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Magnesium Sulfate and Fentanyl for Facilitating Awake Fiberoptic Nasotracheal Intubation: A Randomized Study

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Abstract

Background: Various drugs have been used to facilitate awake fiberoptic intubation (AFOI). Although fentanyl is probably used most frequently, magnesium sulfate can provide muscle relaxation without respiratory depression and attenuate hemodynamic responses.

Methods: We randomly allocated 20 patients of both sexes, aged 18 - 60 years, and ASA status I-II to receive fentanyl 2 μg/kg (group F) or magnesium sulfate 45 mg/kg (group M) before AFOI. The intubating conditions were evaluated by Ramsay sedation score (RSS), cough score, post-intubation score, additional topicalization requirement, and hemodynamic response. Oxygen desaturation, airway morbidity, recall of procedure, and the patient's willingness to return for the same kind of anesthesia, if required, were also studied. Statistical analyses were done using SPSS V. 17.0 software. Numerical data were analyzed using independent and paired *t*-tests and categorical data using the chi-square test. P values of < 0.05 were considered significant.

Results: RSS, cough score, post-intubation score, lignocaine dose, airway-related morbidity, and willingness to undergo the same kind of anesthesia for a second time were comparable between the two groups. Both drugs had comparable effects on hemodynamic response to intubation. However, the incidence of recall of the procedure was significantly lower in group F ($P = 0.003$).

Conclusions: The degree of coughing during fiberoptic bronchoscopy, tolerance of the endotracheal tube after intubation, and the hemodynamic response to intubation were similar after the administration of either fentanyl 2 μg/kg or magnesium sulfate 45 mg/kg.

Keywords: Airway, Intubation, Fiberoptic, Fentanyl, Magnesium Sulfate, Cough Score

1. Background

Awake fiberoptic intubation (AFOI) is the gold standard technique for intubation of patients with an anticipated difficult airway, failed intubation, and unstable cervical spine. The success of AFOI is highly dependent on good patient preparation and safe sedation scheme. Conscious sedation not only minimizes the awareness of the procedure and increases patient acceptance, but also provides a calm and co-operative patient who is able to follow verbal commands (1). Hemodynamic responses to tracheal intubation are mediated by the autonomic nervous system and include hypertension, arrhythmias, and tachycardia, attributed to a reflex increase in sympathetic discharge caused by the stimulation of the upper respiratory tract (2, 3). Various drugs such as benzodiazepines, opioids, propofol, dexmedetomidine, etc. are used alone or in combination to suppress this pressor response (4), with opioids being the most commonly used drugs. Besides facilitating fiberscopy and intubation, they provide analgesia and suppress coughing. However, there is a risk of respiratory depression with consequent hypoxemia.

Magnesium is known to possess muscle-relaxing effects by reducing acetylcholine release. It acts as a membrane stabilizer by intervening in the activation of membrane Ca-ATPase and Na-K ATPase. Magnesium also seems to have antinociceptive and anesthetic properties through its antagonist effect on N-methyl-D-aspartate (NMDA) receptors (5-7). There remains an ongoing search for an ideal agent for conscious sedation that ensures spontaneous ventilation with a patent airway, patient cooperation, smooth intubating conditions, and stable hemodynamics without respiratory depression. We hypothesized that the administration of magnesium sulfate ($MgSO_4$) may facilitate nasotracheal AFOI.

2. Objectives

The present study aimed to assess the effectiveness of $MgSO_4$ in facilitating nasotracheal AFOI and to compare $MgSO_4$ with intravenous fentanyl by assessing the cough score, the degree of sedation, the hemodynamic response to intubation, post-intubation score, patient recall, airway trauma, and willingness to return as secondary outcomes.

3. Methods

This double-blinded randomized prospective trial was conducted at the Department of Anesthesiology of a tertiary care center after being approved by the Institutional Ethics Committee from March 2016 to March 2017. The study recruited 20 adult patients of both sexes, aged 18 - 60 years, with American Society of Anesthesiologists (ASA) physical status I-II, and posted for elective surgical procedures under general anesthesia. We excluded patients with a history of alcohol/drug abuse, allergy to study drugs, bradycardia, significant cardiovascular, neurological, hepatic, renal, and pulmonary diseases, contraindications to nasal intubation (thrombocytopenia/coagulopathy), recent upper respiratory tract infection, anticipated difficult airway, and pregnancy. Written informed consent was obtained.

