

The Effect of Intranasal Administration of Remifentanyl on Hemodynamic Response to Laryngoscopy and Intubation after Sevoflurane Induction of Anesthesia in Children

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Abstract: Background: In general, there are two major concerns about intubation and laryngoscopy when needed after induction of anesthesia in children. The first is to achieve easy endotracheal intubation by obtaining optimal intubation conditions the other concern is how to attenuate hemodynamic response to laryngoscopy and intubation. Aim of the study: Is to assess sevoflurane & remifentanyl impact on pediatric patients endotracheal intubating conditions associated hemodynamic response. **Patient & Method:** In this randomized controlled trial, sixty children, 1-6yr old were enrolled in this study, and were divided into two groups A&B with 30 members of each. we compared intubating conditions and hemodynamic response to intubation after sevoflurane induction and the administration of intranasal remifentanyl (4mcg/kg) or saline. The preinduction, pre-intubation & post intubation hemodynamic readings in children were also compared for assessing benefits of the used remifentanyl as well as its safety on patients. **Result:** Good or excellent intubating conditions were achieved at 3 min (after IN remifentanyl bolus) in 90% of the children who received intranasal remifentanyl versus 3.3% in children who received placebo. There were no complications associated with the use of nasal remifentanyl. HR and MAP were successfully attenuated in 90% of the study group members versus ~4% of the control group members. Unopposed upper HR & MAP readings reported in 96% of the control group members. **Conclusion:** Nasal administration of remifentanyl one minute from sevoflurane induction of anesthesia produces optimal intubating conditions after three minutes of the administration as well as attenuation of hemodynamic response to intubation & laryngoscopy.

Keywords: Intranasal Remifentanyl, Intubation, Hemodynamic Response.

INTRODUCTION

Laryngoscopy and endotracheal intubation are known to cause increase in arterial blood pressure, heart rate and may be associated with various dysrhythmias.

There has been controversy regarding nervous pathway involved in this reflex response.

Reid and Brace attributed both afferent and efferent pathways to Vagus nerve. King et.al observed that mechanism is non-specific, afferent being Vagus but efferent pathway is less clear.

Intubating conditions were judged as acceptable when all scores were 2 or less. If any of the scores were 3 or 4 for any of the five variables, intubating conditions were judged unfavorable.

The choice of a 4mcg/kg dose of nasal remifentanyl was based on an assumption that blood levels of nasally administered drugs are about half that obtained after IV dosing. The optimal dose of IV remifentanyl for tracheal intubation under sevoflurane anesthesia in adults was found by Joo et al to be 2 mcg/kg (Canadian Journal of Anaesth. 2001;48:646-50) hence our 4 mcg/kg dosing.

Patients and Methods

The study has been approved by Scientific Council of Anesthesia and Intensive Care /Iraqi Board.

This study is prospective, randomized, double-blinded clinical trial. The study was conducted in Baghdad Medical City theatres in Baghdad, Iraq in 1st of November 2016 to 1st of February 2017.

Approvals were taken from the patients' parents by a written informed consent.

Inclusion criteria

- Elective operations.
- Age 1-6 years.
- Weight 11-25kg.
- ASA I

Exclusion criteria:

- Patient parents' refusal.
- Cases with contraindicated to the medications used in the study.
- Patients with expected or previously reported difficult intubation.

Sixty children, 1-6yr old were enrolled in this study, and were divided into two groups

- Group A(all the 30 patients in these groups received Intranasal remifentanil in a dose (4 mcg/kg).
 - Group B (all 30 patient in these groups received Intranasal normal saline).
- IV cannulas done for all patients although not been used for induction of anesthesia.

After recoding initial hemodynamic values, nasal remifentanil (4 mcg/kg) or saline was administered one min. after an 8% sevoflurane induction. The sevoflurane was then reduced to 5% in oxygen with ventilation assisted or controlled. A validated score (a score 1-4 for individual intubating condition and a score of 5-20 for overall intubating conditions) was used to evaluate the conditions for laryngoscopy and response to intubation at 3 min after the administration of intranasal solution.

Initial heart rates and mean arterial pressures were taken from all patients of the two groups. The intubating condition scale suggests that intubating conditions accepted when all scores were 2 or less.

