Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)
ISSN 1673-1581 (Print); ISSN 1862-1783 (Online)
www.jzus.zju.edu.cn; www.springerlink.com
E-mail: jzus@zju.edu.cn

Administration of fentanyl via a slow intravenous fluid line compared with rapid bolus alleviates fentanyl-induced cough during general anesthesia induction

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Received Oct. 6, 2016; Revision accepted Jan. 27, 2017; Crosschecked Oct. 20, 2017

Abstract: Objective: Fentanyl-induced cough (FIC) is a common complication with a reported incidence from 18.0% to 74.4% during general anesthesia induction. FIC increases the intrathoracic pressure and risks of postoperative nausea and vomiting, yet available treatments are limited. This study was designed to investigate whether administering fentanyl via a slow intravenous fluid line can effectively alleviate FIC during induction of total intravenous general anesthesia. Methods: A total number of 1200 patients, aged 18–64 years, were enrolled, all of whom were American Society of Anesthesiologists (ASA) grade I or II undergoing scheduled surgeries. All patients received total intravenous general anesthesia, which was induced sequentially by midazolam, fentanyl, propofol, and cisatracurium injection. Patients were randomly assigned to receive fentanyl 3.5 μg/kg via direct injection (control group) or via a slow intravenous fluid line. FIC incidence and the severity grades were analyzed with the Mann-Whitney test. Other adverse reactions, such as hypotension, hypertension, bradycardia, tachycardia, hypoxemia, vomiting, and aspiration, during induction were also observed. The online clinical registration number of this study was ChiCTR-IOR-16009025. Results: Compared with the control group, the incidence of FIC was significantly lower in the slow intravenous fluid line group during induction (9.1%, 95% confidence interval (CI): 6.7%–11.4% vs. 55.9%, 95% CI: 51.8%–60.0%, P=0.000), as were the severity grades (P=0.000). There were no statistical differences between the two groups with regard to other adverse reactions (P>0.05). Conclusions: The administration of fentanyl via a slow intravenous fluid line can alleviate FIC and its severity during induction for total intravenous general anesthesia. This method is simple, safe, and reliable, and deserves clinical expansion.

Key words: General anesthesia; Fentanyl-induced cough; Slow intravenous fluid line; Alleviate; Induction
http://dx.doi.org/10.1631/jzus.B1600442 **CLC number:** R614

1 Introduction

Fentanyl is widely used for perioperative analgesia due to its rapid onset, short duration, intense analgesia, and low histamine release (Li *et al*., 2005; Peter, 2011; Faruqi *et al*., 2014; Karbasy and Derakhshan, 2016). However, fentanyl intravenous injection can cause the so called fentanyl-induced cough (FIC) during the induction, which may be explosive or even life-threatening (He *et al*., 2016; Park *et al*., 2016). It is particularly dangerous for those patients suffering from airway diseases, acute upper airway obstruction, cerebral aneurysm, increased intracranial pressure, brain trauma, brain hernia, or dissecting aortic aneurysm, as severe FIC could lead to pneumothorax, optic nerve injury, or rupture of aneurysms (Lim *et al*., 2013; Saleh *et al*., 2014; Firouzian *et al*., 2015; Park *et al*., 2016; Peringathara

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and Robinson, 2016). In clinical settings, the reported incidence of FIC is variable (18.0%–74.4%) depending on the dosage, infusion speed, and route of administration (Sedighinejad *et al*., 2013; Solanki *et al*., 2016). Exploring a simple, safe, and effective way to reduce FIC, especially for those who have poor tolerance to cough, is therefore of utmost importance.

Several drugs have been used thus far, in an attempt to reduce FIC during general anesthesia induction, such as dexmethorphan (Mukherjee *et al*., 2011), lidocaine (Gecaj-Gashi *et al*., 2013), ketamine (Saleh *et al*., 2014), dexmedetomidine (Saleh *et al*., 2014), propofol (Sedighinejad *et al*., 2013; Firouzian *et al*., 2015), magnesium sulphate (Liu *et al*., 2015), dezocine (Xu *et al*., 2015), and butorphanol (Cheng *et al*., 2016). Non-pharmacological methods have also been used to successfully reduce FIC, such as prolonging the injection time (Lin *et al*., 2005) and diluting the fentanyl with saline (Solanki *et al*., 2016). These methods all require either excessive medication or expensive equipment and complicated procedures in order to alleviate FIC. In this work, we hypothesize that a simple method of administering diluted fentanyl via a slow intravenous fluid line could help to reduce FIC as it replicates the effects of dilution and prolonged injection time.