On the morning of the surgery day, patients were randomly allocated to group M ($MgSO_4$) or group F (Fentanyl). Randomization was done by block randomization using randomly mixed block sizes. The patients were blinded to their group allocation. All patients in both groups were premedicated with alprazolam 0.5 mg tablets on the night before surgery, ranitidine 150 mg and metoclopramide 10 mg tablets 2 hours before surgery, and intramuscular glycopyrrolate 0.2 mg one hour before anesthesia. All patients received 2 - 3 drops of xylometazoline 0.1% in each nostril for decongestion of the nasal mucosa. The toxic dose of topical lignocaine was calculated (8.2 mg/kg as recommended by the British Thoracic Society) according to the weight of the patient. The topicalization of the airway was done with 4 mL of 4% lignocaine. This lignocaine amount (160 mg) was subtracted from the maximum allowable lignocaine dose and the safe number of SAYGO boluses was calculated for each patient. After shifting to the operating room, intravenous access was secured and standard monitors were attached. A well-lubricated nasopharyngeal airway (NPA) was inserted into a nostril with better patency, followed by administering 1 mg midazolam intravenously. After 5 minutes, the study drug infusion started and completed in 10 minutes. Group M received $MgSO_4$ 45 mg/kg and group F received fentanyl 2 μg/kg intravenously. Both study drugs were diluted in normal saline to a final volume of 50 mL by an independent anesthesiologist not involved in the subsequent stages of the study. Fiberscopy was performed by a consultant anesthesiologist who was routinely practicing fiberscopy and had performed at least 10 successful fiberoptic nasotracheal intubations on a mannequin and 20 on patients. Another investigator made observations and recorded the data. Both investigators were blinded to the study drugs and remained constant throughout the study period.

At the end of the study drug infusion, sedation was evaluated by the Ramsay sedation scale (RSS) score as 1 (anxious, agitated, or restless), 2 (cooperative, oriented, and tranquil), 3 (sedated but responding to commands), 4 (asleep, brisk glabellar reflex, or responding to a loud noise), 5 (asleep, sluggish glabellar reflex, or responding to a loud noise), and 6 (asleep with no response to a painful stimulus). The NPA was then removed, the fiberscope was loaded with an appropriately sized cuffed polyvinyl chloride endotracheal tube (ETT), and fiberscopy was performed through the selected nostril. Whenever the patient coughed, additional topicalization was performed with boluses of 1 mL of lignocaine 2% by the SAYGO technique (8, 9). One additional bolus was used when vocal cords were visualized and the total number of required boluses was noted. The number of boluses never exceeded the predetermined toxic dose. After the proper placement of the ETT in the trachea, general anesthesia was induced and the surgery was allowed to proceed.

Intubating conditions were evaluated by the cough score (10) during fiberscopy on a scale of 0 to 3 (0 = no cough, 1 = single cough, 2 = persistent cough lasting < 5 seconds, and 3 = persistent cough lasting ≥ 5 seconds or bucking). The tolerance to intubation was evaluated by the post-intubation score (11) after the placement of the ETT in the trachea as score 1 (co-operative), 2 (minimal resistance), and 3 (severe resistance). The mean, systolic, and diastolic blood pressures (MAP, SBP, DBP), heart rate (HR), and arterial oxygen saturation (SpO_2) were noted at six time-points: T0 (baseline), T1 (after completion of study drug infusion), T2 (immediately after intubation), T3, T4, T5, T6, and T7 for every 1 minute for the next 5 minutes, and T8 (10 minutes after intubation). Any trauma/bleeding event due to intubation was noted. The patients were followed up 24 hours post-surgery and enquired about sore throat/discomfort, the ability to recall the procedure of AFOI, and their willingness to undergo the same kind of anesthesia again if necessary. The recall was graded as no recollection, vague recollection (not remembering the entire sequence of events but recalling ≤ 2 events when asked specifically), recall of some details (not remembering the entire sequence of events but recalling > 2 events when asked specifically), and recall of all details.

