

Original Article

Magnesium sulphate suppresses fentanyl-induced cough during general anesthesia induction: a double-blind, randomized, and placebo-controlled study

Hai-Lin Liu^{1*}, Li-Jun An^{1*}, Zhen Su¹, Yang Zhang¹, Bo Gui²

¹Department of Anesthesiology, Huai'an First People's Hospital, Nanjing Medical University, Huai'an, Jiangsu, China; ²Department of Anesthesiology, The 1st Affiliated Hospital, Nanjing Medical University, Nanjing, Jiangsu, China. *Equal contributors.

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Abstract: Fentanyl-induced cough is a common phenomenon during anesthesia induction. Magnesium sulphate (MgSO_4) is reported to have a powerful relaxation of airway smooth muscle. This study is to investigate the effects of prophylactic MgSO_4 on the incidence and severity of fentanyl-induced cough. A total of 120 patients, scheduled for elective surgery under general anesthesia, were randomly allocated into three groups ($n = 40$, each group) and injected with 50 ml normal saline, 30 mg/kg and 50 mg/kg of MgSO_4 (diluted with normal saline into 50 ml) in groups I, II and III, respectively. One minute later all patients were injected with 5.0 $\mu\text{g}/\text{kg}$ of fentanyl within 5 s. The incidence and severity of cough were recorded 30 s after fentanyl injection. Hemodynamic parameters and plasma magnesium concentration of the patients were also noted. Three patients dropped off the study due to obvious burning sense during injection of 50 mg/kg of MgSO_4 . Injection with 50 mg/kg of MgSO_4 increased plasma magnesium level at the end of its infusion, but the latter still remained within therapeutic range (2-4 mmol/L). The incidence of cough in group I was much higher than those in groups II and III (45.0% vs. 15.0% and 8.1%, $P < 0.05$). Compared with the group I, both the groups II and III had lower incidence of moderate cough ($P < 0.05$). There were no differences in the hemodynamic data at three timepoints among the three groups. In conclusion, fentanyl-induced cough may be suppressed effectively and safely by prophylactic 30 mg/kg of MgSO_4 during anesthetic induction.

Keywords: Magnesium sulphate, fentanyl, cough

Introduction

During general anesthesia induction fentanyl is widely used as an analgesic due to its rapid onset, short duration of action, intense analgesia as well as relative cardiovascular stability. But intravenous administration of fentanyl often elicits cough reflex with its frequency ranging from 28%-70% [1, 2]. Cough plays the protective role in the respiratory system, however fentanyl-induced cough during anesthesia induction is an undesirable act which may cause serious questions in patients with increased intracranial, intraocular, or intra-abdominal pressure. Therefore, it is clinically important to prevent from this "bad" cough.

Pretreatment with some drugs, such as lidocaine, propofol, and dexmedetomidine, have been used effectively to suppress cough during

anesthetic induction [3-5]. However, these drugs have some limits owing to their side effects and slow onset time. Magnesium sulphate (MgSO_4) is reported to have a powerful relaxation of airway smooth muscle, so it is often proposed to treat severe exacerbations of asthma [6]. In many aspects cough is similar to asthma. So we performed this study to investigate the effects of MgSO_4 on the incidence and severity of fentanyl-induced cough during anesthetic induction for future reference in clinical application.

Material and methods

Study population and study design

After getting approval from the Ethics Committee of Huai'an First People's Hospital affiliated with Nanjing Medical University and

