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ORIGINAL RESEARCH **AIRWAY MANAGEMENT**

Comparison of high dose fentanyl, magnesium and lidocaine for effective and consistent attenuation of hemodynamic responses during laryngoscopy and intubation

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Abstract

Background & objective: Laryngoscopy and endotracheal intubation provoke stress response with consequent hemodynamic instability. Fentanyl is a short acting potent opioid commonly used to control stress response. Magnesium sulphate can attenuate stress response through inhibiting catecholamines release. Systemic administration of lidocaine helps in blocking stress response. This study aimed to compare the effectiveness of high dose fentanyl, magnesium, and lidocaine versus conventional anesthesia on consistent attenuation of stress response to laryngoscopy and endotracheal intubation.

Methods: 160 patients were randomly allocated into one of the 4 study groups. Group C: received fentanyl 2µg/kg, Group F: received fentanyl 4 µg/kg, Group M: received magnesium sulphate 30mg/kg combined with fentanyl 2µg/kg and Group L: received lidocaine 1.5 mg/kg combined with fentanyl 2 µg/kg. Outcome measures included heart rate (HR) values and mean arterial blood pressure (MAP) values during endotracheal intubation and over the following 5 min in addition to coughing and lacrimation during intubation.

Results: HR in group C and group L increased compared to baseline readings following intubation and at 1,3,5 min and was statistically significant for group C but comparable for group L. In group F and group M, HR decreased significantly compared to baseline following intubation and the rest of the times studied. MAP in group C and L were maintained for the period of 5 min following intubation whereas group F and L showed a statistically significant reduction in their MAP values compared to baseline readings.

Conclusion: High dose fentanyl, fentanyl-magnesium combination, and fentanyl- lidocaine combination can attenuate stress response to laryngoscopy and endotracheal intubation when compared to conventional anesthesia. Furthermore, using high dose fentanyl and fentanyl-Magnesium combination results in consistent attenuation of the response.

Abbreviations: HR – heart rate; MAP – mean arterial blood pressure; PPV - positive pressure ventilation

Key words: Fentanyl; Magnesium sulphate; Lidocaine; Hemodynamics; Intubation

Trial registration: This trial was prospectively registered at Clinical Trials.gov on 3 September 2020 with registration number NCT04544163. https://clinicaltrials.gov/ct2/show/NCT04544163

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1. Introduction

Airway manipulation and instrumentation by laryngoscopy and endotracheal intubation provokes stress response and hemodynamic instability that manifests itself by an increase in heart rate (HR) and blood pressure. [1, 2] Although this increase lasts for only s few min, but it carries deleterious effects to the patients who cannot withstand sympathetic stimulation, such as hypertensive patients and patients with cardiovascular or cerebrovascular diseases. [3, 4] Blocking stress response to intubation is important in maintaining patient hemodynamic stability. Various techniques and drugs have been used to blunt stress response, including topical use of local anesthetics, inhalational administration of alpha 2 agonists and intravenous drug administration. [5, 6] Intravenous drugs used include opioids, local anesthetics, magnesium, beta blockers and alpha-2 agonists. [7-10] Fentanyl is used as an effective short acting opioid that can blunt the stress response with fast onset of action. [7] It exerts its action through acting on opioid receptors and inhibiting the sympathetic pathway. [11, 12] Magnesium sulphate ($MgSO_4$) is an anesthetic adjuvant, which can effectively reduce stress response to intubation through inhibiting catecholamine release. [8, 13] $MgSO_4$ has anesthetic, analgesic and muscle relaxant enhancing effects. [14] Lidocaine is a local anesthetic that is primarily used in the treatment and prevention of ventricular arrythmia, it can be used as an adjuvant drug to attenuate stress response to intubation. Its action is established by inhibiting nerve impulse transmission through reversible block of sodium channels. [5, 14] Additionally, systemic lidocaine has an N-methyl-D-aspartate receptor (NMDA) antagonist effect and reduces substance P release. [16, 17] Several studies investigated the effect of different drugs on attenuating stress response to intubation. We investigated the effectiveness of routinely used low dose fentanyl 2 µg/kg, high dose fentanyl 4 µg/kg, fentanyl−$MgSO_4$ combination and fentanyl–lidocaine combination on consistent attenuation of hemodynamic stress response to intubation.

