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Magnesium sulphate pretreatment obtunds fentanyl-induced cough during general anaesthesia induction

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Abstract

Introduction: Fentanyl-induced cough is common during induction of general anaesthesia. This unpleasant cough may increase the intraocular, intracranial, and intraabdominal pressure. We hypothesised that 30 mg/kg of prophylactic intravenous magnesium sulphate is effective in obtunding 2 µg/kg fentanyl-induced cough.
Methods: One hundred and forty patients scheduled for general anaesthesia, aged between 18 to 70 years old with American Society of Anesthesiologists physical status I were randomised into two groups. Group I and Group II patients received 30 mg/kg intravenous magnesium sulphate and normal saline, respectively. The solution studied was infused over 15 minutes followed by a fentanyl bolus 2 µg/kg delivered within 3 seconds. The incidence of cough and severity were documented. Mean arterial pressure and heart rate were recorded every 5 minutes during the infusion.
Results: Eight patients (11.4%) had cough in Group II and one (1.4%) in Group I. Compared to Group II, the incidence and severity of cough were significantly lower in Group I (p = 0.003 and p = 0.037), respectively. There was no significant

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difference regarding the haemodynamic status between the two groups during the infusion of both solutions.
Conclusion: During general anaesthesia induction, 30 mg/kg of intravenous magnesium sulphate effectively obtunded fentanyl-induced cough.

Keywords: cough, fentanyl, general anaesthesia, magnesium sulphate

Introduction

Fentanyl is a rapid-onset opioid used to assist in the production of loss of consciousness and to obtund the sympathetic nervous system during the intubation process.[1,2] However, one of its side effects during general anaesthesia induction is fentanyl-induced cough, ranging from 6.6% to 61.0%, depending on the dose and speed of injection.[3] A typical induction dose of 2 μg/kg was reported to produce a fentanyl-induced cough in 38% of patients.[4]

Coughing can cause wide fluctuations of intrathoracic pressure, which stimulates the reflex activation of the sympathetic nervous system leading to stress on the cardiovascular system.[5] This effect could be detrimental in patients who suffer from hypertension, ischaemic heart disease, heart failure, high intraocular pressure, or intracerebral bleed.[3]

A few drugs have been shown to suppress fentanyl-induced cough, such as lidocaine, ketamine and dexmedetomidine.[6-8] Magnesium sulphate 30 mg/kg was proven effective in obtunding cough due to fentanyl 5 μg/kg, which is a very high dose.[9] A dose of 20 mg/kg of magnesium sulphate was not statistically significant in reducing the incidence of such cough with fentanyl 2 μg/kg.[4] Hence, we decided to study the effectiveness of 30 mg/kg of magnesium sulphate in obtunding 2 μg/kg fentanyl-induced cough.

Methods

This prospective, double-blind randomised clinical trial was approved by the departmental Research Committee and the Research Ethics Committee of our institute (FF-2018-656). Within a period of 1 year, 140 patients scheduled for general anaesthesia, aged between 18 to 70 years old with American Society of Anesthesiologists (ASA) physical status I were recruited. Any patients with a known allergy to magnesium sulphate, chronic cough, history of upper respiratory tract infection during the previous 4 weeks, or any history of chronic administration of antitussive medication, opioids, or steroids were excluded. Written informed consent was

obtained from all patients, who were fasted preoperatively for a minimum of 6 and 2 hours for solids and clear fluids, respectively. Premedication was not prescribed to all patients. Prior to general anaesthesia induction, standard ASA monitoring including 3-lead electrocardiogram, non-invasive blood pressure monitoring, and arterial oxygen saturation was applied, and intravenous access was established.