The sample size selection was based on the results of previous studies (11) taking the cough score as the primary variable, assuming that $MgSO_4$ was as good as dexmedetomidine in ameliorating the pressor responses to anesthetics and surgical manipulations (12), and that a cough score of ≤ 2 would provide favorable intubation conditions (10). A sample size of 6 patients in each group was calculated to achieve a power of 0.8 and type one error of 0.05. Ten patients were recruited in each group to account for attrition. Data were collected and analyzed using SPSS V. 17.0 software. The secondary outcome variables included the sedation score, hemodynamics, and post-intubation score. The numerical data were expressed as means ± SD and categorical data were put into tables. The numerical data were compared between the two groups using the independent t-test and within the same group using the paired *t*-test. The categorical data were compared between the two groups using the chi-square test. A P value of < 0.05 was considered statistically significant.

4. Results

Overall, 26 patients took part in the study. There were six dropouts. The demographic characteristics were comparable in the two groups (Table 1).

The RSS scores were similar in both groups (P = 0.214). The cough score, i.e., the degree of coughing during fiberscopy (P = 0.952) and the tolerance to intubation, as evaluated by the post-intubation score, (P = 0.890) were comparable between the groups (Table 2).

The mean number of additional boluses of lignocaine required during AFOI was 3.30 ± 1.89 in group F and 4.50 ± 1.90 in group M (P = 0.174). Both groups were also similar in the dose of lignocaine used for airway topicalization, calculated as 1/3rd of the nebulization dose, i.e., 1/3 × 160 mg = 53 mg plus 20 mg on NPA plus 20 mg per the bolus dose of lignocaine (1 mL, 2%). The mean dose of lignocaine used was 139 ± 1.89 mg in group F and 163 ± 1.90 mg in group M (P = 0.174), which did not exceed the toxic dose in any patient.

Table 1. Patient Characteristics[a,b]

Patient characteristics	Group F	Group M	P Value
Age, y	34.40 ± 11.24	29.30 ± 9.35	0.284
Height, cm	168.40 ± 8.81	167.90 ± 13.27	0.922
Weight, kg	58.60 ± 7.20	61.10 ± 10.84	0.551
BMI, kg/m²	20.88 ± 3.15	22.08 ± 4.44	0.495
ASA grade I	100	100	-
MPC	2.10 ± 0.74	1.80 ± 0.92	0.431
MO > 3 cm	100	100	-

[a] Values are expressed as mean ± SD or percent.
[b] The patient characteristics were comparable in both groups.

Table 2. RSS, Cough Score, and Post-Intubation Score[a,b]

	Group F	Group M	P Value
RSS			0.214
1	0 (0)	1 (10)	
2	6 (60)	8 (80)	
3	4 (40)	1 (10)	
Cough Score			0.952
0	1 (10)	1 (10)	
1	3 (30)	2 (20)	
2	3 (30)	3 (30)	
3	3 (30)	4 (40)	
Post intubation Score			0.89
1	5 (50)	6 (60)	
2	4 (40)	3 (30)	
3	1 (10)	1 (10)	

[a] RSS, cough score, and post-intubation score were comparable in both groups.
[b] Values are expressed as No. (%).

The baseline hemodynamic parameters were comparable. Hemodynamic responses to intubation were seen in both groups with maximum values of BP and HR seen at T2 (immediately after intubation). The sympathetic response to intubation led to a 5% rise in MAP in group F and 15% rise in group M (P = 0.320) and a rise of 35% in HR in group F and 19% in group M (P = 0.583) (Table 3; Figures 1 to 4); however, the differences were not significant. All patients maintained oxygen saturation throughout the procedure without any episodes of desaturation. The incidence of any intubation-related upper airway trauma/bleeding and postoperative sore throat was comparable in both groups with two cases of mild trauma in group F and three cases in group M (P = 1.000). Two patients complained of mild sore throat and one of moderate sore throat in group F while no patient complained of sore throat in group M (P = 0.171). Willingness to return for a similar procedure was comparable in both groups (P = 0.081). However, the recall of the procedure of awake intubation was significantly less in group F with 80% of patients having no or only vague recollection of the events while 60% of patients in group M could recall the details of the procedure (P = 0.003) (Table 4).