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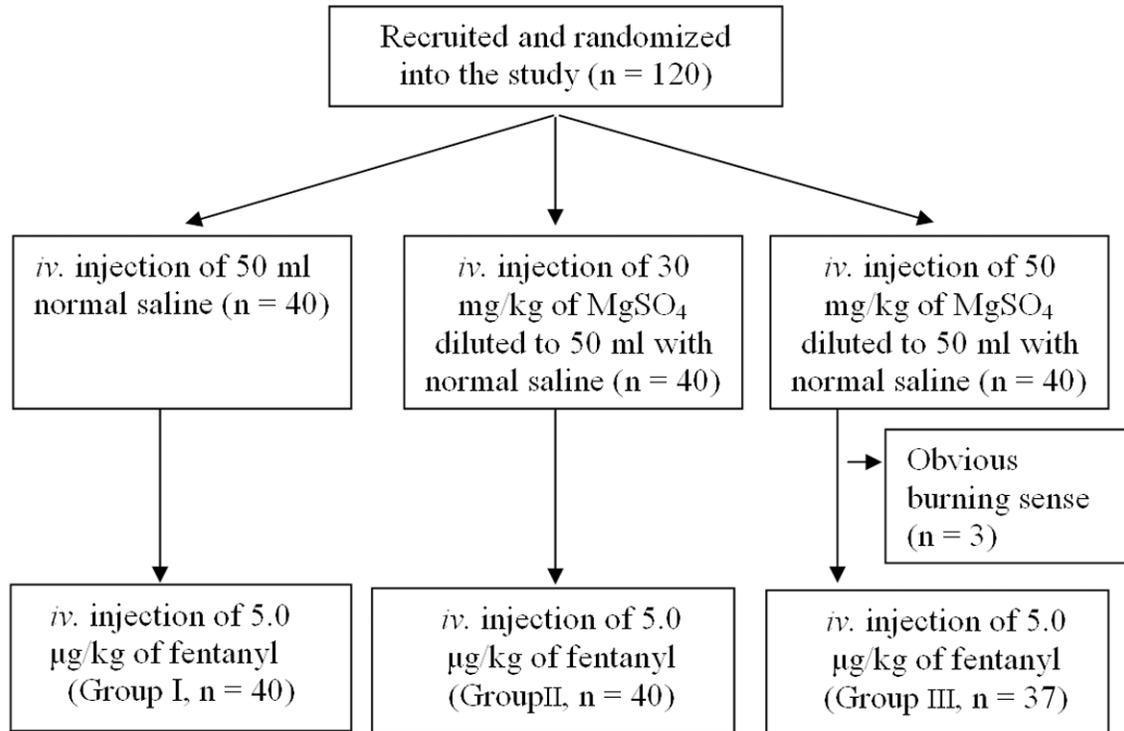


Figure 1. CONSORT flow diagram.

written informed consents from the eligible patients, a total of 120 patients, aged 18-65 years, classified as American Society of Anesthesiologists (ASA) physical status I or II, scheduled for elective surgery under general anesthesia, were enrolled in this study. Exclusion criteria included a history of chronic administration of anti-tussive medication, opioids, steroid, or ACE-inhibitors, asthma, smoking, chronic cough, upper respiratory tract infection in the previous four weeks, renal insufficiency, gastroesophageal reflux, hypermagnesemia, neuromuscular disease, morbid obesity, hypertension, cardiac disease such as conduction block, bradycardia, arrhythmia and coronary artery disease. Patients with increased intracranial, intraabdominal or intraocular pressure were also excluded.

The patients were fasted for 8 h before the anesthesia. Upon arrival, monitoring was accomplished by pulse oxygen saturation (SpO_2), electrocardiogram (ECG), non-invasive blood pressure (NIBP), and heart rate (HR). Oxygen gas flow of 2 L/min was given to the patients via a facial mask. Then a 20 G intravenous cannula was inserted into the forearm and connected to a T-connector for drug admin-

istration. Ringer's lactate was infused at a rate of 4-6 ml/min. The patients were randomly allocated 1:1:1 to 50 ml normal saline, 30 mg/kg and 50 mg/kg of $MgSO_4$ (diluted with normal saline into 50 ml) injection. Randomization was based on reproducible computer-generated codes that were maintained in sequentially numbered opaque envelopes until the end of anesthesia. Patients in group I were given 50 ml normal saline for 10 min via the T-connector at a steady rate. Patients in groups II and III received either 30 mg/kg or 50 mg/kg $MgSO_4$ (250 mg/ml; Minsheng Pharma., Hangzhou, China) diluted with normal saline into 50 ml respectively, both intravenously for 10 min at the former rate. The $MgSO_4$ and placebo solutions were identical in appearance. Blood was taken for measurement of plasma magnesium levels at 1 min before infusion and 30s after the end of infusion. 5.0 $\mu g/kg$ of fentanyl (50 $\mu g/ml$; Renfu Co., Hubei, China) was injected within 5 s through the same route 1 min after the end of $MgSO_4$ infusion.

