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Comparing Fentanyl Dosages of 1 Microgram per Kilogram of Body Weight and of 1.5 Micrograms per Kilogram of Body Weight in Relation to Cough Suppression during Bronchoscopy Procedures

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ABSTRACT

BACKGROUND: Anaesthesia at bronchoscopy is a unique challenge for the anaesthesiologist as both the anaesthesiologist and operator work in the same airway. It is essential that administration of sedative agents must achieve the desired depth of sedation without risking airway patency, ventilation function and cardiovascular function. About 25% of bronchoscopy patients cite cough as the most unpleasant effect of this procedure. Fentanyl is widely chosen for a sedative agent because of their analgesic, sedative, and antitussive effects, however there has been no data regarding the optimal dose of fentanyl to suppress cough in bronchoscopy procedures.

METHODS: We designed a research with 18 subjects received fentanyl in a dose of 1 µg / kgBW, 18 subjects received fentanyl in a dose of 1.5 µg / kgBW and 18 subjects received propofol in a dose of 2 mg / kgBW as a control group. We observed the depth of sedation using the Ramsay sedation score and duration of cough suppression in their bronchoscopy procedures. We also observed the alteration of blood pressure, pulse rate, respiratory rate and oxygen saturation.

RESULTS: There was a significant difference in the depth of patient sedation between the control group and the treatment groups; as patients without fentanyl treatment were sedated deeper on the Ramsay 4 scale, patients in the treatment groups with either fentanyl of 1 µg / kgBW or 1.5 µg / kgBW had the depth of sedation on the Ramsay 2 scale and unable to reach moderate sedation as expected. Subjects with fentanyl treatments showed significantly better suppression effects against coughing compared to control group patients. As there also was a significance difference in suppression effects for coughing between the group receiving fentanyl treatment of 1 µg / kgBW and the group receiving fentanyl treatment of 1.5 µg / kgBW, we noticed a fentanyl treatment of 1 µg / kgBW was adequate to suppress cough although a dose of 1.5 µg / kgBW would show better cough suppression effect. Subjects in control group with 2 mg / kgBW of propofol experienced a more significant alteration in vital signs than the fentanyl group, either with a dose of 1 µg / kgBW or 1.5 µg / kgBW. Comparing and statistically analysing the two treatment groups of different dose of fentanyl, we found no significant difference in vital signs alteration between the two groups.

DISCUSSION: Our study revealed that as fentanyl significantly suppressed cough reflex and larger dose would provide longer period of suppression. Subjects with fentanyl treatment showed more favourable altercation in systolic and diastolic blood pressure, pulse rate, respiratory rate and oxygen saturation compared to subjects in control group with 2 mg / kgBW of propofol, but comparing and statistically analysing the two groups of different dose of fentanyl, we found no significant difference in vital signs alteration.

KEYWORDS: fentanyl, bronchoscopy, sedation, cough

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INTRODUCTION

Flexible bronchoscopy (FB) is a routinely utilized procedure for diagnosis and therapy of various bronchopulmonary disorders.[1] Bronchoscopy itself is the gold standard of endoscopic visualization of deeper airway. The requirement of anaesthesiologists in bronchoscopy procedures are growing along the time bronchoscopy techniques for diagnostic purpose are developed,[2-4] and also in regards that such procedure requires a meticulous technique for airway management in which both the anaesthesiologist and the operator sharing the same working field.[5] Bronchoscopy procedure can be performed as a day care procedure in the surgery theatre or in a critical care unit.[2,3] As recent development shows the application of moderate sedation technique or conscious sedation technique more regularly utilized for simple bronchoscopy procedure, general anaesthesia is still the standard for more complex procedures.[6-8]

As flexible bronchoscopy facilitates visualization of airway all the way to the segmental bronchus. It is routinely performed for the diagnosis of various lung conditions. Generally flexible bronchoscopy can be performed outside the operating room with moderate sedation. Recent guidelines for flexible bronchoscopy recommend the procedure to be performed under sedation. One study showed that the use of midazolam assists the operator in carrying out the procedure, but not increasing patient comfort, therefore most operators use sedation and anxiolytic agents to improve patients' comfort.[2,9,10] As bronchoscopy techniques are evolving, the level of difficulty and the duration of procedure increasing, general anaesthesia is now more frequently used.[2]

Flexible bronchoscopy can be performed with or without sedation. The concept of sedation is complex to a certain extent, with varying degrees of consciousness: the minimum of it is anxiolytic (minimal) sedation, followed by conscious (moderate) sedation, deep sedation, and lastly general anaesthesia. Many reports stated almost all institutions in the US use moderate sedation, wherein induction drugs decrease the level of consciousness in which the patient endures the procedure with adequate spontaneous ventilation and normal cardiovascular function, while he/she can still respond verbally.[7] Should the patient be verbally unresponsive during the procedure and he/she can only respond to the pain stimuli, the patient are into a deep sedation state already, in which his/her airway patency and spontaneous ventilation should be more carefully monitored.[11] The depth of sedation should always be monitored during the procedure and documented with a measuring scale. Anaesthesiologists usually utilize the Ramsay sedation scale as may studies also use. To apply moderate sedation, the depth of sedation should not be more than level 3.[2]

Table 1. Ramsay sedation scale.