5. Discussion

We compared the efficacy of intravenous fentanyl 2 μg/kg and magnesium sulfate 45 mg/kg as premedicants in AFOI by the nasotracheal route and found comparable intubation conditions and similar tolerance to the tracheal tube after intubation in both groups. However, the

Table 3. Hemodynamic Response to Intubation

	T0	T1	T2	T3	T4	T5	T6	T7	T8
SBP, mmHg									
Group F	128.60 ± 7.76	123.10 ± 7.25	125.70 ± 17.16	113.80 ± 19.46	107.80 ± 17.78	105.70 ± 12.02	102.80 ± 15.28	101.10 ± 10.08	104.60 ± 9.77
Group M	123.90 ± 6.84	118.40 ± 14.00	140.60 ± 22.41	119.10 ± 13.02	121.90 ± 32.05	117.60 ± 31.58	104.90 ± 11.62	102.50 ± 12.45	103.00 ± 11.83
P value	0.168	0.358	0.159	0.483	0.240	0.280	0.733	0.785	0.745
DBP, mmHg									
Group F	83.50 ± 5.44	79.90 ± 5.24	85.10 ± 14.73	71.70 ± 13.87	65.70 ± 10.98	65.60 ± 9.55	64.00 ± 8.59	63.20 ± 8.27	67.20 ± 7.87
Group M	81.90 ± 6.37	75.80 ± 9.72	83.50 ± 6.28	77.10 ± 12.26	73.20 ± 12.02	67.50 ± 10.12	65.40 ± 8.36	63.90 ± 10.50	63.10 ± 9.49
P value	0.339	0.255	0.756	0.368	0.216	0.671	0.716	0.870	0.307
MAP, mmHg									
Group F	96.70 ± 7.09	93.00 ± 6.98	98.40 ± 15.83	86.30 ± 15.38	79.80 ± 12.32	79.00 ± 8.78	77.20 ± 9.51	74.20 ± 8.01	78.50 ± 7.14
Group M	94.40 ± 5.50	90.50 ± 10.22	104.10 ± 10.72	91.90 ± 13.76	83.90 ± 10.33	81.70 ± 8.56	78.90 ± 8.31	76.90 ± 9.67	78.20 ± 9.88
P value	0.428	0.531	0.415	0.402	0.431	0.495	0.675	0.505	0.939
HR, bpm									
Group F	90.50 ± 23.73	84.40 ± 23.28	114.50 ± 16.47	96.30 ± 11.59	89.60 ± 15.27	88.70 ± 13.23	83.90 ± 14.63	83.30 ± 11.69	80.40 ± 17.21
Group M	92.80 ± 16.11	92.0 ± 11.79	110.00 ± 25.27	94.90 ± 18.10	94.00 ± 19.17	86.20 ± 17.06	81.90 ± 18.89	80.50 ± 17.68	78.80 ± 12.16
P value	0.803	0.369	0.643	0.839	0.577	0.719	0.794	0.681	0.813

Table 4. Incidence of Recall of the Procedure[a]

Recall	Group F	Group M	P Value
No	1	4	0.003
Vague recollection	7	0	
Some details	0	5	
Yes	2	1	

[a]The incidence of recall was more in group M (P = 0.003).