Outcome measurements

The primary outcome measurement was the incidence and severity of cough 30 s after fen-

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Table 1. Demographics of the patients (n = 117)

Characteristics	Group I (n = 40)	Group II (n = 40)	Group III (n = 37)	P-value
Age (yr)	35 ± 11	38 ± 13	37 ± 10	0.9542
Gender (M/F)	23/17	20/20	26/11	0.4511
Weight (kg)	51.2 ± 13.6	55.7 ± 15.2	59.3 ± 18.8	0.7703
ASA (I/II)	28/12	30/10	26/11	0.8724

Data are expressed as number and means ± SD. There are no statistically significant differences among the three groups with regard to age, gender, weight and ASA class. M: Male. F: Female. ASA: American Society of Anesthesiologists.

Table 2. Plasma magnesium levels (mmol/L, n = 117)

Plasma magnesium	Group I (n = 40)	Group II (n = 40)	Group III (n = 37)
Baseline	1.22 ± 0.28	1.14 ± 0.37	1.19 ± 0.33
After infusion	1.16 ± 0.33	2.67 ± 0.73	3.13 ± 0.42*

Data are expressed as means ± SD. There are no significant differences among the three groups at baseline. *P < 0.05, group III vs group I.

tanyl administration, which was recorded by an observer who was blinded to the former treatment. The severity of cough was graded based on its frequency, as mild (1-2 times), moderate (3-4 times), and severe (> 5 times) [7]. Then anesthetic induction was continued with midazolam 0.05 mg/kg, etomidate 0.3 mg/kg, and vecuronium 0.15 mg/kg. Secondary outcome was HR and mean arterial pressure (MAP) at the time of establishment monitoring, the beginning and the end of 50 ml solutions infusion were noted as T0, T1 and T2 respectively.

Statistical analysis

In our pilot study, we found that the incidence of cough induced by 5.0 µg/kg of fentanyl was 55% (11/20) given over a period of 5 s. Therefore, we assumed that if the incidence of cough decreased to 20%, the effect of prophylactic MgSO₄ could be considered statistically significant. To achieve 80% statistical power with α = 0.05, each group would need a minimum of 33 patients. So we recruited 40 patients per group to allow for any dropouts.

Data were analyzed using the statistical package SPSS 15.0 for windows (SPSS Inc, Chicago, USA). Quantitative data, such as age and weight, were presented as means ± standard deviation and compared using one-way analysis of variance (ANOVA) among the three groups. Repeated ANOVA was used to compare

serially measured values. If intra-group differences were found, post hoc Turkey's test was further performed. The chi-square test was employed to compare qualitative data, and the Jonckheere-Terpstra test was utilized for the comparison of ranked data. A P-value < 0.05 was considered statistically significant.

Results

Demographic characteristics

One hundred and twenty patients were recruited into the study, with 117 included in the final analysis. Three patients dropped off the study due to obvious burning sense during injection of 50 mg/kg of MgSO₄. Forty patients were allocated into group I. Forty and Thirty-seven patients received 30 mg/kg and 50 mg/kg of MgSO₄, respectively (Figure 1).

There were no significant differences among the three groups with regard to age, gender, weight, or ASA class (Table 1).

Plasma magnesium levels

As shown in Table 2, injection with 50 mg/kg of MgSO₄ increased plasma magnesium level at the end of its infusion, but the latter still remained within therapeutic range (2-4 mmol/L).

Incidence and severity of cough

As shown in Table 3, the incidence of cough in group I was much higher than those in groups II and III (50.0% vs. 20.0% and 5.4%, P < 0.05). Compared with the group I, both the groups II and III had lower incidence of moderate cough (P < 0.05).

Hemodynamic data

There were no differences in the hemodynamic data at three timepoints among the three groups with regard to HR and MAP (Table 4).

Discussion

Because injecting MgSO₄ can cause hypermagnesemia, which may lead to serious inhibition

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Table 3. Severity and incidence of fentanyl-induced cough (n = 117)

Groups	Severity of cough			Total (n)	Incidence of cough (%)
	Mild (n, %)	Moderate (n, %)	Severe (n, %)		
I (n = 40)	3 (7.5)	13 (32.5)	2 (5.0)	18	45.0
II (n = 40)	3 (7.5)	2 (5.0)*	1 (2.5)	6	15.0*
III (n = 37)	1 (2.7)	2 (5.4)*	0 (0)	3	8.1*

Data are expressed as numbers (percentages). *P < 0.05, groups II and III vs. group I.

