجم) يمكن مقارنته بالفنتانيل الوريدى بجرعة (٢.٥ مجم كجم). نظراً لأن كلاهما قلل من ظهور الانفعالات، وقلل من آثاره الضارة ولم يطيل وقت الشفاء، وبالتالى حافظ على سرعة استعادة الوعى الذى شوهد مع تخدير سيفوفلوران.