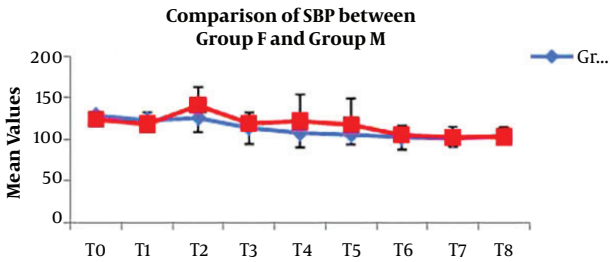

Figure 1. Trends in SBP

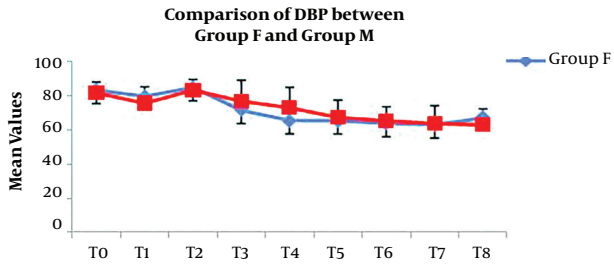

Figure 2. Trends in DBP

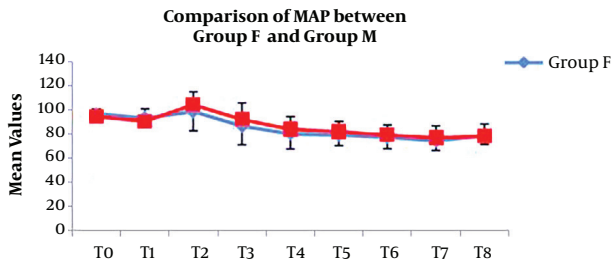

Figure 3. Trends in MAP

degree of recall of the awake intubation procedure was significantly less in group F.

In patients subjected to AFOI, one can frequently observe anxiety, hypertension, and tachycardia associated with coughing and bucking on the ETT. Their safe attenuation is important, especially in patients with the cardiac or cerebrovascular disease where maintenance of hemodynamic stability and adequate oxygenation and ventilation are necessary without compromising safety. Various drugs and their combinations have been evaluated to achieve conscious sedation during AFOI. Fentanyl provides sedation and analgesia along with hemodynamic stability. Opioids are also known to suppress coughing that provides an additional advantage when the manipulation of the airway is required in awake patients; however, their use is associated with the risks of respiratory depression, nausea, vomiting, and chest wall rigidity. $MgSO_4$, on the other hand, provides hemodynamic stability and some degree of muscle relaxation via decreased catecholamine re-

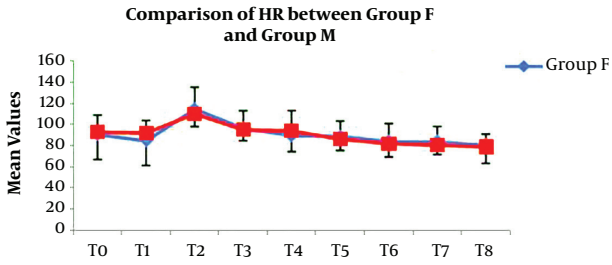

Figure 4. Trends in HR

lease and antagonism at NMDA receptors. It is unlikely to cause significant sedation or respiratory depression, which may be advantageous in the truly difficult airway patients or in patients with a full stomach and at risk of aspiration. The muscle relaxant properties of $MgSO_4$ may help in attenuating the coughing and bucking associated with fiberscopy and intubation in awake patients, leading to reduced cough scores. This, along with the hemodynamic stability associated with its use, makes $MgSO_4$ an attractive option for facilitating intubation in awake patients.

Mondal et al. (11) reported that fentanyl 2 μg/kg during AFOI provided satisfactory intubating conditions and "arousable" sedation without respiratory depression. We chose to use this dose in the fentanyl group. Unlike fentanyl, $MgSO_4$ is not usually associated with significant sedation. However, previous studies reported some sedation after the use of $MgSO_4$ (13, 14). In our study, we also observed a comparable degree of sedation in both groups that was sufficient to allow for AFOI (RSS $\geq$ 2). The sedative action of $MgSO_4$ can be attributed to central NMDA antagonism.

At the studied doses, the degree of coughing was also similar in both groups. Various studies have demonstrated the cough-suppressing ability of opioids (15, 16). Although $MgSO_4$ is not known to possess cough-suppressing properties, a study by Elgebaly and Eldabaa (12) showed contradictory results. They compared the ease of fiberoptic intubation after administration of $MgSO_4$ 45 mg/kg versus midazolam 0.07 mg/kg and concluded that fiberoptic nasotracheal intubation was easier and faster in the $MgSO_4$ group than in the midazolam group, without hemodynamic or respiratory adverse effects. They did not study the degree of coughing but coughing and bucking should have contributed to difficulty during fiberoptic intubation. This cough-suppressing ability of $MgSO_4$ can be attributed to the sedative and muscle relaxant properties of magnesium, leading to an inability to sustain a cough. Higher doses of $MgSO_4$ may lead to respiratory muscle weakness, which occurs at plasma levels of 5 to 6.5 mmol/L but this plasma concentration is achieved only with prolonged continuous infusions or at very high doses (17, 18) that was not the case in our study. None of the patients showed the signs of muscle weakness and we did not consider it necessary to monitor serum Mg levels after the use of a single loading dose.