2 Materials and methods

2.1 Patient recruitment

The study was approved by the Medical Ethics Committee of Shenzhen Third People's Hospital, Guangdong, China, on April 8, 2016 (approval No. 2016-042), and was registered with the Chinese Clinical Trial Register (No. ChiCTR-IOR-16009025). Written informed consent was obtained from all participants. Altogether 1200 patients aged between 18 and 64 years were recruited and were classified as Grade I or II in accordance with the physical status classification system of American Society of Anesthesiologists (ASA). All of them were scheduled for general anesthesia for elective surgeries. The exclusion criteria include those with body weight exceeding 20% of the ideal body weight, with impaired kidney or liver functions, with a history of bronchial asthma or chronic obstructive pulmonary disease, smokers, those who had an upper airway infection in the last two weeks, with a history of circulated system disease, with hypersensitivity to general anesthetics, with treatment of angiotensin-converting enzyme inhibitors, with drug abuse, with a known hypersensitivity to fentanyl, and those who were anticipated to have difficult airway intubation. Patients were also excluded after recruitment for coughing or having a basal heart rate (HR) <50 or >100 beats/min, or a mean arterial pressure (MAP) <60 mmHg (1 mmHg= 0.133 kPa), or a pulse oxygen saturation (SpO_2) <90% after administration in the operation room.

2.2 Study design

Patients were randomly assigned to one of two groups of 600 using a computer-generated table of random numbers, assigning odd-numbered patients to the control group (Group C) and even-numbered ones to the slow intravenous fluid line group (Group S). All patients received an intramuscular injection of atropine (0.5 mg) and sodium phenobarbital (0.1 g) 30 min prior to being taken to the operating room. Electrocardiography, non-invasive blood pressure, SpO_2, end tidal CO_2 partial pressure, axillary temperature, bispectral index, and the degree of neuromuscular blockade were monitored continuously during the whole procedure. Peripheral venous access was secured using a 20-G intravenous cannula on the dorsal hand, which was connected to 0.9% (9 g/L) NaCl infusion via a slow intravenous fluid line (Murphy's dropper system). A volume of 4 ml of saline was left in the Murphy's dropper, the whole dose of the fluid line was 10 ml, and the infusing rate was 10 ml/(kg·h). During the induction period, patients in Group C received a sequential injection (with 2 min-interval between each drug) of 0.1 mg/kg midazolam injection (Jiangsu Nhwa Pharmaceutical Co., Ltd., Xuzhou, China), 3.5 μg/kg fentanyl citrate injection (Yichang Humanwell Pharmaceutical, China; injected within 5 s), 1.0–1.5 mg/kg propofol (AstraZeneca Pharmaceutical Co., Ltd., Shanghai, China) to achieve the bispectral index around 40–60, and 0.15 mg/kg cisatracurium besilate for injection (Jiangsu Hengrui Medicine Co., Ltd., China) via direct injection (Fig. 1a). The same dose of fentanyl was added to the Murphy's dropper (added within 2 s) in Group S (Fig. 1b), and the other drugs were injected in the same way as in Group C. In addition, patients in Group S also

received an injection of the same amount of normal saline with the same rate via infusion, and patients in Group C received the same amount of saline injection into the slow intravenous fluid line. Endotracheal intubation was conducted when the first twitch response of train-of-four stimulation fell to its lowest and repeated no less than three times.