The patients were randomised into two groups using the allocation concealment mechanism. Prior to administration of 2 µg/kg fentanyl for general anaesthesia induction, Group I patients received 30 mg/kg of intravenous magnesium sulphate diluted to a volume of 20 ml with normal saline, whereas Group II patients received 20 ml of normal saline. The investigator prepared the syringes containing either of the above solutions, while the anaesthetists who performed the cough assessments and the patients were blinded to the content of the solution. The randomised study drug was given intravenously via the T-connector of the peripheral intravenous access over 15 minutes using a syringe pump. Before commencing the infusion, the patients were asked to inform if there was presence of pain, discomfort, or none at the infusion site.

Upon near completion of the solution delivery, all patients were preoxygenated with 100% oxygen as per the usual protocol. One minute after the completion of the infusion, 2 µg/kg of fentanyl was given over a period of 3 seconds through the same route. The incidence and severity of the cough were then assessed within a period of 1 minute after the administration of fentanyl using a standard stopwatch. The scoring of severity of the cough was based on the following four-point scale: Grade 0: no cough (none); Grade 1: single cough (mild); Grade 2: more than one attack of non-sustained cough (moderate); and Grade 3: repeated and sustained coughing with head lift (severe).[4]

One minute following fentanyl administration, general anaesthesia was induced with 2–3 mg/kg of propofol. General anaesthesia was then maintained with sevoflurane with a minimum alveolar concentration of 1.0–1.2 in an oxygen/air mixture. The airway management was at the discretion of the attending doctor.

Haemodynamic status of mean arterial pressure (MAP) and heart rate (HR) were documented at the time of initiation of magnesium sulphate infusion (T_0), every 5 minutes until the completion of infusion (T_1, T_2, and T_3) and immediately after administration of fentanyl (T_4). Any episodes of hypotension (MAP < 20% of baseline) or bradycardia (HR < 45/min) was treated with boluses of intravenous phenylephrine 50 µg or intravenous atropine 0.5 mg, respectively. Any intolerable pain at the infusion site or persistent hypotension and bradycardia despite treatment that resulted in discontinuation of magnesium sulphate infusion was considered as dropped out.

By using the Fleiss formula,[9] the sample size calculation was determined based on a study by Liu *et al.*[10] A total of 140 patients (70 patients for each group) was required to provide the study with a power of 95% and significance level of 5% while allowing a 10% dropout rate. All data analysis was performed using SPSS for Windows version 23.0 (IBM Corp, Armonk, NY, USA). Results were presented as mean ± standard deviation or frequency (percentage) where appropriate. For inter-group analysis, repeated measure ANOVA with post-hoc Bonferroni test was used. The qualitative data were analysed using Pearson's chi-square or Fisher's exact test if the assumption was not met. A p-value of < 0.05 was considered statistically significant.

Results

A total of 140 patients participated in this study with no dropouts. There were no significant differences in terms of demographic data between the two groups, as shown in Table 1.

Table 2 shows a significantly higher incidence of fentanyl-induced cough in Group II compared to Group I ($p < 0.05$). However, there was no significant difference in the severity of fentanyl-induced cough between the two groups.

There was no significant difference in MAP and HR between the two groups at the different time points during the study drug infusion ($p > 0.05$), as seen in Table 3. Further analysis within each group revealed a statistically significant difference in MAP when T_0 was compared to T_4 ($p = 0.005$) in Group I.

The haemodynamic status of patients in Group II was compared between those who developed fentanyl-induced cough and those who had no cough. There were no significant differences in the MAP and HR ($p > 0.05$), as seen in Table 4.

Table 1. Demographic data

Variable	Group I (*n* = 70)	Group II (*n* = 70)	*p*-value
Age (year)	42.1 ± 14.8	42.8 ± 16.0	0.793[a]
BMI (kg/m^2)	23.8 ± 3.4	23.6 ± 3.0	0.752[a]
Gender			
Male	21 (30.0)	29 (41.4)	0.158[b]
Female	49 (70.0)	41 (58.6)	
Race			
Malay	46 (65.7)	49 (70.0)	0.335[c]
Chinese	18 (25.7)	12 (17.1)	
Indian	2 (2.9)	6 (8.6)	
Other	4 (5.7)	3 (4.3)	

Data expressed in mean ± standard deviation or frequency (percentage) as appropriate.