2. Methodology

This double blinded (patient and outcome assessor) parallel study was conducted at National Cancer Institute, Cairo University from September 2020 to May 2021, after approval of the institutional review board (No. IRB 201920017.2P) and was prospectively registered on www.clinicaltrials.gov (NCT 04544163). The study followed the standard of Declaration of Helsinki and Consolidated Standards of Reporting Trials (CONSORT) 2010 guidelines.

One hundred and sixty patients were included in the study, who fulfilled the inclusion criteria, being an adult ≥ 18 y old, ASA-I and II, scheduled for surgeries under general anesthesia with single lumen endotracheal intubation. Exclusion criteria included patients with allergy to any of the used drugs, suspected difficult intubation, impaired renal or liver functions, uncontrolled hypertension, cardiovascular or cerebrovascular disease, or thyroid function abnormalities. Patients were recruited after preoperative anesthesia assessment. Patients were randomly allocated using computer generated permuted random blocks into one of the four study groups. Upon arrival to the holding area and after obtaining a written informed consent, anesthesia resident assigned patients into one of the 4 groups using sealed envelope technique. All patients were premedicated with 2 mg midazolam after insertion of a 20 G intravenous cannula. Standard monitoring was applied. Induction of anesthesia for all patients was done using propofol 2 mg/kg and rocuronium 0.6 mg/kg. Group C (control group) received fentanyl 2 µg/kg; Group F received fentanyl 4 µg/kg with induction of anesthesia; Group M received $MgSO_4$ 30 mg/kg in 100 ml saline infusion over 10 min, ended 10 min before induction in addition to IV fentanyl 2 µg/kg with induction and Group L received IV lidocaine 1.5 mg/kg 90 sec prior to intubation in addition to IV fentanyl 2 µg/kg with induction. Induction was followed by positive pressure ventilation (PPV) and oral intubation. Anesthesia was maintained with sevoflurane 2% in 50% oxygen / air mixture. A 20% increase in the blood pressure or HR above the baseline was considered significant and treated accordingly. A decrease by 20% below the baseline in blood pressure was treated by 5 mg ephedrine, a decrease in HR below 45/min was treated by 1 mg atropine. Primary outcome measure included HR values in beats/min at baseline, after induction of anesthesia, after intubation and after 1, 3, and 5 min. Secondary outcome measures included mean arterial blood pressure (MAP) at baseline, after induction of anesthesia, after intubation and after 1, 3, and 5 min in addition to intubating conditions and lacrimation during endotracheal intubation. Cases with more than one intubating attempt or prolonged intubating time > 20 sec were excluded from the study.

Based on the previous papers by Gurulingappa et al., [5] and Chaithanya et al., [8] the expected difference between at least 2 groups in HR at 5 min is 7 ± 8. Using power 95% and 5% significance level, 35 patients in each group were required. The sample size was increased to 40 in each group to compensate for possible excluded cases due to failure. Sample size calculation was achieved using PS: Power and Sample Size Calculation Software Version 3.1.2 (Vanderbilt University, Nashville, Tennessee, USA).

Table 1: Demographic data and clinical characteristics in the 4 studied groups

Variable	Group C n = 35	Group F n = 36	Group M n = 37	Group L n = 37	P value
Age (y)	48.94 ± 11.31	45.47 ± 9.83	50.24 ± 9.03	50.73 ± 7.85	0.086
Sex					
• Male	13(37.1%)	14(38.9%)	15(40.5%)	14(37.8%)	0.992
• Female	22(62.9%)	22(61.1%)	22(59.5%)	23(62.2%)	
BMI (kg/m^2)	28.27 ± 4.12	27.60 ± 3.64	28.28 ± 2.96	28.08 ± 2.93	0.820
Comorbidity					
• HTN	9(25.7%)	11(30.6%)	14(37.8%)	12(32.4%)	0.740
• DM	6(17.1%)	7(19.4%)	9(24.3%)	7(18.9%)	0.886

Data presented as Mean ± SD or n (%); HTN, hypertension; DM, diabetes mellitus; $p < 0.05$ statistically significant

Table 2: Heart rate values following induction in comparison to midazolam in the 4 studied groups