Intubating conditions were judged as acceptable when all scores were 2 or less. If any of the scores were 3 or 4 for any of the five variables, intubating conditions were judged unfavorable.

For example, a sustained coughing for more than 10 seconds associated with whole trunk movement was recorded as severe response to endotracheal intubation or a cough score 3- 4 which reflect an unacceptable intubating condition, while airway response involving mild diaphragmatic movement scored with 2, and intubation without cough ranked with 1 score.

In our study the intranasal remifentanil group show almost complete jaw relaxation compared to stiff jaw in nasally placebo group. Regarding laryngoscopy, it was nearly easily achieved in the study group while being generally difficult in the control group.

Vocal cords were mostly opened and least moving in the remifentanil treated group versus being closing in the normal saline administered group.

Coughing and limb movement were not detected in the remifentanil given patients while being mostly moderate in the other patients.

Hence, we can conclude that the intubating conditions were generally accepted in the nasally administered remifentanil members.

Table 1: scoring system that applied in the study.

	Score			
	1	2	3	4
Jaw relaxation	Complete	Slight tone	Stiff	Rigid
Laryngoscopy	Easy	Fair	Difficult	Impossible
Vocal cords	Open	Moving	Closing	Closed
Coughing	None	Slight	Moderate	Severe
Limb movement	None	Slight	Moderate	Severe

All patients in both groups were prepared to undergo elective operation.

Both group patient relative or parents receive same adequate explanation about the study.

Adequate history taking, medical examination and appropriate investigations were conducted before induction of anesthesia.

Position was same for all patients (supine).

Appropriate monitoring was conducted with ECG, NIBP, SPO₂, PR.

Age, weight, height, patient identification number, ASA class and initial vital signs all were recorded. Baseline heart rate and mean arterial pressure readings were recorded.

After one minute from induction with sevoflurane 8% intranasal remifentanil (4mcg/kg) or saline was administered. The sevoflurane concentration was then reduced to 5% in oxygen with ventilation

assisted/controlled. After 2 minutes from intranasal solution HR & MAP were retaken.

HR & MAP were recorded also after 1 minute , 3 minutes, and 5 minutes after endotracheal intubation for all patients.

Data were collected and analyzed between the two groups.

The statistical analysis of this cohort-prospective study performed with the statistical package for social sciences (SPSS) and Microsoft Excel.

Categorical data formulated as count and percentage. Chi-square test used to describe the association of these data. Numerical data were described as mean and standard deviation. Independent sample t-test used for comparison between two groups. The lower level of accepted statistically significant difference is bellow or equal to 0.05.

RESULTS

This study included 60 patients, 30 for each group, were completed the study and were included in the data analysis.

The patient characteristics data did not differ between the two groups regarding age, weight, height, gender& ASA.

Table 2: Patient characteristics data

Patient characteristics	Study group S+IN Remifentanil	Control group S± IN placebo	P Value
Age	4.9 ± 1.39	5.00 ± 1.43	0.784
Weight	18.07±4.09	17.03±3.97	0.321
Height	99.4±5.12	100.6±6.54	0.432
Gender m/f	25m/25f(50%)	25m/25f(50%)	1
ASA(1E)	25(1E) / 25 (1E) (50%)	25(1E) / 25 (1E)(50%)	1

Table 3: Comparing the intubating conditions between the two groups regarding values are the means ± standard deviations.

Intubating Conditions	Study Group S+IN Remifentanil	Control Group S+IN placebo	P Value
Jaw relaxation (score 1-4)	1.23±0.56	3.5±0.5	< 0.0001
Laryngoscopy (score 1-4)	1.10±0.40	3.17±0.46	< 0.0001
Vocal cords (score 1-4)	1.23±0.56	3.77±0.5	< 0.0001
Coughing (score 1-4)	1.17±0.46	3.87±0.43	< 0.0001
Limb movement (score 1-4)	1.20±0.55	3.47±0.57	< 0.0001
The overall intubating condition (score 5-20)	6.00±1.38	17.80±1.68	< 0.0001 [*]

*All p values here reflect a highly significant difference in the individual and overall intubating conditions between the two groups.

