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ORIGINAL ARTICLE

Swallowing action immediately before intravenous fentanyl at induction of anesthesia prevents fentanyl-induced coughing: a randomized controlled study

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Abstract
Purpose Fentanyl is a strong μ-opioid analgesic which attenuates the stimulation of surgical invasion and tracheal intubation. However, intravenous fentanyl often induces coughing [fentanyl-induced coughing (FIC)] during induction of anesthesia. We found that the swallowing action, when requested at induction of anesthesia, attenuated FIC. In the current study, we investigated the relationship between the occurrence of FIC and the swallowing action.
Methods The study included American Society of Anesthesiologists physical status I or II patients, aged 20–64 years, who were undergoing elective surgery. They were divided into two groups—one group was urged to perform the swallowing action immediately before intravenous fentanyl (S group), and the other group performed no swallowing action (non-S group). The patients first received intravenous fentanyl and were observed for 90 s. Each patient's background, dose of fentanyl and occurrence of coughing were investigated from their records and a motion picture recording. The incidence of FIC was evaluated by chi-squared test, and severity was tested by Wilcoxon rank-sum test. $P < 0.05$ was considered statistically significant.
Results The incidence of FIC in the S group and non-S group was 14.0 and 40.4%, respectively. The risk of FIC was reduced in the S group by 75%; risk ratio (95% confidence interval) was 0.35 (0.20, 0.60). The number of coughs in the S group were less than in the non-S group ($P < 0.001$).
Conclusion The swallowing action immediately before intravenous fentanyl may be a simple and clinically feasible method for preventing FIC effectively.
Clinical trial number: UMIN000012086 (https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&recptno=Rn000014126&language=J).

Keywords Analgesics · Opioid · Cough · Deglutition · Fentanyl · Swallowing

Introduction

Fentanyl is a strong μ-opioid analgesic which attenuates the excitement caused by the stimulation of surgical invasion and tracheal intubation. Fentanyl is characterized by quick onset, cardiovascular stability and low histamine release [1, 2]. Although μ-opioids generally possess antitussive potential, intravenous fentanyl often induces coughing [fentanyl-induced coughing (FIC)] during the induction of anesthesia [3, 4]. FIC can sometimes be long lasting and severe, and can increase intracranial and intrathoracic pressure. Furthermore, it may cause episodes of hypertension, arrhythmia, or other unexpected problems which may require immediate therapeutic intervention [3, 4]. A previous report showed that the incidence of FIC during induction reached 80% [5]. However, although various methods have been tried to decrease the incidence of FIC, the mechanism of FIC is still not clear [5–12].

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At induction of anesthesia, we first ask the patients to perform the swallowing action to reduce pharyngeal discharge. In such cases, we felt that the incidence of coughing seemed to be decreased. We, therefore, hypothesized that the swallowing action might reduce the incidence of FIC. To verify our hypothesis, we conducted a randomized controlled study to investigate the relationship between the incidence of FIC and the swallowing action.

Materials and methods

Ethics

Ethical approval for this study was obtained from the Ethics Committee of Kyushu University Hospital and St. Mary's Hospital on December 14, 2012. This study was registered with the UMIN clinical trials registry number UMIN000012086.

Patients and protocol

Patients were recruited from two hospitals (Kyushu University Hospital, Fukuoka, and St. Mary's Hospital, Fukuoka). Inclusion criteria were American Society of Anesthesiologists physical status I or II, aged 20−64 years, either sex, and undergoing elective surgical procedures under general anesthesia. We excluded patients with a history of asthma, chronic cough or medication containing angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, bronchodilators and steroids. Patients with upper respiratory tract infection within 2 weeks before the operation were also excluded.

The primary endpoint was the incidence of FIC within 90 s after completion of the fentanyl injection. A cough was defined as any tussive reaction not consistent with normal quiet breathing. Primary outcome was assessed by a motion picture recorded by one of the members of the Ethics Committee of Kyushu University Hospital. The experienced observer was unaware of the patient groups. Secondary endpoints were the number and severity of FIC within 90 s after completion of the fentanyl injection. We also evaluated changes in blood pressure and heart rate.