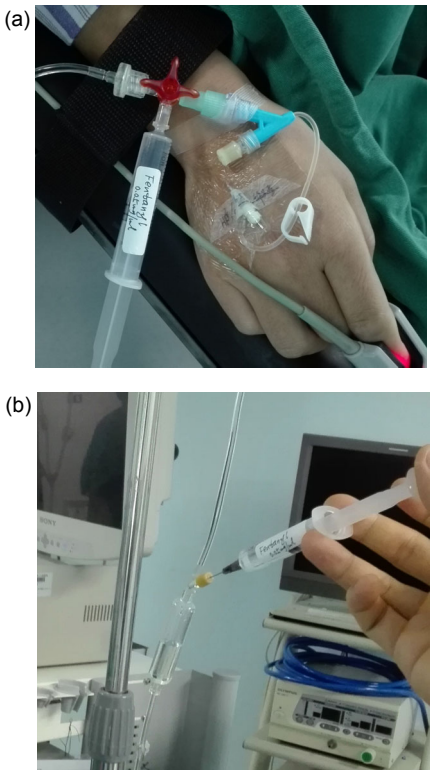

Fig. 1 Applying fentanyl via direct injection (a) and Murphy's dropper (b)

2.3 Data collection

The anesthesiologist involved in induction and maintenance of anesthesia knew which group each patient was allocated to, so coughing and other parameters were observed and recorded by another anesthesiologist who was blinded to the group allocation. Any episode of coughing movement after fentanyl administration (within 2 min) was classified as FIC. The severity of FIC was graded as follows: none (0), mild (1–2), moderate (3–4), or severe (5 or more) based on previous studies (Saleh *et al*., 2014; Xu *et al*., 2015). Vital signs were recorded every 2 min during induction (from drug administration to 5 min after endotracheal intubation). Hypotension was defined as a decrease in MAP of over 20% or noninvasive blood pressure (NIBP) ≤90/60 mmHg (Kalezic *et al*., 2013; Walsh *et al*., 2013). Hypertension was defined as an increase in MAP of over 20% or NIBP≥140/90 mmHg (Joseph and Paul, 2008; O'Shaughnessy and Adams, 2015). Bradycardia was defined as HR≤50 beats/min (Kinsella and Tuckey, 2001), while tachycardia was defined as HR≥100 beats/min (Kurokochi, 2001). SpO_2<90% was diagnosed with hypoxemia (Rozé *et al*., 2011; de Graaff *et al*., 2013). The adverse reactions such as vomiting and aspiration during the induction period were also recorded.

2.4 Statistical analyses

Statistical analyses were performed using SPSS 13.0 statistical package (SPSS Inc., Chicago, IL, USA). Group comparisons of age, weight, and height were analyzed using the independent *t*-test. Frequency of FIC was analyzed with the Mann-Whitney test. The proportions of sex and other adverse reactions between groups were compared using the Chi-square test or Fisher's exact test. Data are presented as mean±standard deviation (SD), number, or percentage. P<0.05 was considered to be statistically significant.

3 Results

3.1 Demographic profile

A total of 1200 patients were assessed for eligibility. Among them, 62 (5%) patients were excluded from the analysis. No severe adverse events were observed that would lead to a termination of the study. The data from a total of 1138 (95%) patients were analyzed, including 565 cases in Group C and 573 patients in Group S (Fig. 2). The demographic profile of the patients was similar between two groups (P>0.05; Table 1).

3.2 Incidence and its severity of FIC

There was a statistically significant difference in the incidence of FIC between the two groups, with 55.9% (316/565) of patients experiencing FIC in Group C (95% confidence interval (CI): 51.8%–60.0%), and 9.1% (52/573) in Group S (95% CI: 6.7%–11.4%) (P=0.000).