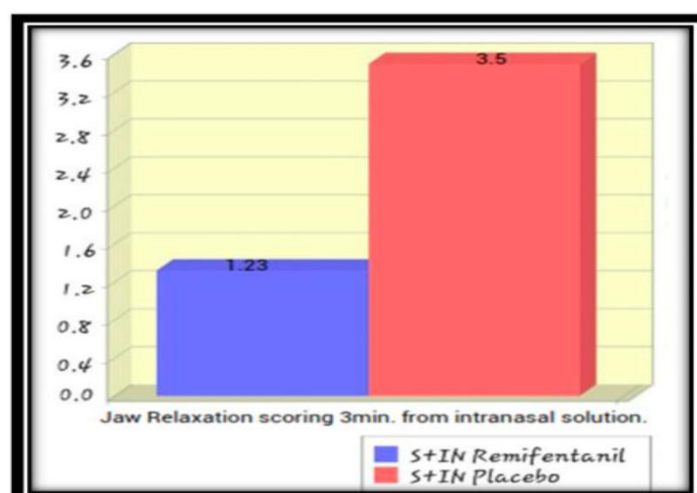


Figure 1: Jaw Relaxation condition three minutes from IN solution in sevoflurane anesthetized children for both groups. It shows a significant lower score of jaw relaxation in the IN Remifentanil treated group (p value < 0.001).

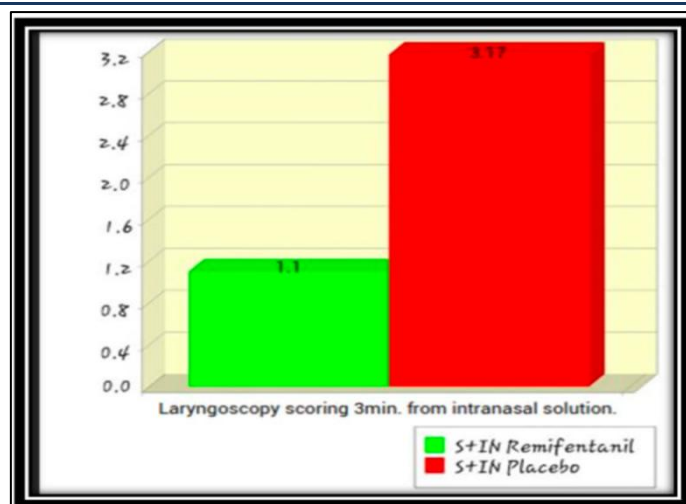


Figure 2: Laryngoscopy condition 3minutes from IN solution in sevoflurane anesthetized children for both groups. It shows a significant lower score of laryngoscopies in the IN Remifentanil treated group (p value < 0.001).

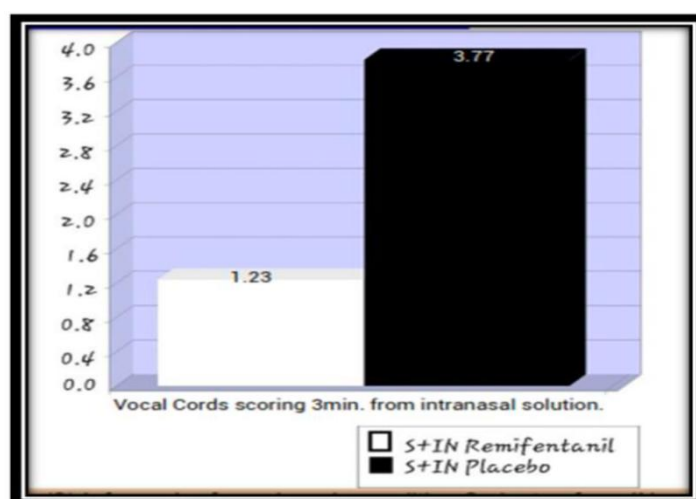


Figure 3: Vocal cords condition 3minutes from IN solution in sevoflurane anesthetized children for both groups. It shows a significant lower score of vocal cords condition in the IN Remifentanil treated group (p value < 0.001).