SCORE	PATIENT'S RESPONSE / SEDATION STATE
1	Anxious, restless or both
2	Cooperative, orientated and tranquil
3	Responding to commands
4	Brisk response to stimulus
5	Sluggish response to stimulus
6	No response to stimulus

To achieve the required level of sedation clinically and physiologically, anaesthesiologists start a sedative agent in a small and incremental doses, in bolus or in continuous infusion.[10] The ideal sedative agents for bronchoscopy procedures should provide easy preparation/usage, rapid onset, short duration of action, and speedy cognitive recovery. The pharmacokinetic and pharmacodynamic profile of sedative agents must be foreseeable so that dynamic interactions with other drugs and their antagonist drugs can anticipated.[10] Some of sedative agents commonly utilized for bronchoscopy procedures are benzodiazepines, opioids, a combination of benzodiazepines and opioids, propofol, phospropofol, ketamine, and dexmedetomidine.[7]

COUGH

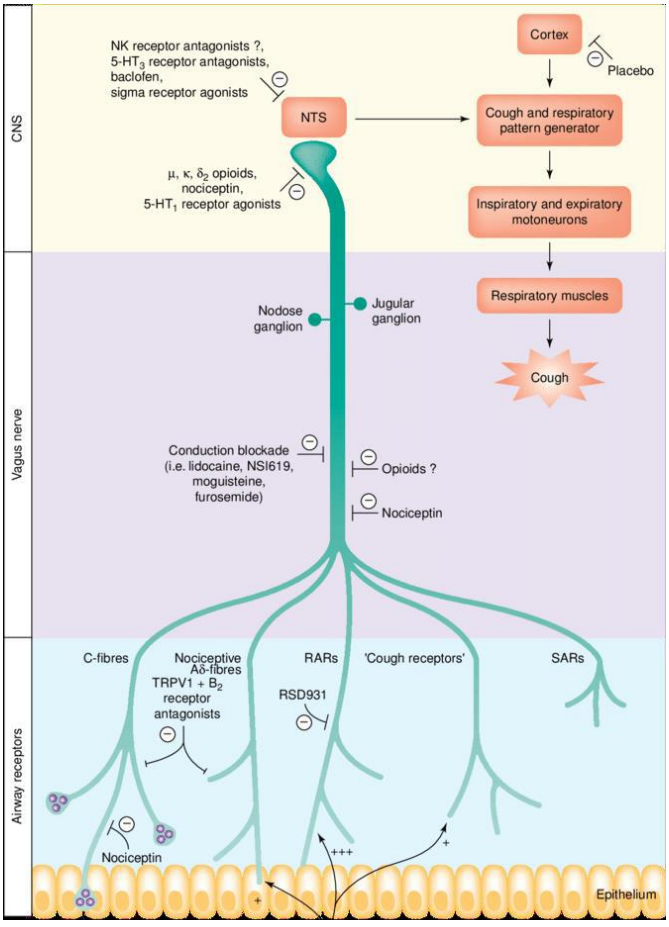
Cough, an unavoidable symptom of bronchoscopy procedures, results from intense stimulation of the airway surface by a scope instrument.[12] About 25% of bronchoscopy patients cite cough as the most unpleasant effect of this procedure. Under physiological conditions, cough has an important role in airway and lung protection, but in some circumstances, coughing can be excessive, non - productive, and sometimes has the risk to jeopardize the airway mucosa.[12] Cough is an important defensive reflex resulting from stimulations to the reflex arc; it clears secretions and particulates from the airway, protects against aspiration/inhalation of particular, pathogens, accumulated secretions, post nasal drip, inflammation mediators and others.[12] Cough suppression is important for quality, safety

and comfort of intra-bronchoscopic procedures and consequently facilitates better visualization of bronchoscopy and easier biopsy procedures if necessary. Sedation during anaesthesia has a variable effect on the cough reflex, depending on the anaesthetic agent utilized.[13]

Cough is initiated by irritation of cough receptors located in the trachea, carina, and larger upper airway, as well as in smaller lower airway and in the pharynx. Laryngeal and tracheobronchial receptors respond to mechanical and chemical stimuli. Chemical receptors are sensitive to acid substance, heat, and chemical substance like capsaicin (type-1 vanilloid). Other airway receptors scattered in places like in the ear, pharynx, diaphragm, pleura, and pericardium are more likely to be mechanical receptors, so they are stimulated by touch.