Previous studies reported that fentanyl 2 μg/kg administered 5 minutes before tracheal intubation was effective (in dose and time) to minimize the hemodynamic changes and achieve adequate conditions for the shortest intubation time during fiberoptic bronchoscopy (19, 20). Elgebaly and Eldabaa (12) in patients undergoing elective nasotracheal AFOI concluded that $MgSO_4$ 45 mg/kg led to easy, fast intubation without adverse hemodynamic or respiratory effects. We used a similar dose in our study and achieved hemodynamic stability. The maximum rise in hemodynamics was seen immediately post-intubation. Although both study drugs were able to obtund the hemodynamic response to intubation to a similar extent, the rise in the HR was obtunded more by $MgSO_4$ while the rise in BP was obtunded more by fentanyl.

On the day after surgery, the patients were asked how much they remembered the procedure. The patients in the magnesium group had a higher incidence of recall (Table 4) and could remember more the details of the procedure than the fentanyl group (P = 0.003). Although fentanyl is not known to cause amnesia, it does cause significant anxiolysis (21). The anxiolytic effects of fentanyl, when combined with the anxiolytic and anterograde amnesia effects of midazolam, may have resulted in significantly less recall in the fentanyl group than in the $MgSO_4$ group. However, the fact that all patients in both groups received midazolam may be a confounding factor when studying the degree of amnesia and anxiolysis induced by the study drugs.

The $MgSO_4$ use during anesthesia provides smooth muscle relaxation and hemodynamic stability (5-7). We hypothesized that the muscle relaxation activity of $MgSO_4$ and its hemodynamic stability with lacked or minimal sedation may make it an ideal drug for use in patients with a difficult airway requiring AFOI. Although the employed dose of $MgSO_4$ (45 mg/kg) provided hemodynamic stability similar to that provided by fentanyl 2 μg/kg, it was unable to cause better suppression of the cough reflex, as it was similar in both study groups. The selected sample size was calculated assuming that magnesium is as effective as dexmedetomidine (22) in ameliorating the pressor responses to anesthetics and surgical manipulations, as both $MgSO_4$ and dexmedetomidine have been found to be effective in suppressing coughing and providing good intubation conditions during AFOI in separate studies (11, 12). Further studies are required to compare $MgSO_4$ and dexmedetomidine at various doses for this purpose. More-

over, we studied only single doses of both study drugs. The use of higher doses of $MgSO_4$ along with the monitoring of serum Mg levels may allow us to achieve better intubating conditions without compromising patient safety. Thus, further dose-response studies are required to find the optimum dose of $MgSO_4$ facilitating AFOI.

5.1. Conclusions

The study showed that fentanyl 2 μg/kg and $MgSO_4$ 45 mg/kg are similar in the response of patients to the AFOI procedure by the nasal route as evaluated by the degree of coughing during fiberoptic bronchoscopy, tolerance of the endotracheal tube after intubation, and the hemodynamic response to intubation.

Footnotes

Authors' Contribution: Study concept and design: Shweta Dhiman, Ruchi Kumari, Anju Romina Bhalotra, Uttam Chand Verma, and Kavita Rani Sharma; patient recruitment, data collection, and data analysis: Shweta Dhiman, Ruchi Kumari and Anju Romina Bhalotra; writing of the first draft of the paper: Shweta Dhiman, Anju Romina Bhalotra, and Kavita Rani Sharma; interpretation of data: Shweta Dhiman, Anju Romina Bhalotra, Kavita Rani Sharma, and Uttam Chand Verma.

Conflict of Interests: The authors declare no conflict of interests.

Ethical Approval: Ethical approval for this study was provided by the Ethics Committee of Maulana Azad Medical College, New Delhi, India (No. 11/MAMC/2015/317).

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