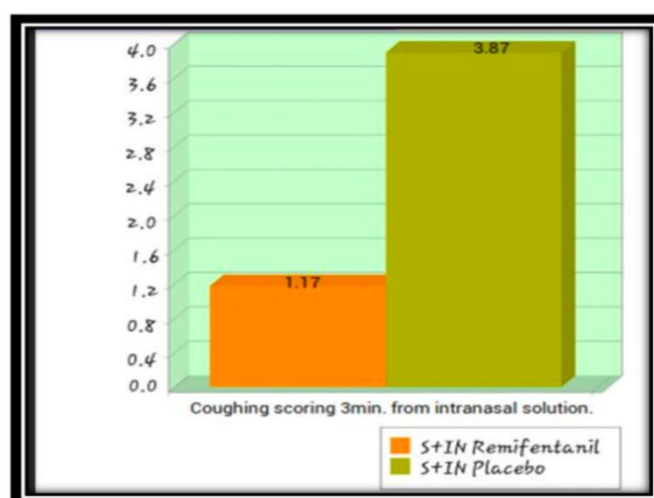


Figure 4: Coughing condition 3minutes from IN solution in sevoflurane anesthetized children for both groups. It shows a significant lower score of coughing condition in the IN Remifentanil treated group (p value < 0.001).

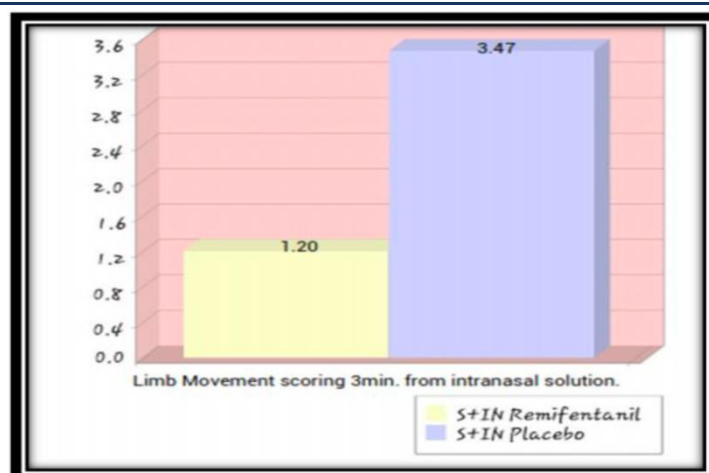


Figure 5: Limb movement condition 3minutes from IN solution in sevoflurane anesthetized children for both groups. It shows a significant lower score of limb movement condition in the IN Remifentanyl treated group (p value < 0.001).

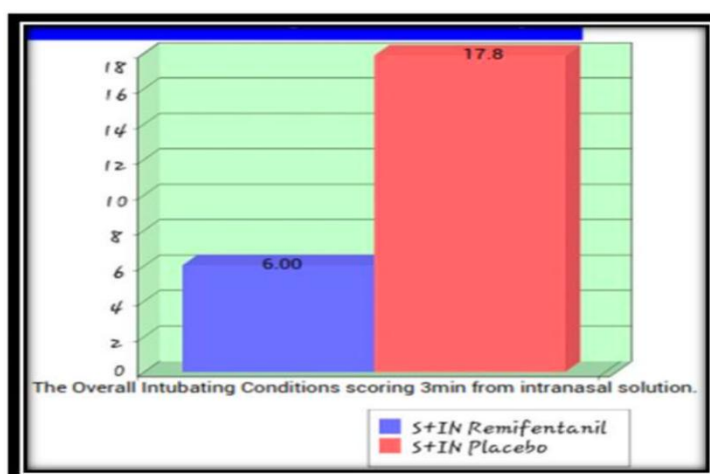


Figure 6: The overall intubating conditions 3minutes from IN solution in sevoflurane anesthetized children for both groups. It shows a significant lower score of intubating conditions in the IN Remifentanyl treated group (p value < 0.001).

The intubating condition scale suggests that intubating conditions accepted when all scores were 2 or less. If any of the scores were 3 or 4 for any of the five variables, intubating conditions unfavorable.



Figure 7: The percentage incidence of acceptable and unacceptable intubating conditions in each group. Note that the percentage of acceptable intubating conditions was 90% in the remifentanyl IN administered group versus 4% in the placebo IN administered group.