The patients were informed that some simple actions might be requested and their reactions would be recorded on a video at the induction of anesthesia, and vital signs were also taken at the same time. After written informed consent was obtained, the patients were assigned to their groups by block randomization. A computer-generated random number was used to select random permutated blocks. The block length was varied randomly. The random allocation numbers were concealed in opaque closed envelopes. Patients missing either administrative or outcome data, or both were excluded (Fig. 1). Patients undergoing elective surgery were enrolled and allocated to one of two groups—one group included patients who were requested to perform the swallowing action when fentanyl was administered (S group) and the other group included patients who performed no swallowing action (non-S group).

No premedication was administered. In the operating room, the patients were continuously monitored by electrocardiogram (ECG), pulse oximetry (SpO_2), non-invasive blood pressure measurements [systolic blood pressure (SBP) and diastolic blood pressure (DBP)], and a video recording for 90 s from the time of the fentanyl injection. The fentanyl injection was started immediately after completing the swallowing action >5 times. All patients received intravenous fentanyl within a period of 2 s via a T-connector, followed by fast-running intravenous fluid (1% glucose lactated Ringer's solution or lactated Ringer's solution). In this study, we divided the dose of the fentanyl into 4 and 2 μg kg^{-1} depending on the estimated operation time; patients received 4 μg kg^{-1} of fentanyl when the estimated operation time was >2 h, and patients received 2 μg kg^{-1} of fentanyl when the estimated operating time was <2 h. The patients were aware of the type of medication but they were unaware of the purpose of the trial. The motion picture was deleted after confirmation. All records and datasets were stored in key with Bookcase.

Coughs were classified according to the number of times during the observation period as mild (1–2), moderate (3–4) and severe (>5). Induction of general anesthesia was started 90 s later as usual.

Statistics

In our preliminary trial with 48 patients on the same intervention, the incidence of coughing in the S group was 17.4%, while that in the non-S group was 52.0%. From these observations, we expected that the cough incidence would be reduced by 20% in the intervention group and by 45% in the group without intervention. To achieve 80% power to detect a significant difference with two sided $P < 0.05$ using the chi-squared test, 89 patients were required for each study group. To compensate for 10% ineligible and dropout patients, we planned to enroll 100 patients per group.

The characteristics of the patients are shown as the median (interquartile range) or number of patients. The difference in the incidence of FIC between allocation groups was tested by the chi-square test, and severity was tested by the Wilcoxon rank-sum test or analysis of covariance. The mean difference in change of SBP and DBP, baseline SpO_2 and eosinophil (%) and relative risks of cough incidence were estimated for each stratum. Relative risks were compared between the strata and the test of interaction by