Sensory branches of the vagus nerve are located in the ciliated epithelium of the upper airway and cardiac and oesophageal branches of the diaphragm. Afferent pathways have three main receptor groups: the Rapidly Adapting Receptors (RAR) which respond to dynamic lung inflation, bronchospasm, or lung collapse; the Slowly Adapting Stretch Receptors (SASR) which are sensitive to mechanical stimuli; and C-fibers: which are responsive to chemical disturbances and mechanical stimuli. Impulses from cough receptors travel on afferent pathways via the vagus nerve and spread diffusely to the medulla where the cough center is located. The cough center is in the in the upper brainstem and pons, and under control of higher cortex centers. It later transmits the efferent signals down via the laryngeal branches of vagal nerve to the larynx, via phrenic nerves to the diaphragm, and via spinal motor nerves to the abdominal muscles to produce cough (**see Figure 1**).[12]

Figure 1. Cough reflex.

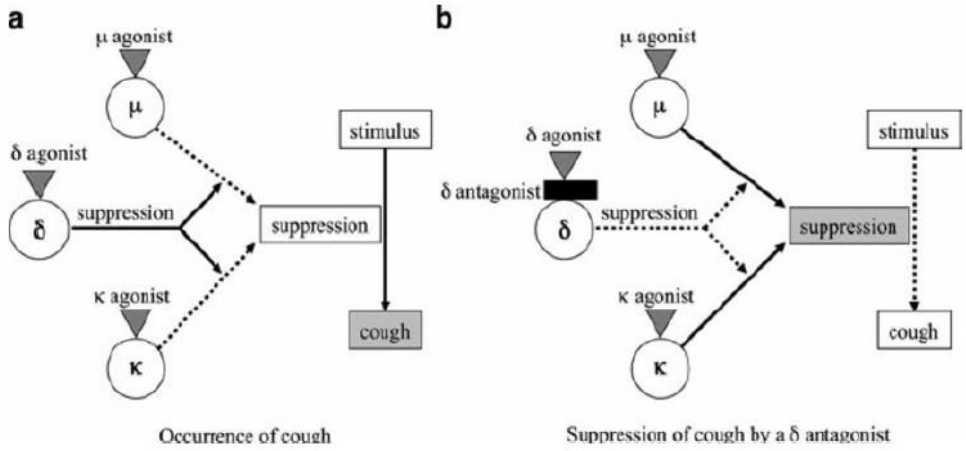


The specific pattern and various sounds of coughing depend on the location and type of stimulation. Mechanical stimulation of the larynx causes immediate expiratory stimulation to immediately keep the airway from aspiration, distal laryngeal stimulation causes a prominent inspiratory phase.[12] Stimulation of the larynx causes a choking - type cough, without inspiration, for example in coughing that occurs on bronchoscopy. During active coughing, the intra-thoracic pressure can reach 300 mmHg and the expiratory velocity can reaches 800 km/hour; both are accountable for mucus clearance.[12]

Opioids are known to be the only drugs that clearly act centrally to suppress the cough center in the brainstem through the action of μ- (mu-) opioid receptor and κ- (kappa-) opioid receptor agonists. All opioid medications for cough

suppression have side effects of sedation, constipation, and nausea.

Figure 2. Effects of opioid on cough suppression.



Sedation during anaesthesia has variable effects on the cough reflex, depending on the anaesthetic agent applied.[13] One study stated that subjects who experienced cough suppression did not experience significant sedation. Physicians commonly used Pasero opioid-induced sedation scale to measure sedation effect,[14] but the obtained results might be inaccurate because this scale was actually validated for postoperative pain management.[12] Anaesthesiologists usually use a combination of anxiolytics and opiates for sedation in bronchoscopy procedures with consideration of the anticipation and prevention of cough.

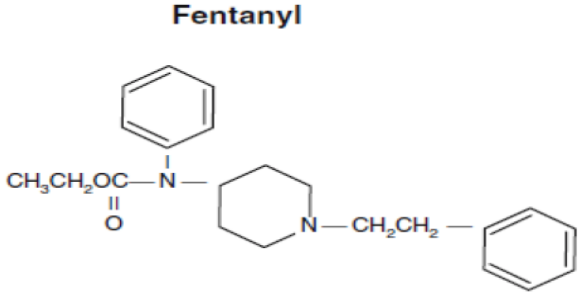
Table 2. Pasero opioid - induced sedation scale.