Time	Group C		Group F		Group M		Group L	
	mean ± SD	P value	mean ± SD	P value	mean ± SD	P value	mean ± SD	P value
Midazolam	80.23 ± 10.49		83.50 ± 9.47		80.70 ± 6.05		79.97 ± 9.86	
Induction	79.11 ± 9.81	0.407	79.92 ± 8.51	< 0.001	77.24 ± 8.07	0.007	77.76 ± 9.65	0.049
Intubation	89.89 ± 13.90	< 0.001	78.72 ± 9.06	0.003	76.68 ± 10.78	0.024	80.78 ± 13.47	0.193
1 minute	87.00 ± 11.35	< 0.001	77.36 ± 9.39	0.001	74.81 ± 9.26	0.001	83.89 ± 13.54	0.071
3 min	85.17 ± 11.10	0.002	76.22 ± 11.01	0.001	75.24 ± 10.39	0.005	82.92 ± 12.34	0.121
5 min	85.83 ± 10.94	0.001	75.00 ± 11.20	< 0.001	71.98 ± 10.20	< 0.001	82.22 ± 10.16	0.129

$p < 0.05$ statistically significant

Table 3: MAP values following induction in comparison to midazolam in the 4 studied groups

MAP	Group C		Group F		Group M		Group L	
	mean ± SD	P value	mean ± SD	P value	mean ± SD	P value	mean ± SD	P value
Midazolam	90.20 ± 5.22		89.56 ± 6.37		90.68 ± 6.23		90.24 ± 5.52	
Induction	83.37 ± 8.60	< 0.001	73.83 ± 7.13	< 0.001	74.38 ± 8.19	< 0.001	83.32 ± 8.04	< 0.001
Intubation	90.03 ± 11.84	0.927	76.06 ± 9.96	< 0.001	75.84 ± 8.65	< 0.001	87.68 ± 12.51	0.210
1 minute	88.57 ± 11.77	0.399	72.25 ± 7.63	< 0.001	72.89 ± 7.14	< 0.001	87.73 ± 13.73	0.287
3 min	87.11 ± 11.37	0.101	71.61 ± 6.04	< 0.001	71.70 ± 7.89	< 0.001	85.68 ± 12.24	0.032
5 min	87.06 ± 10.78	0.068	72.11 ± 8.19	< 0.001	69.92 ± 6.68	< 0.001	87.03 ± 10.82	0.098

$p < 0.05$ statistically significant

Table 4: Number of patients who experienced Lacrimation and coughing during intubation

	Group C N (%)	Group F N (%)	Group M N (%)	Group L N (%)	P value
Lacrimation	3(8.6%)	0(0.0%)	0(0.0%)	2(5.4%)	0.091
Coughing with intubation	0(0.0%)	0(0.0%)	0(0.0%)	0(0.0%)	------

Statistical analysis

Statistical analysis was performed using SPSS v.25 (IBM©, Chicago, IL, USA). Data for age, BMI, HR and MAP values were displayed as mean and standard deviation and were analyzed using unpaired Student's t-test. Patient's gender, clinical characteristics and data for patients who experienced coughing or lacrimation during intubation were presented in the form of number and percentage and either Chi-square (X^2) or Fisher's Exact tests were used as applicable to evaluate these data. $P < 0.05$ was considered statistically significant.

3. Results

One hundred and ninety-seven patients were consecutively enrolled in the study, 37 patients were excluded, 28 patients did not meet the eligibility criteria and 9 patients refused to participate (Figure 1).

The studied groups were comparable regarding their demographic data and clinical characteristics (Table 1).

Preoperative (holding area) and baseline HR and MAP values were comparable in the groups. Compared to the baseline values HR showed statistically significant reduction after induction of anesthesia in all the studied groups ($p < 0.05$) except HR values for Group C which showed comparable reduction to their baseline values ($P = 0.407$). Whereas HR showed an increase in comparison to their baseline values for Group C and Group L following intubation and after 1, 3, and 5 min, which was statistically significant in Group C but comparable in Group L. On the other hand, both Group F and Group M showed consistent statistically significant reduction in their HR values following intubation and over the next 5 min. There was a significant difference in heart rate values between the groups after intubation ($P < 0.001$) being higher for Group C compared to the other 3 groups; after 1-min values were higher for Group C compared to Group F and Group M ($P < 0.001$). Furthermore, HR values were significantly higher after 3-min, and 5-min for Group C and Group L compared to Group F and Group M, ($P < 0.001$, $P < 0.001$ respectively) (Figure 2, Table 2).

Following induction of anesthesia statistically significant reduction in MAP values compared to baseline were recorded in all studied groups ($P < 0.05$).