Heart rate and mean blood pressure were taken from all the patients firstly before induction of anesthesia (HR1 & MAP1), 2 minutes after intranasal solution (HR2 & MAP2) then 1 minute, 3 minutes, and 5 minutes after endotracheal intubation (HR3 & MAP3), (HR4&MAP 4), (HR5& MAP 5).

HR&MAP marked as 3, 4&5 in the intranasal remifentanil treated group were significantly lower than the intranasal normal saline treated group after endotracheal intubation in sevoflurane anesthetized children.

Table 4: Hemodynamic Records.

Timing		Study Group S+IN Remifentanil	Control Group S+IN placebo	P Value
Before induction of anesthesia	HR1	140.09±14.50	139.13±12.59	0.785
	MAP1	72.33±2.17	73.3±1.85	0.067
2 min. after IN solution	HR2	106.17±21.33	111.8±5.01	0.164
	MAP2	69.00±3.21	70.20±1.65	0.073
1 min. after intubation	HR3	95.33±24.08	128.00±6.07	* < 0.0001
	MAP3	67.33±3.88	73.17±1.53	* < 0.0001
3 min. after intubation	HR4	95.22±2.48	130.17±6.76	* < 0.0001
	MAP4	67.00±0.68	74.27±2.46	< 0.0001
5 min. after intubation	HR5	95.83±1.26	129.27±13.38	< 0.0001
	MAP5	68.00±0.83	72.33±2.17	< 0.0001

Baseline heart rate (HR1) records show no significant difference between the two groups.

Heart rate (HR2) was Insignificantly lowered after IN Remifentanil in sevoflurane anesthetized children.

Heart rate (HR3, 4&5) in the IN remifentanil treated group was significantly lower than the intranasal normal saline treated group after endotracheal intubation in sevoflurane anesthetized children.

Table 5: Heart Rate Records (HR).

Timing	Study Group S+IN Remifentanil	Control Group S+IN placebo	P Value
HR1 Before induction	140.09±14.50	139.13±12.59	0.785
HR2 2 min. after IN solution	106.17±21.33	111.8±5.01	0.164
HR3 1 min. after intubation	95.33±24.08	128.00±6.07	* < 0.0001
HR4 3 min. after intubation	95.22±2.48	130.17±6.76	* < 0.0001
HR5 5 min. after intubation	95.83±1.26	129.27±13.38	* < 0.0001

There is no significant difference in the baseline heart rate(HR1)records between the two groups.

Heart rate (HR2) was IN significantly lowered after IN Remifentanil in sevoflurane anesthetized children.

Heart rate (HR3, 4&5) in the IN remifentanil treated group were significantly lower than the intranasal normal saline treated group after endotracheal intubation in sevoflurane anesthetized children.

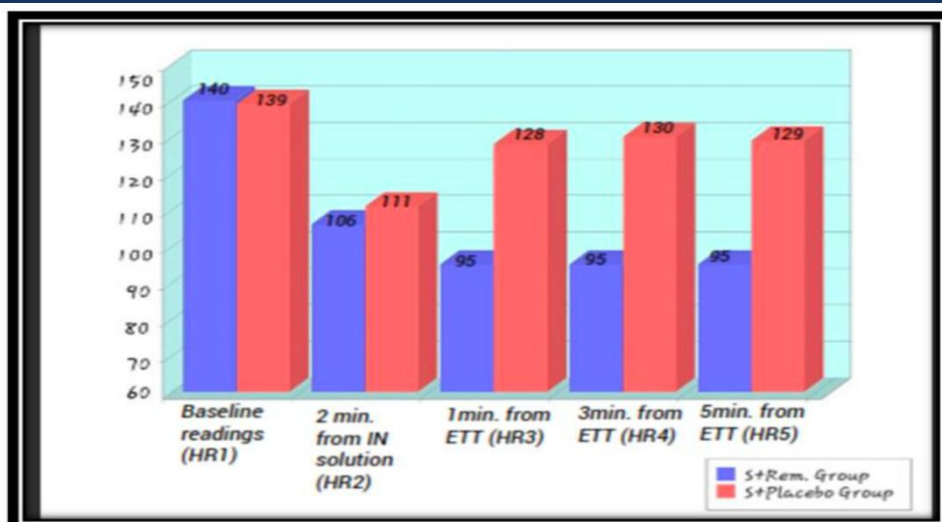


Figure 8: Heart Rate Records.