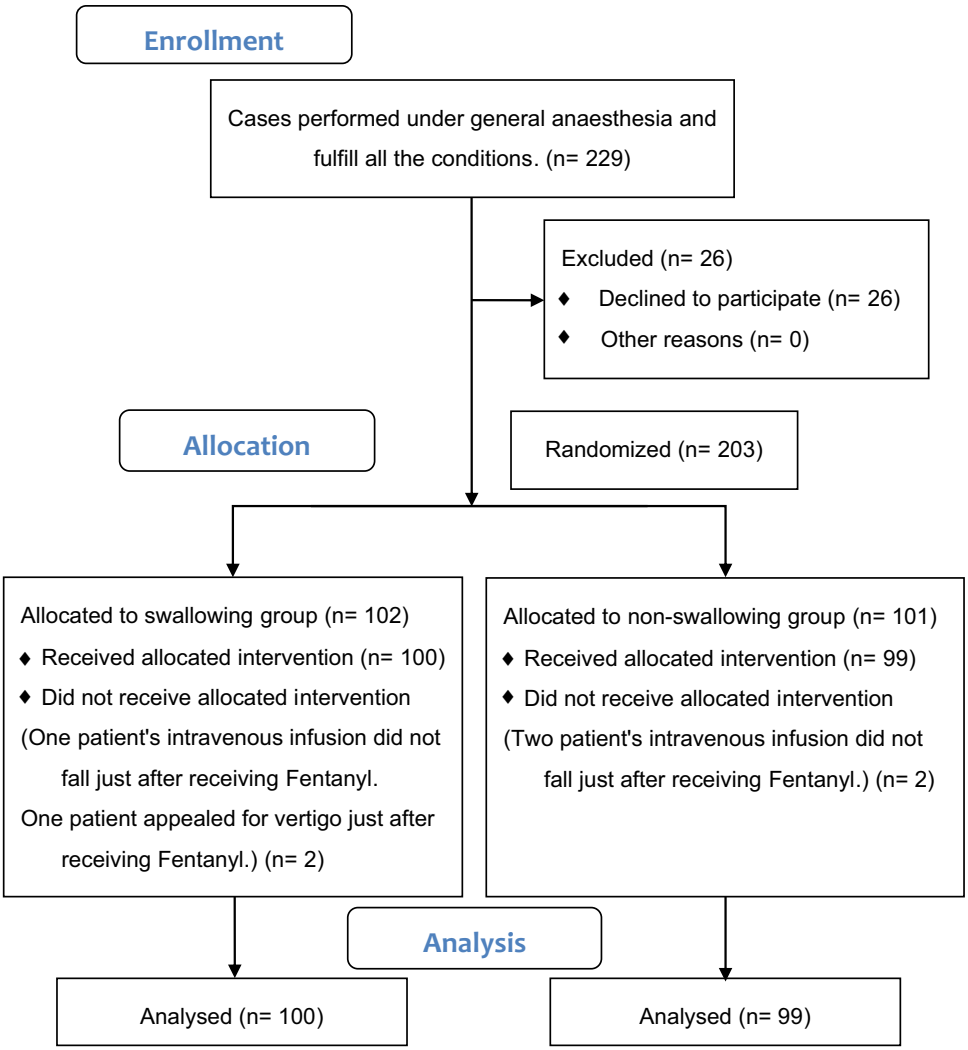

Fig. 1 The CONSORT style flow diagram showing systematic research

including a dummy variable for strata multiplied by baseline value in the logistic regression model. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using Stata version 13 statistical analysis software (Stata, College Station, TX, USA).

Results

From December 2012 to August 2014 we recruited 229 patients receiving general anesthesia who fulfilled all the conditions. Of the 229 patients, 26 refused to participate and the remaining 203 patients were allocated to two groups (Fig. 1). Four patients did not receive the allocated intervention due to vertigo (one patient) and infusion trouble (three patients). Consequently, 199 patients remained for the statistical analyses. No patients suffered from any side-effects of fentanyl.

Patient characteristics (age, body mass index, and gender) are shown in Table 1. The results of the analyses on the primary and secondary endpoints are shown in Table 2. The incidence of FIC in the S group and non-S group was 14.0 and 40.4%, respectively. The risk of FIC was reduced in the S group by 75%; risk ratio (95% confidence interval; CI) was 0.35 (0.20, 0.60).

The number of coughs in the S group was less than in the non-S group ($P < 0.05$). For patients with an incidence of coughing, the differences in the proportions of cough type and the duration until the emergence of cough were not statistically significant in the two groups ($P = 0.29$ and 0.83, respectively). The changes in DBP and SpO_2 from baseline values in the S group were higher by 2.54 mmHg (95% CI 0.59–4.49 mmHg) and 0.26% (95% CI 0.01–0.51%), respectively, with statistical significance. The change in SBP from baseline value in the S group was higher by 2.02 mmHg (95% CI −0.04 to 4.09 mmHg) with marginal significance ($P = 0.05$).

The results of preplanned subgroup analysis to find interactions between intervention and backgrounds of patients are shown in Table 3. None of the interactions

Table 1 Background of eligible patients who completed the trial

Characteristics	Swallowing group ($n = 100$)	Non-swallowing group ($n = 99$)
Sex		
Male	64 (64.0)	64 (64.7)
Female	36 (36.0)	35 (35.4)
Age (years)		
20–29	27 (27.0)	29 (29.3)
30–39	22 (22.0)	24 (24.2)
40–49	19 (19.0)	16 (16.2)
50–59	20 (20.0)	16 (16.2)
60–64	12 (12.0)	14 (14.1)
Body mass index (kg m^{-2})	21.8 (19.6, 24.8)	22.2 (20.1, 24.5)
SBP (mmHg) before i.v. fentanyl	124 (117, 140)	126 (114, 138)
DBP (mmHg) before i.v. fentanyl	75 (66, 84)	74 (67, 84)
Heart rate (times min^{-1}) before i.v. fentanyl	72 (62, 82)	69 (60, 80)
Oxygen saturation of peripheral artery (%) before i.v. fentanyl	99 (98, 100)	99 (98, 100)
Eosinophil (%)	2.3 (1.6, 3.8)[a]	2.5 (1.7, 4.2)[b]
Dose of fentanyl		
2 μg/kg	76 (76.0)	68 (68.7)
4 μg/kg	24 (24.0)	31 (31.3)
Use of medicine		
Yes	5 (5.0)	6 (6.1)
No	95 (95.0)	93 (93.9)
Smoking history		
Yes	46 (46.0)	41 (41.4)
No	54 (54.0)	58 (58.6)

Number (%) or median (interquartile range). Percentages may not total 100 because of rounding

Due to missing values, the number of subjects were [a]$n = 87$ and [b]$n = 88$

was statistically significant, suggesting that the reduction of coughing by swallowing was little affected by the background of the patients.