BMI: body mass index; a: independent T test; b: Pearson's chi-square; c: Fisher's exact test

Table 2. Incidence of discomfort or pain at infusion site, and incidence and severity of fentanyl-induced cough

Variable	Group I (*n* = 70)	Group II (*n* = 70)	*p*-value
Number of patients with discomfort or pain at infusion site	3 (4.3)	0 (0)	0.245[c]
Number of patients who coughed	1 (1.4)	8 (11.4)	*0.033[c]
Severity of cough			
Mild	1 (1.4)	6 (8.6)	0.059[c]
Moderate	0 (0)	1 (1.4)	
Severe	0 (0)	1 (1.4)	

Data expressed as numbers (percentages).

c: Fisher's exact test, *$p < 0.05$

Table 3. Haemodynamic status of both groups during solution infusion

Variable	Group I (*n* = 70)	Group II (*n* = 70)	*p*-value
MAP (mmHg)			
T_0	98.0 ± 16.3	98.9 ± 15.0	0.738[a]
T_1	96.1 ± 16.5	95.7 ± 13.4	0.849[a]
T_2	94.2 ± 15.6	94.6 ± 14.8	0.850[a]
T_3	92.7 ± 16.2[d]	95.0 ± 12.2	0.354[a]
HR (beats/min)			
T_0	82.6 ± 16.9	79.4 ± 15.2	0.237[a]
T_1	83.0 ±16.8	79.4 ±14.1	0.173[a]
T_2	84.7 ± 17.3	79.4 ± 15.5	0.058[a]
T_3	83.3 ± 16.7	79.3 ± 14.5	0.138[a]

Data expressed in mean ± standard deviation.

MAP: mean arterial pressure; HR: heart rate; a: independent T-test; d: repeated measure ANOVA with post-hoc Bonferroni test

Table 4. Haemodynamic status during fentanyl-induced cough in Group II

Variable	Cough present (*n* = 8)	Cough absent (*n* = 62)	*p*-value
MAP (mmHg)	97.5 ± 19.9	95.5 ± 18.2	0.768[a]
HR (beats/min)	79.3 ±19.9	80.1 ± 17.2	0.558[a]

Data expressed in mean ± standard deviation.

MAP: mean arterial pressure; HR: heart rate; a: independent T-test

Discussion

The exact mechanism of fentanyl-induced cough is still unknown with several hypotheses proposed.[3] One of them suggested that fentanyl activates the μ opioid receptor, which then stimulates the rapidly adapting receptors present on the mucosa of the proximal tracheobronchial airway, causing bronchoconstriction and cough.[3,11] Another hypothesis suggests fentanyl inhibits central sympathetic outflow which stimulates the vagus nerve, producing bronchoconstriction and cough.[3] Therefore, the role of magnesium sulphate in obtunding fentanyl-induced cough was investigated in clinical trials based on its properties as a calcium antagonist and smooth muscle relaxant.[12,13]

In this study, the incidence of fentanyl-induced cough in the control group was 11.4%, where the dose of fentanyl was 2 μg/kg delivered over 3 seconds. The incidence of fentanyl-induced cough differs according to the patient's age group, fentanyl dosage, and the speed of fentanyl administration.[3] Han *et al.* demonstrated an incidence of 46.3% of fentanyl-induced cough in children after administration of 1 μg/kg fentanyl, whereas with the same dose, Iida *et al.* reported an incidence of only 6.6% in the adult population.[14,15] For a typical induction dose of 2 μg/kg fentanyl, Golmohammadi *et al.* found the incidence of fentanyl-induced cough to be 54.5% in children compared to 11.4% of the adults in this study.[6] Iida *et al.* also reported that a higher dose of fentanyl increased the incidence of cough from 6.6% to 22.5% in relation to 1 μg/kg and 3 μg/kg of fentanyl, respectively.[15] The speed of fentanyl injection has also been shown to influence the incidence of fentanyl-induced cough, which was 18%, 8%, and 1.3% when 2 μg/kg of fentanyl was injected over 2, 15, and 30 seconds, respectively.[16] On the other hand, Schäpermeier and Hopf found no difference in the incidence of fentanyl-induced cough when the study drug was injected over 2, 5, and 10 seconds.[17]