Baseline MAP (MAP1) records show no significant difference between the two groups. Mean Arterial Pressure (MAP 2) was Insignificantly lowered after IN Remifentanyl in sevoflurane anesthetized children.

Mean Arterial Pressure (MAP 3, 4&5) in the IN remifentanyl treated group was significantly lower than the intranasal normal saline treated group after endotracheal intubation in sevoflurane anesthetized children.

Table 6: Mean Arterial Pressure Records (MAP).

Timing	Study Group S+IN Remifentanyl	Control Group S+IN placebo	P Value
MAP1 Before induction of anesthesia	72.33±2.17	73.3±1.85	* 0.067
MAP2 2 min. after IN solution	69.00±3.21	70.20±1.65	* 0.073
MAP3 1 min. after intubation	67.33±3.88	73.17±1.53	* < 0.0001
MAP4 3 min. after intubation	67.00±0.68	74.27±2.46	* < 0.0001
MAP5 5 min. after intubation	68.00±0.83	72.33±2.17	* < 0.0001

There is no significant difference in the baseline Mean Arterial Pressure (MAP 1) records between the two groups.

Mean Arterial Pressure (MAP 2) was Insignificantly lowered after IN Remifentanyl in sevoflurane anesthetized children.

Mean Arterial Pressure (MAP 3, 4&5) in the IN remifentanyl treated group was significantly lower than the intranasal normal saline treated group after endotracheal intubation in sevoflurane anesthetized children.

This study aims to deduce the capability of intranasal remifentanyl to improve intubating

conditions and to depress the hemodynamic response to intubation and laryngoscopy both in the early anesthesia period.

The patients' demographic characteristics show no significant differences between the two groups.

When looking at table (2) we notice that the p values of the patients age, weight, height, gender and ASA class are 0.7, 0.3, 0.4, 1 and 1 respectively indicating no significant difference regarding the above parameters between the two groups. The same can be said for the baseline hemodynamic values (p value 0.7 & 0.06 for HR1 & MAP1 respectively - table 4).

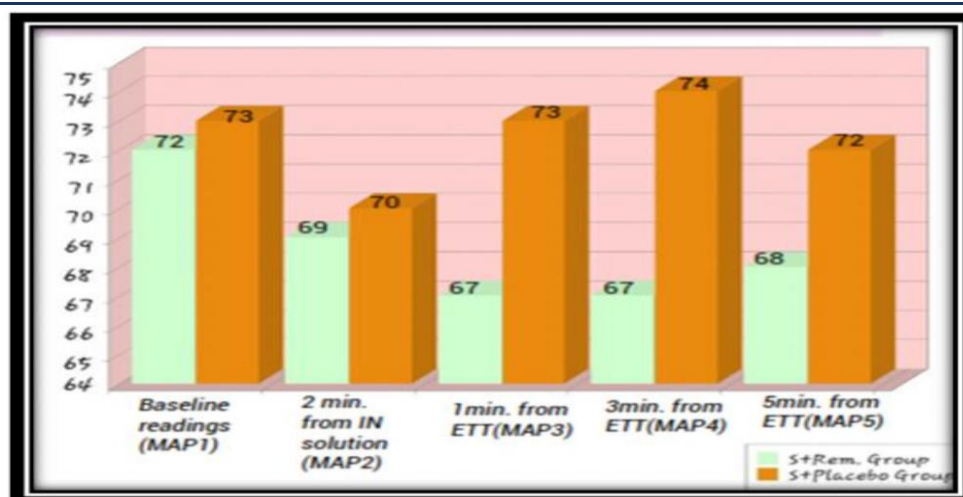


Figure 9: Mean Arterial Pressure (MAP) Records.

DISCUSSION

Comparing to the control group, the study group (sevoflurane + remifentanyl) showed insignificant decrease in hemodynamic readings 2 minutes after intranasal solution (p value 0.1 & 0.07 for HR2 & MAP2 respectively - table 4).