Discussion

Circulatory dynamics change drastically during induction of anesthesia, since laryngoscopy and tracheal intubation are stimulating procedures. Fentanyl is a useful analgesic agent for stabilizing circulation conditions. It is widely used at the induction of general anesthesia. Intravenous fentanyl, however, often induces coughing during induction of anesthesia [3, 4]. Our study demonstrated that the swallowing action immediately before intravenous fentanyl decreased the incidence of FIC from 40.4 to 14.0%, which was consistent with our hypothesis.

According to previous reports, the mechanism of FIC is still not clear [5–12]. Kamei et al. reported that fentanyl may enhance the excitability of rapidly adapting receptors to cause coughing, and enhancement of histamine release in the airways might be related to fentanyl-induced enhancement of cough sensitivity [10]. Others reported that fentanyl constricts the tracheal smooth muscles by stimulating μ-adrenal receptors, or FIC might be caused by stimulation of vagal C-fiber receptors [11, 12].

In this study, the patients were asked to perform the swallowing action, which includes a series of reflexes. Some parts of the swallowing action are shown to be induced by the vagus nerve, and in particular by one of its branches, the superior laryngeal nerve [13]. This nerve is usually excited by the mechanical stimulation of the passage of food/water through the pharynx [14]. Another report indicated that vagal efferent pathways may not be involved in FIC [15]. Tsubouchi et al. reported that the vagal nerve was related to FIC since atropine suppressed the cough reflex [16]. In our study, the swallowing action attenuated FIC. We, therefore, speculated that the afferent vagal nerve fiber was activated by the swallowing action which might disturb conduction of the nerve impulse for FIC.

On the other hand, we speculated that that coughing and swallowing coordinately protect the airway using the

Table 2 Primary and secondary endpoints

Endpoint	Swallowing group ($n = 100$)	Non-swallowing group ($n = 99$)	Risk ratio	P
Cough reflex	14 (14.0)	40 (40.4)	0.35 (0.20, 0.60)	$P < 0.001^{\dagger}$
Number of coughs				$P < 0.001^{\ddagger}$
0	86 (86.0)	59 (59.6)		
1–5	10 (10.0)	36 (36.4)		
6–10	3 (3.0)	4 (4.0)		
15	1 (1.0)	0 (0)		
Type of cough				$P = 0.29^{\ddagger}$
Mild	4 (28.6)	13 (32.5)		
Moderate	3 (21.4)	16 (40.0)		
Severe	7 (50.0)	11 (27.5)		
Seconds until cough				$P = 0.83^{\ddagger}$
1–9	2 (15.4)	1 (2.7)		
10–19	2 (15.4)	10 (27.0)		
20–29	5 (38.5)	16 (43.2)		
30–39	3 (23.1)	5 (13.5)		
40–61	1 (7.7)	5 (13.5)		
Change from baseline			Difference between groups	
SBP (mmHg)	0.85 (−0.56, 2.26)	−1.13 (−2.71, 0.451)	2.02 (−0.04, 4.09)	$P = 0.05^{\P}$
DBP (mmHg)	1.98 (0.50, 3.46)	−0.61 (−2.02, 0.80)	2.54 (0.59, 4.49)	$P = 0.01^{\P}$
SpO_2 (%)	0.18 (−0.01, 0.37)	−0.07 (−0.26, 0.12)	0.26 (0.01, 0.51)	$P = 0.04^{\P}$

Number (%), risk ratio for cough (95% CI) or difference in means (95% CI)

Methods of statistical tests: †chi-squared test, ‡Wilcoxon rank-sum test, ¶analysis of covariance

laryngeal adductor muscles and upper esophageal sphincter. However, both muscle activities have opposite effects during coughing and swallowing [17]. During swallowing, laryngeal adductor muscle activity increases to close the glottis, and upper esophageal sphincter activity decreases to promote pharyngeal clearance. This combination also prevents aspiration. In contrast, laryngeal adductor muscle activity decreases during coughing, but only moderately increases at inspiration–expiration transition, and the upper esophageal sphincter increases to prevent the loss of intrathoracic pressure. Therefore, as the swallowing action reduces intrathoracic pressure to minimize coughing, its action might suppress the FIC.