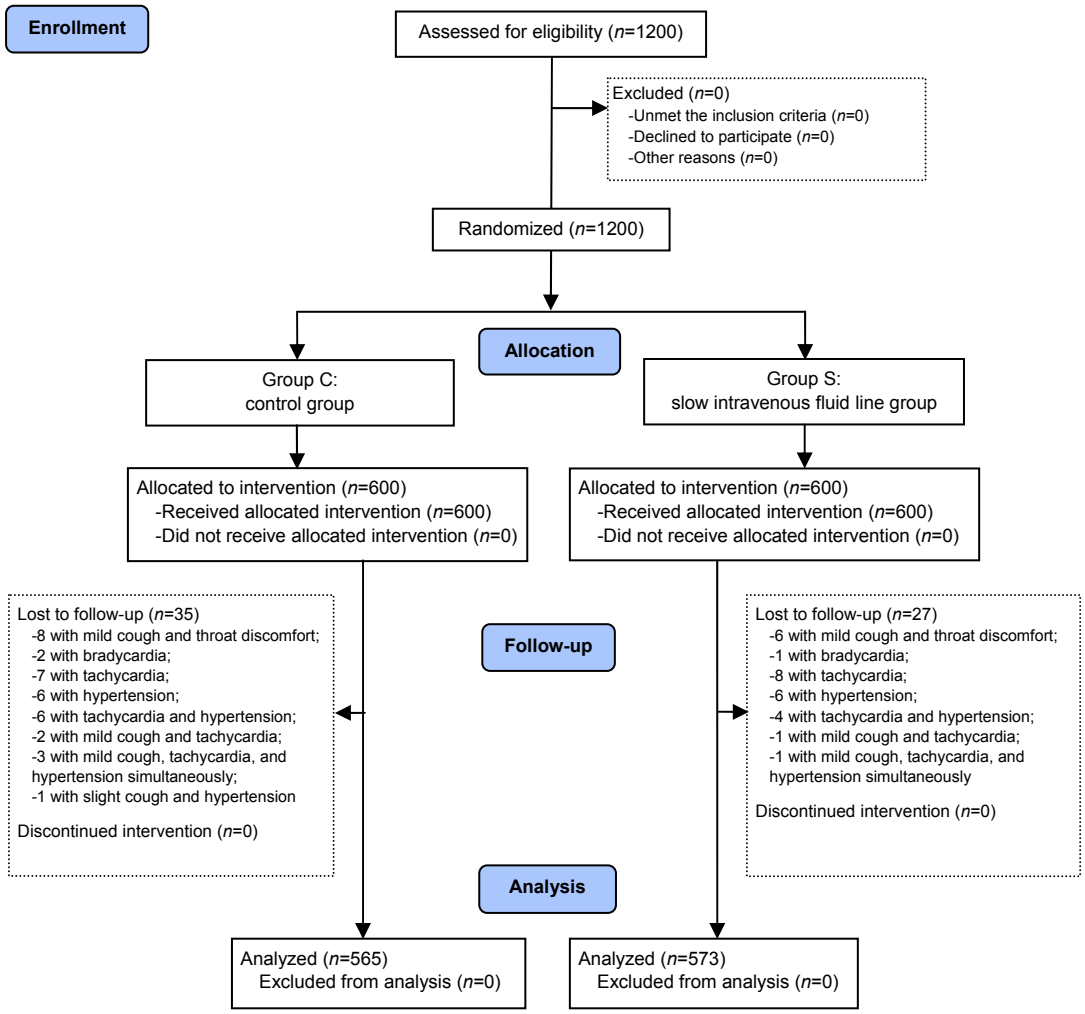

Fig. 2 Flow diagram of the study

The difference in the cough severity for Group C vs. Group S was also statistically significant (all P=0.000): none, 44.1% (95% CI: 40.0%–48.2%) vs. 90.9% (95% CI: 88.6%–93.3%); mild, 26.0% (95% CI: 22.4%–29.6%) vs. 5.1% (95% CI: 3.3%–6.9%); moderate, 18.9% (95% CI: 15.7%–22.2%) vs. 4.0% (95% CI: 2.4%–5.6%); severe, 11.0% (95% CI: 8.4%–13.6%) vs. 0, and no one in Group S suffered from severe cough (Table 2).

3.3 Other adverse reactions

There was no significant difference in hypotension, hypertension, bradycardia, or tachycardia between the two groups (P>0.05). Furthermore, no patient suffered from hypoxemia, vomiting, or aspiration during the induction period in either group (Table 3).

4 Discussion

The incidence of FIC is variable in different countries and disparate departments. Sedighinejad *et al*. (2013) from Iran observed 74.4% of FIC when patients directly received 4 μg/kg fentanyl (Fentanyl-hamlen Pharmaceutical Co., Germany) while the rate dropped to 25.6% with a pre-emptive use of 20 mg propofol (Pofol 1%, Dangkook Pharm. Co., Ltd., Korea). This study found that the order of medication administration during anesthesia induction was very important. Liu *et al*. (2015) from China found that the incidence of FIC was 45.0% via injection with 5.0 μg/kg of fentanyl within 5 s. Solanki *et al*. (2016) from India found an incidence of 12.7% when patients received undiluted fentanyl at 3 μg/kg but only 6.8% in the diluted group. The latter two studies