This study demonstrated that 30 mg/kg of intravenous magnesium sulphate could significantly reduce fentanyl-induced cough incidence during induction of general anaesthesia. This is supported by the result of a study conducted by El Motlb *et al.* in which a higher dose of magnesium sulphate was recommended in view that a dose of intravenous 20 mg/kg of magnesium sulphate produced a non-significant reduction in the incidence of fentanyl-induced cough.[4] Although 30 mg/kg of magnesium sulphate significantly reduced the incidence of fentanyl-induced cough, the severity was not statistically significant in both groups when such cough occurred, similar to a study by Liu *et al.*[10] Liu *et al.* also found significantly less incidence of fentanyl-induced cough with 50 mg/kg compared to 30 mg/kg of magnesium sulphate, but a higher dose of 5 μg/kg fentanyl was utilised in their study.[10]

Only three out of 140 patients experienced discomfort or pain at the infusion site. This finding was likely due to a relatively lower dose of magnesium sulphate compared to a study by Park *et al.* where 15.7% of patients experienced a burning sensation in the veins when they received 50 mg/kg of intravenous magnesium sulphate.[18] Similar to this study, Liu *et al.* found that three patients experienced a burning sensation during the injection of 50 mg/kg magnesium sulphate compared to none when receiving 30 mg/kg magnesium sulphate.[10]

Magnesium sulphate is widely used as a vasodilator due to its calcium antagonist property, producing hypotension.[19] However, in this study, there was no significant difference in MAP and HR between the two groups. Although there was a statistically significant reduction of MAP among the patients who received magnesium sulphate, this was within 20% of the baseline and required no medical intervention. This response was probably due to the usage of a lower dose of magnesium sulphate, similar to the result demonstrated by Panda *et al.*, in which there was a significant dose-dependent decrease in MAP requiring intervention in patients who received 40 and 50 mg/kg of intravenous magnesium sulphate as compared to those who received 30 mg/kg of magnesium sulphate.[20] Juibari *et al.* also reported a non-significant difference in blood pressure and HR between those who received 30 mg/kg magnesium sulphate and those who received saline.[21] Mroczek *et al.* reported that magnesium sulphate reduced blood pressure by a greater degree in the hypertensive population as it caused a greater decrease in peripheral resistance compared to the normotensive population.[22] This supported the results in this study as the subjects were all in ASA class I.

A cough could generate a large intrathoracic pressure fluctuation, resulting in increased blood pressure during the intra-cough phase compared to the pre-cough phase.[5,23] However, in this study, the haemodynamic status was insignificant between those who developed fentanyl-induced cough compared to those who had no cough. The limitation of this study was that non-invasive blood pressure was used for MAP monitoring. Apart from not having beat-to-beat monitoring, the time taken for cuff inflation and deflation could potentially miss the detection of significant haemodynamic changes during a fentanyl-induced cough. Thus, invasive monitoring of MAP is recommended for future studies.

Conclusion

In conclusion, during general anaesthesia induction, 30 mg/kg of intravenous magnesium sulphate effectively obtunded 2 μ/kg fentanyl-induced cough.

Declarations

Ethics approval and consent to participate
This prospective, double-blind, randomised clinical trial was approved by the departmental Research Committee and the Research Ethics Committee of our institute (FF-2018-656). Written informed consent was obtained from all patients prior to enrolment.

Competing interests
The authors declare that they have no conflicts of interest.

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