Hemodynamic values (HR & MAP) labeled as 3, 4 & 5 in table 6 were taken within 5 minutes after endotracheal intubation and showed significant decrease in the study group compared to the control group (p value < 0. 0001 at 1 minute, 3minutes and 5 minutes after endotracheal intubation). This indicates the intranasal remifentanyl ability to depress the hemodynamic response to intubation and laryngoscopy.

A validated score was used to evaluate conditions for laryngoscopy and response to intubation at 3 minutes after the administration of intranasal solution just before endotracheal intubation for all members of the both groups.

The score uses 1-4 points for an individual intubating condition (jaw relaxation, laryngoscopy, vocal cords, cough & limb movement) and 5-20 points for the sum of the five intubating conditions scores for each patient.

Table 3 shows that every intubating condition as well as the overall intubating conditions scores in the study group are significantly lower than the correspondent score points of the control group indicating more optimal intubating conditions obtained in the study group than the control group 3 minutes after intranasal solution (p value < 0.0001 for each & overall intubating conditions).

The intubating conditions were classified as acceptable when all scores were 2 or less. If any of

the scores were 3 or 4 for any of the five variables, intubating conditions were judged unacceptable. figure (7) shows the percentage incidence of acceptable and unacceptable intubating conditions in each group and reveal that the percentage of acceptable intubating conditions was 90% in the remifentanyl IN administered study group versus 4% in the placebo IN administered group. Thus, more optimal intubating conditions in terms of scoring points and percentage of patients with acceptable intubating conditions were obtained in the study group than the control group.

This study like other studies trying to make easy induction of anesthesia for the anxious infants and children. In addition, it illustrates an important way to optimize intubating conditions, omit the muscle relaxant needed for laryngoscopy and intubation, and attenuate the hemodynamic response to laryngoscopy and intubation.

The international anesthesia research society in October 2008 had published a study on the (The Effect of Intranasal Administration of Remifentanyl on Intubating Conditions and Airway Response After Sevoflurane Induction of Anesthesia in Children) but with a different intubating conditions scorer and correlating scoring points with plasma remifentanyl concentrations had shown little different results but reached identical aim of this research.

Assuming that nasally administered drugs are about half that obtained after IV dosing can make good comparison of this study with studies used intravenous remifentanyl for optimizing intubating conditions and/ or hemodynamic response to intubation and laryngoscopy. (Optimal remifentanyl dose for light-wand intubation without muscle relaxants in healthy patients with

thiopental coadministration) was another study published in euro-journal of Anesthesiology in November 2012 concluded that remifentanyl 2 mic/kg combined with thiopental 5 mg/kg provides acceptable conditions for light-wand intubation without muscle relaxants but here the hypnotic agent was administered intravenously rather than inhalational induction.

A review published as a journal article in (Anaesth Intensive Care 2016) had concluded that remifentanyl and sufentanyl were the best among opioids in obliterating the hemodynamic response to intubation and laryngoscopy in pediatric population and that was equal to our aim and conclusion for remifentanyl.

An investigation published at (Medicinski pregled 2007) indicate that intravenous bolus dose of remifentanyl of 0.5 mic/kg, combined with thiopental, reduces the cardiovascular response to laryngoscopy and tracheal intubation, whereas bolus doses of remifentanyl, 1 and 1.5 mic/kg, provide cardiovascular stability, as well as safe and efficient induction of anesthesia.

CONCLUSION

Nasal administration of remifentanyl one minute after sevoflurane induction of anesthesia in children produces optimal intubating conditions after three minutes of the administration as well as attenuation of hemodynamic response to intubation and laryngoscopy.

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Source of support: Nil; **Conflict of interest:** Nil.

Cite this article as:

Al-Hamashi, M. E. M., Al-Badri, B. M. L. & Al-Qassab, R. A. Y. "The Effect of Intranasal Administration of Remifentanyl on Hemodynamic Response to Laryngoscopy and Intubation after Sevoflurane Induction of Anesthesia in Children." *Sarcouncil journal of Medical sciences* 5.9 (2026): pp 15-23.