Table 1 Demographics of the two groups

Group	Sex (M/F)	Age (year)	Weight (kg)	Height (cm)
Group C (*n*=565)	244/321	40±12	57±8	162±8
Group S (*n*=573)	259/314	39±12	56±9	163±7
P	0.512	0.210	0.326	0.225

Data are presented as number or mean±SD

Table 2 Incidence and the severity of fentanyl-induced cough (FIC)

Group	Incidence of FIC severity				
	None	Mild	Moderate	Severe	Total
Group C (*n*=565)	249 (44.1%)	147 (26.0%)	107 (18.9%)	62 (11.0%)	316 (55.9%)
Group S (*n*=573)	521 (90.9%)	29 (5.1%)	23 (4.0%)	0 (0.0%)	52 (9.1%)
P	0.000	0.000	0.000	0.000	0.000

Data are presented as number (percentage)

Table 3 Incidences of other adverse reactions

Group	Adverse reaction						
	Hypotension	Hypertension	Bradycardia	Tachycardia	Hypoxemia	Vomiting	Aspiration
Group C (*n*=565)	175 (30.9%)	40 (7.1%)	73 (12.9%)	90 (15.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Group S (*n*=573)	166 (28.9%)	34 (5.9%)	63 (11.0%)	69 (12.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
P	0.477	0.472	0.361	0.060	1.000	1.000	1.000

Data are presented as number (percentage)

revealed the significance of the dose and dilution of fentanyl in FIC. Mukherjee *et al*. (2011) from India, however, found an incidence rate of 59.8% while injecting fentanyl 2 μg/kg in 2 s, which indicated the injection time also played an important role. Lim *et al*. (2013) from Korea reported that the literature suggests an incidence rate of FIC between 18.0% and 68.0%. Unfortunately, rare brand names and manufacturers of fentanyl were used in the above studies; therefore, we were not able to confirm whether the preservatives and other pharmaceutical components in fentanyl were the same across different reports.

Several mechanisms are described for FIC, including: (1) an inhibition of central sympathetic activity, leading to vagal predominance, causing reflex bronchial contract and inducing a cough (Rozé *et al*., 2011); (2) inducing pulmonary columnar epithelial cells to release histamine, which enhances cough sensitivity and causes bronchospasm (Kamei *et al*., 2013; el Baissari *et al*., 2014); (3) enhancing the excitability of rapidly adapting bronchial receptors or forming a reflex cough (Cinelli *et al*., 2013); (4) in combination with the μ receptors and κ receptors in the bronchial trees, activating the presynaptic C fiber to release neuropeptides, which cause bronchial smooth muscle contraction and increase vascular permeability, resulting in a choking cough (Jung *et al*., 2011; Cinelli *et al*., 2013); (5) the citric acid in citrate fentanyl can trigger bradykinin to be released by the peripheral tissue primary nerve, activating neurokinin-1 and neurokinin-2 receptors and causing neurogenic inflammation and bronchoconstriction and a choking cough (Kamei *et al*., 2013). All of these mechanisms are well studied; however, there are few methods that can effectively inhibit FIC.

Previous studies with several anesthetic adjuncts, such as sodium chromoglycate (Agarwal *et al*., 2003), beclomethasone (Agarwal *et al*., 2003), dexmethorphan (Mukherjee *et al*., 2011), lidocaine (Gecaj-Gashi *et al*., 2013), salbutamol (Saleh *et al*., 2014), dexmedetomidine (Saleh *et al*., 2014), ketamine (Saleh *et al*., 2014), propofol (Sedighinejad *et al*., 2013; Firouzian *et al*., 2015), dezocine (Xu *et al*., 2015), magnesium sulphate (Liu *et al*., 2015) and butorphano (Cheng *et al*., 2016), have been demonstrated to effectively decrease FIC. However, there

was no unified standard, and the use of preventative drugs might produce other drug-related complications, thus prophylactic use of drugs should be strictly limited. Furthermore, some non-pharmacological methods, such as prolonged injection time (Lin *et al*., 2005; Yu *et al*., 2007) and dilution of fentanyl (Yu *et al*., 2007; Solanki *et al*., 2016) have been used to suppress FIC, which were attributed to the decreasing fentanyl concentration of blood. Yet, excessive dilution or injecting too slow would reduce the adherence of anesthesiologists.