Many methods have been reported for prophylaxis of FIC. For example, Horng et al. reported that pre-intravenous rocuronium (0.06 mg kg^{-1}) could suppress the cough reflex [7]. Serious complications were not described in their study. In another report, however, serious complications, such as regurgitation and severe muscle weakness due to pre-intravenous administration of rocuronium, were observed [18]. Yu et al. reported that premedication with intravenous dexmedetomidine and midazolam reduced the incidence of FIC [8]; however, their method may be not practical since this premedication required 12 min before fentanyl injection and may cause side-effects.

Prevention of FIC by the swallowing action may be beneficial for both the patient and the anesthesiologist. This method is simple and requires no other drugs or devices. Therefore, although we perform anesthetic management using remifentanil under general anesthesia in our clinical situations, we did not use remifentanil in our study. In addition, we need not pay attention to side-effects from additional medication to avoid FIC. Although it was not the main focus of our study, we noted that the blood pressure in the S group increased after intravenous fentanyl, while that in the non-S group decreased. The difference in DBP between the groups reached statistical significancc; however, these changes were too small to have clinical meaning.

Ambesh et al. reported that a huffing maneuver performed immediately before intravenous fentanyl reduced the incidence and severity of FIC [9]. Their method is also noninvasive and simple. An advantage of the swallowing action, however, is that it may provide a clear vision of the laryngoscopy since the swallowing action might decrease pharyngeal discharge. A better result may be provided by a combination of the swallowing action and the huffing maneuver.

Our study has some limitations as the results are applicable only to Japanese adult patients. According to previous

Table 3 Relative risk for coughing in subgroups

Subgroup	Deglutition (patients with cough/total number)	No deglutition (patients with cough/total number)	Relative risk for cough (95% confidence interval)	*P* value for interaction
Age (years)				0.65
20–37	7/46	24/52	0.33 (0.16, 0.69)	
38–64	7/54	16/47	0.38 (0.17, 0.85)	
Sex				0.31
Male	8/64	28/64	0.29 (0.14, 0.58)	
Female	6/36	12/35	0.49 (0.21, 1.15)	
Body mass index (kg m^{-2})				0.57
16.3–22.1	10/54	22/48	0.40 (0.21, 0.77)	
22.2–32.0	4/46	18/51	0.25 (0.09, 0.67)	
Use of medicine				0.63
Yes	1/5	4/6	0.30 (0.05, 1.89)	
No	13/95	36/93	0.35 (0.20, 0.62)	
Smoking history				0.21
Yes	4/46	17/41	0.21 (0.08, 0.57)	
No	10/54	23/58	0.47 (0.25, 0.89)	
Baseline SBP (mmHg)				0.35
92–124	8/54	23/45	0.29 (0.14, 0.58)	
125–184	6/46	17/54	0.41 (0.18, 0.96)	
Baseline DBP (mmHg)				0.38
52–74	6/44	24/51	0.29 (0.13, 0.64)	
75–100	8/56	16/48	0.43 (0.20, 0.91)	
Baseline heart rate (times min^{-1})				0.92
45–69	6/47	19/51	0.34 (0.15, 0.78)	
71–127	8/53	21/48	0.35 (0.17, 0.70)	
Baseline SpO_2 (%)				0.39
95–98	3/31	14/33	0.23 (0.07, 0.72)	
99–100	11/69	26/66	0.40 (0.22, 0.75)	
Eosinophil (%)				0.84
≤4%	9/68	25/65	0.34 (0.17, 0.68)	
<4%	3/19	11/23	0.33 (0.11, 1.01)	

reports, race may have a possible influence on the incidence of FIC [19]. Schäpermeier et al. observed that the incidence of FIC was greater in Asiatic and Chinese people than in Europeans [20]. In our daily clinical practice, children also seem to show a higher incidence of FIC than adult patients. Therefore, further investigation for children and other races are necessary.

In conclusion, the swallowing action immediately before intravenous fentanyl may be a simple and clinically feasible method for preventing FIC effectively.

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