Table 4. Hemodynamic data of the patients (n = 117)

	Group	T0	T1	T2
HR (bpm)	I (n = 40)	73.9 ± 12.4	76.4 ± 13.0	72.4 ± 12.8
	II (n = 40)	73.5 ± 12.8	75.1 ± 13.3	77.9 ± 13.7
	III (n = 37)	70.3 ± 12.5	72.7 ± 13.6	77.5 ± 14.2
MAP (mmHg)	I (n = 40)	83.0 ± 11.8	86.9 ± 12.1	81.5 ± 12.4
	II (n = 40)	80.3 ± 13.3	84.6 ± 11.9	85.5 ± 12.0
	III (n = 37)	82.9 ± 12.5	83.0 ± 14.8	83.2 ± 11.3

Data are expressed as means ± SD. There are no significant differences among the three groups with regard to HR and MAP. HR: heart rate. MAP: Mean Arterial Pressure.

of neuromuscular excitability, plasma magnesium level must be monitored closely. Injection with 50 mg/kg of MgSO₄ increased the plasma magnesium levels at the end of its infusion, but the latter always remained within therapeutic range (2-4 mmol/L). The incidence of fentanyl-induced cough declined from 50.0% to 20.0% and 5.4% after the usage of 30 mg/kg and 50 mg/kg of MgSO₄, respectively. Three patients dropped off the study due to obvious burning sense during injection of 50 mg/kg of MgSO₄. A relative high concentration might be attributed to this phenomenon.

The incidence of cough induced by 5.0 µg/kg of fentanyl varied in different studies, where were 43% and 70%, respectively [2, 8]. In the present study, fifty percentage patients had fentanyl-induced cough. This discrepancy may be due to different fentanyl injection speed and age of the patients. Various fentanyl dosage and injection speed resulted in different plasma concentration or plasma concentration fluctuation, which could cause different incidence and severity of cough [9, 10]. Pulmonary C fiber receptors (J receptors) or irritant receptors present in the respiratory tract. Their activation is likely involved in the mediation of the pulmonary chemo-reflex which then leads to different expression of cough [11, 12]. Furthermore, Hung KC *et al* suggested that sudden adduction of the vocal cords or supraglottic obstruction induced by fentanyl-induced

muscle rigidity might be the causes of cough during anesthesia induction [13]. Fentanyl has an excellent central nervous system penetration due to its high lipid solubility. The pre-emptive use of opioids can inhibit the cough reflex by directly inhibiting the cough center in the medulla [14, 15]. Fentanyl was also reported to inhibit central sympathetic outflow, increase vagal activity, and lead to cough finally [1, 8].

Magnesium plays a fundamental role in many cellular functions. There might be two aspects of reason accounting for inhibitory effects

of MgSO₄ on fentanyl-induced cough. On the one hand, MgSO₄-induced bronchodilation may be mediated by several pathways such as inhibition of cholinergic neuromuscular transmission and attenuation of calcium-induced muscle contractions [16, 17]. Evidence also shows that prostaglandin-mediated vascular smooth muscle relaxation may be magnesium-dependent, and magnesium possesses mild sedative effects that are valuable to achieving relaxation in acute bronchoconstriction [18]. The direct bronchodilating effect of magnesium may also account for the blockade of NMDA receptors in the larynx, lung, and airways [19]. On the other hand, MgSO₄ acts as a calcium channel blocker at presynaptic nerve endings and decreases acetylcholine release at the motor endplate, which diminishes muscle fiber excitability and reduces the amplitude of endplate potential [12]. Therefore, sudden adduction of the vocal cords or supraglottic obstruction from sufentanil-induced muscle rigidity can be suppressed.

There are some limitations relevant to our study. The severity of cough appeared 0 case once, so a larger samples might need to be involved. More studies also need to be done to reveal the exact mechanism of MgSO₄ in suppressing sufentanil-induced cough.

In conclusion, due to several patients accounting for obvious burning sense during injection

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of 50 mg/kg of MgSO₄, pretreatment with MgSO₄ 30 mg/kg can safely suppress the incidence and severity of cough induced by fentanyl (5.0 µg/kg) during anesthetic induction.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Bo Gui, Department of Anesthesiology, The 1st Affiliated Hospital with Nanjing Medical University, 300 Guangzhou Road, Nanjing 210029, Jiangsu, China. Tel: +86-25837-188366760; Fax: +86-25837188366760; E-mail: guibosy@163.com

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