To address a feasible way to dilute fentanyl during induction, we added it into a slow intravenous fluid line, and this was equivalent to having a continuous and dynamic process of dilution. When the added drugs came into contact with the original liquid in the Murphy's dropper, the first dilution began. The second dilution occurred in the saline flow which was continuously coming from the infusion bags. And when the drugs continuously dropped down to the flow tube, the third dilution process was achieved. This method was not only simple and feasible, but also limited the medicine concentration and the maximum infusion speed. In Group C, 3 μg/kg fentanyl was injected within 5 s, the actual rate was faster than 0.7 μg/(kg·s). In Group S, however, the original amount of saline in the fluid line (from Murphy's dropper to intravenous cannula) was about 10 ml, as the infusing rate was 10 ml/(kg·h), the fentanyl injection time was 1 min or so, and the actual infusion rate was roughly 0.058 μg/(kg·s). Moreover, the osmolality and pH of fentanyl had been changed to an ideal extent. Changes in osmolality and pH reduce stimulation of irritant receptors in tracheal smooth muscle cells and C fiber receptors in pulmonary vessels, thus suppressing the cough reflex (Yu *et al*., 2007). In this case, the FIC incidence and severity triggered by fentanyl were decreased dramatically.

Our study evaluated a simple method to administer fentanyl via a slow intravenous fluid line, which successfully reduced FIC during induction for total intravenous general anesthesia. Furthermore, this system can also alleviate the severity of FIC without any other pharmacological treatment.

There are some limitations in our study. Firstly, it was a single-blind study, some subjective differences between two groups may be observed in a double-blind study. Secondly, to reduce the patients' discomfort and the incidence of intraoperative awareness, fentanyl was applied after midazolam, which may impair the actual occurrence of FIC through Murphy's dropper, thus a larger sample size without premedication would be beneficial to remove this bias.

5 Conclusions

The application of fentanyl via Murphy's dropper can effectively alleviate FIC during the general anesthesia induction. This method is simple, safe and reliable, especially for developing countries or for under-equipped hospitals, or even for emergency situations such as in the battlefield.

Acknowledgements

Thanks to Prof. Hui-qiang YU (Department of Teaching and Research Section of Statistics, Nanchang University, China) for providing the statistical guidance for this study.

Compliance with ethics guidelines

Min-qiang LIU, Feng-xian LI, Ya-kun HAN, Jun-yong HE, Hao-wen SHI, Li LIU, and Ren-liang HE declare that they have no conflict of interest.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (Medical Ethics Committee of Shenzhen Third People's Hospital, Shenzhen, China) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study. Additional informed consent was obtained from all patients for whom is included in this article.

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中文概要

题　目：全麻诱导期经静脉输液管缓慢滴注和快速输注芬太尼对该药诱发呛咳的影响

目　的：探讨全麻诱导期经静脉输液管（墨菲氏管）给药能否减轻芬太尼诱发的呛咳。

创新点：寻找一个简单易行、安全可靠的方法减轻全麻诱导期芬太尼诱发的呛咳。与既往芬成尼和呛咳相关的研究相比，本研究试验组操作不仅简便、快速，而且无需额外使用其它药物或设备，不增加人力成本或病人经济负担。

方　法：择期行全身麻醉手术 1138 例，所有患者均采用咪达唑仑-芬太尼-丙泊酚-顺式阿曲库铵-气管插管麻醉，随机分为静脉输液管缓慢滴注组（S 组，573 例）与经三通快速输注组（C 组，565 例），记录麻醉诱导期两组患者呛咳发生率及严重程度和其它不良反应发生情况。

结　论：静脉输液管缓慢滴注组呛咳发生率及严重程度较快速输注组明显降低，其它不良反应发生率比较差异无统计学意义。全麻诱导期经静脉输液管缓慢滴注芬太尼可明显降低该药所致呛咳的发生率，且该法简单易行、安全可靠，值得推广。

关键词：全麻；芬太尼诱发呛咳；缓慢滴注；减轻；诱导