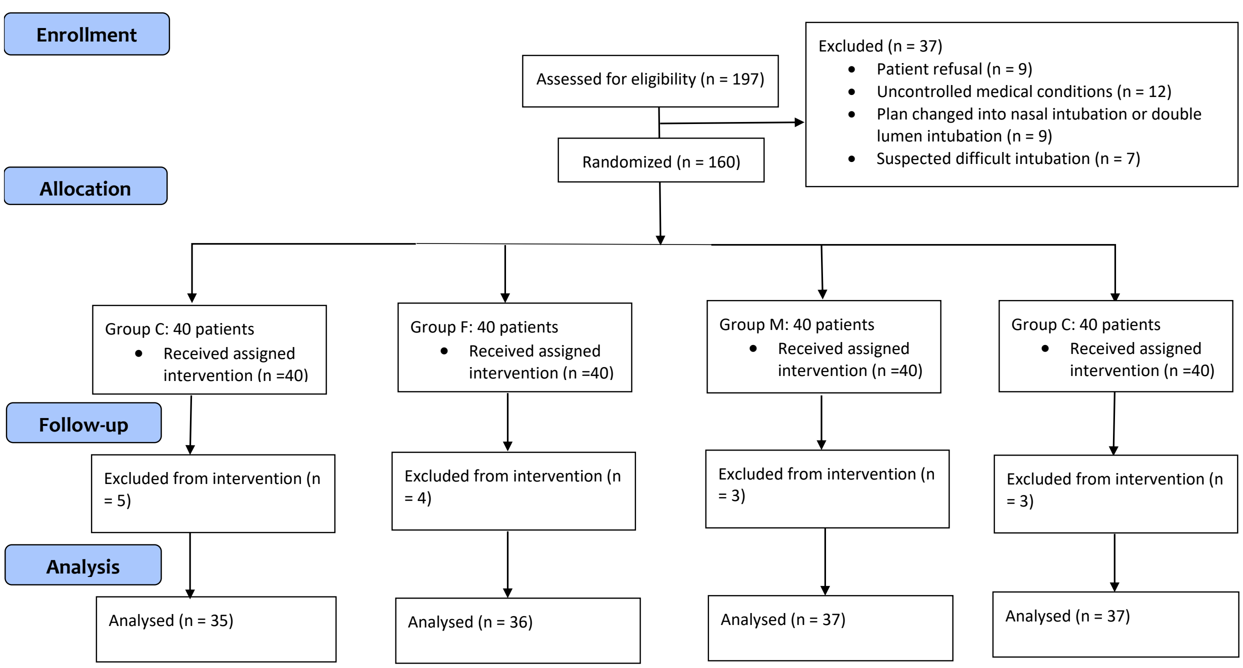

Figure1 : CONSORT flow chart

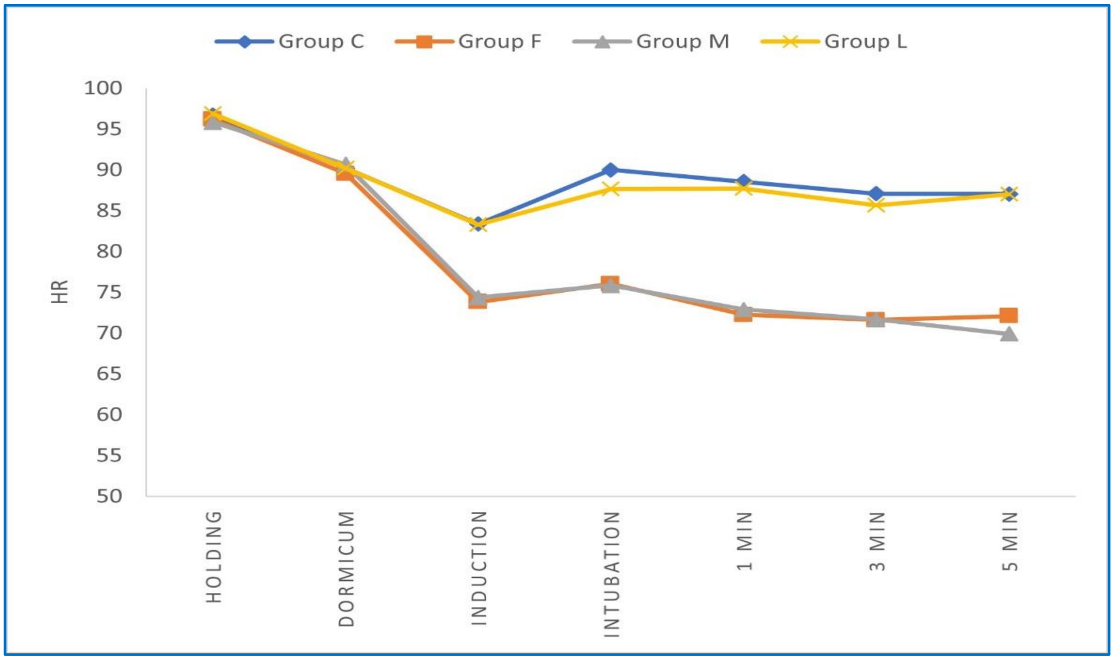

Figure 2: Comparative heart rates at different times in three groups

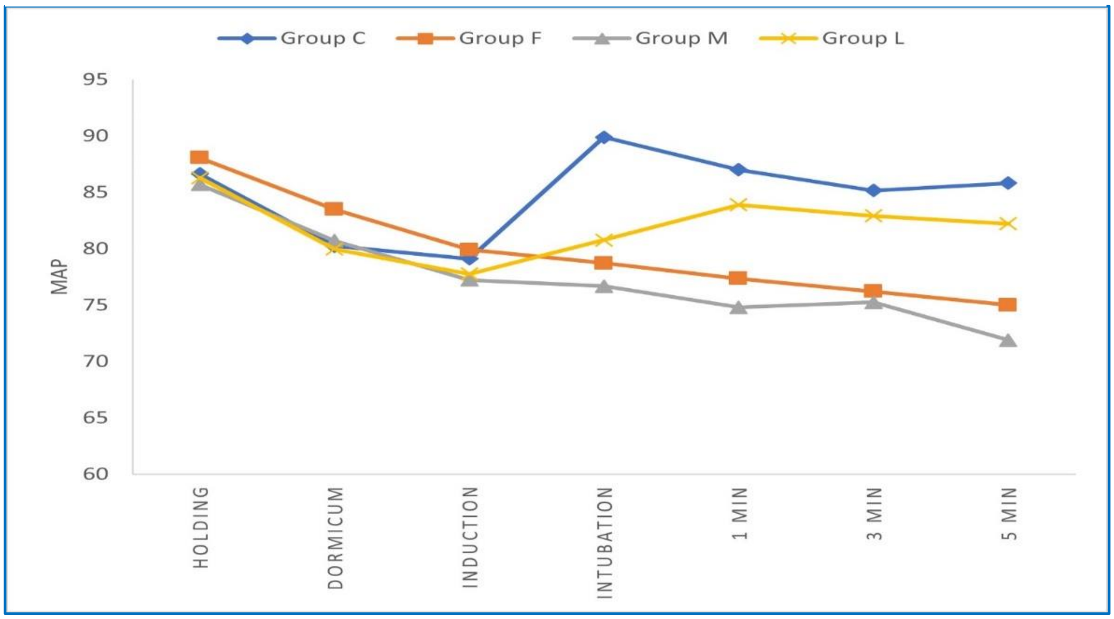

Figure 3: Comparative mean blood pressure values at different times in three groups

At the rest of the recorded times MAP values were maintained in both Group C and Group L compared to their baseline readings ($P > 0.05$). On the other hand, both Group F and Group M exhibited a statistically significant reduction in MAP values compared to their baseline. MAP values were significantly higher in both Group C and Group L compared to Group F and Group M following intubation, after 1, 3 and 5 min (Figure 3, Table 3).

There were no reported cases of coughing with intubation in the 4 groups. Only 3 patients in Group C and 2 patients in Group L experienced lacrimation during intubation (Table 4).

4. Discussion

The sympathoadrenal reflex associated with laryngoscopy and endotracheal intubation can lead to serious alteration in blood pressure and precipitate cardiac arrythmias. The aim of the current study was to reach an adequate measure that can effectively and consistently attenuate hemodynamic response to airway manipulation. The results of this study revealed that the conventional fentanyl 2 µg/kg regimen could not effectively block the stress response to intubation while fentanyl 4µg/kg and fentanyl−magnesium combination were associated with effective and consistent attenuation. On the other hand, fentanyl−lidocaine combination only maintained the hemodynamics during intubation but not afterwards. Following induction of anesthesia, MAP and HR exhibited significant reduction which is in agreement with previous studies. [18, 19] In accordance with the current study, Sharma and colleagues compared adding lidocaine 1.5 mg/kg versus fentanyl 3 µg/kg to conventional dose fentanyl 2 µg/kg on attenuation of stress response at different time points. They reported that both can attenuate the stress response but adding 3 µg/kg fentanyl prior to endotracheal intubation showed better effect on consistent attenuation of the stress response to intubation in cardiac patients. [18] Similarly, Jalili and colleagues investigated the effect of different methods of lidocaine administration and high dose fentanyl 5 µg/kg versus conventional dose of fentanyl 2 µg/kg on blocking stress response to intubation, they recommended that adequate measures should be adopted over the conventional one to attenuate stress response to intubation in elderly patients, whereas high dose fentanyl prominently attenuated stress response to intubation compared to the conventional 2 µg/kg fentanyl.[19] Furthermore, Hashemian and colleagues studied the efficacy of fentanyl 3 µg/kg, lidocaine 1.5 mg/kg and fentanyl−lidocaine combination on blocking stress response to rapid sequence intubation, they documented that lidocaine and fentanyl−lidocaine combination was superior to fentanyl in blocking stress response. [20] Hassani and colleagues investigated the effect of adding lidocaine 1.5 mg/kg to fentanyl 2 µg/kg versus fentanyl 2 µg/kg on stress response to intubation in hypertensive patients. They concluded that although both groups helped in reducing response to intubation with predominance of fentanyl−lidocaine combination but both could not inhibit the evoked response. [21] Similarly, Kim and colleagues investigated the role of lidocaine combined with fentanyl 1.5 µg/kg versus fentanyl 1.5 µg/kg in attenuation of hemodynamic response to intubation. They concluded that although addition of lidocaine attenuated the increase in MAP, but it could not prevent the increase in HR values following intubation. [22] In a systematic review, Qi and colleagues reported that administration of intravenous lidocaine 1.5 mg/kg prior to laryngoscopy and endotracheal intubation can reduce HR stress response in diversity of age groups which was predominant in elderly but not in pediatric age group with effective maintenance of blood pressure values in different age group. [23] Panda and colleagues concluded that optimal dose for magnesium pretreatment is 30 mg/kg, and this was superior to the effect of lidocaine. [24] Mendonca and colleagues compared the effect of adding magnesium sulfate in a dose of 30 mg/kg versus lidocaine 1.5 mg/kg to fentanyl 2 µg/kg and reported that although both groups experienced an increase in HR and blood pressure following laryngoscopy and intubation, but this was clinically insignificant and that both drugs can be considered as safe and efficient alternatives in controlling hemodynamic response to laryngoscopy and intubation. [25] These results differ from ours regarding the statistical significance of $MgSO_4$ in attenuation of the stress response, we assume that such difference may be attributed to the difference in $MgSO_4$ administration timing as $MgSO_4$ infusion in the current study ended 10 min prior to induction of anesthesia. In another study by Padmawar and colleagues although they reported that pretreatment with $MgSO_4$ 40 mg/kg was superior to lidocaine 1.5 mg/kg in providing sustained control in stress response to intubation, both drugs could not block the immediate response to intubation with increase in heart rate and blood pressure values, yet the values returned to baseline 5 min following intubation in the $MgSO_4$ group. [26] The encountered difference with our study results regarding the increase in post-intubation hemodynamic values for the $MgSO_4$ group may be attributed to the additional dose of fentanyl 2 µg/kg we used.

5. Limitations

A limitation of the present study was the lack of age and gender stratification which may affect the hemodynamic response to intubation.

6. Recommendations

It would also be beneficial to study these methods on patients who require nasotracheal intubation or double lumen tube intubation which often results in more pronounced hemodynamic response. Furthermore, it would be worthwhile to investigate the response of hypertensive and cardiac patients to these approaches.

7. Conclusion

High dose fentanyl, fentanyl−magnesium combination, and fentanyl−lidocaine combination can attenuate stress response to laryngoscopy and endotracheal intubation when compared to conventional anesthesia. Furthermore, using high dose fentanyl and fentanyl−magnesium combination results in consistent attenuation of the response, thus it is recommended that whenever effective and consistent attenuation of stress response to intubation is required, using higher doses of fentanyl or adding $MgSO_4$ is better to be adopted over conventional anesthesia.

8. Disclosure/Conflict of Interest

None declared by the authors.

9. Financial Disclosures

No institutional or industry funding was involved in the study.

10. Data availability

The numerical data related to this study is available with the authors and can be provided on suitable request.

11. Authors' contribution

Both authors read and approved the final version of the manuscript

Both authors shared concept, patient recruitment, interpretation and analyzation of data, writing and editing the manuscript

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