Pasero Opioid-Induced Sedation Scale (Pasero, 2009)		
POSS Score	**Description**	**Nursing Action**
S	Sleep, easy to arouse	Acceptable, no action necessary
1	Awake and alert	Acceptable, no action necessary
2	Slightly drowsy, easily aroused	Acceptable, no action necessary
3	Frequently drowsy, arousable, drifts off to sleep during conversation	Unacceptable; monitor respiratory status and sedation level closely until stable at less than 3; recommend to decrease opioid dose 25%-50%; consider administering a nonsedating, opioid-sparing nonopioid
4	Somnolent, minimal or no response to verbal or physical stimulation	Unacceptable, stop opioid; consider administering naloxone; notify prescriber or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory

Fentanyl

Fentanyl is one of a series of opioids synthesized by Janssen Pharmaceutica company in the 1950s and 1960s in an attempt to produce opioid of higher analgesic activity and potency with fewer side effects compared to widely used morphine or meperidine. Fentanyl, *N-(1-phenethyl-4-piperidyl) propionanilide*, is structurally related to meperidine (**see Figure 3**).[12,15]

Figure 3. Chemical structure of Fentanyl.



Fentanyl is an opioid agonist that acts on μ- (mu-) opioid receptors and binds to κ- (kappa-) and δ- (delta-) opioid receptors in the central nervous system. Fentanyl acts as analgesia and sedation; its therapeutic action depresses the respiratory center and suppresses the cough reflex. Fentanyl has a rapid onset and short duration of action; its onset of action is 30 - 60 seconds, with its peak effect after 5 - 15 minutes and its duration of action is 30 - 45 minutes.

Intravenous boluses of 1 - 2 micrograms Fentanyl per kilogram of bodyweight are usually given before the start of the infusion. The infusion rate of 1 - 2 micrograms per kilogram of bodyweight hourly can be adjusted up or down according to fluctuations in analgesic requirement or increased side effects. Small additional bolus of Fentanyl can rapidly increase plasma concentration before the infusion rate is increased.[13] Fentanyl infusion especially at a rate of 1.5 - 2.5 micrograms per kilogram of bodyweight hourly can provide good postoperative analgesia. At rest, the quality of analgesia remains stable; with movement (ambulation, coughing) was significantly reduced, even with higher infusion rates. The plasma concentration of fentanyl is directly related to the rate of infusion, and good analgesia at rest corresponds to a concentration of 0.5 - 2.3 nanograms/mililiter.[13,14]

In term of non - cardiorespiratory adverse effect, Fentanyl can cause nausea, vomiting, and stiffness of skeletal muscles. The incidence of nausea and vomiting after fentanyl infusion varies about 20 - 60%, pruritus in less than 30% and urinary retention in 40 - 45%. In term of cardiorespiratory adverse effect, Fentanyl may risk respiratory depression myocardial depression and bradycardia. Respiratory depression is common after Fentanyl infusion, but the majority of occurrences are insignificant. Methods of detecting and measuring respiratory depression include intermittent or continuous breathing measurements, pulse oximetry, respiratory inductive plethysmography and intermittent arterial blood sampling. The combination of fentanyl and midazolam is a popular regimen, with a good safety profile if both drugs are titrated carefully. One study observing plasma concentration of Fentanyl in terms of analgesia (its desired effect) and respiratory depression (its most dangerous adverse effect) concluded the intensity of its adverse effect is correlated with the drug concentration at the site of action and not necessarily of the plasma concentration.[11,14,15]

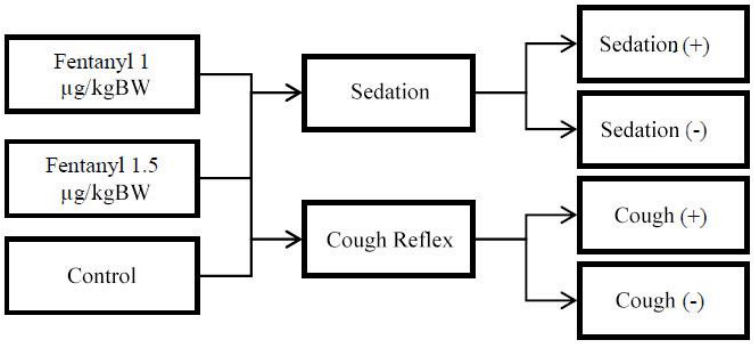
Fentanyl is an essential drug for bronchoscopy sedation. It was stated that giving 1 milliliter (equal to 50 micrograms) of fentanyl resulted in better sedation and comfort for both the patient and the operator.[11] Many previous studies have shown that fentanyl supplementation provides significant benefits in bronchoscopy procedures, but as there has been no data from such studies regarding the optimal dose, we worked to find out the optimal dose of fentanyl to suppress cough risk in bronchoscopy procedures.

METHODS

We designed a research mainly to identify the difference between administration of fentanyl in a dose of 1 microgram per kilogram of body weight (μg / kgBW) and fentanyl in a dose of 1.5 micrograms per kilogram of body weight (μg / kgBW) in relation to the depth of sedation and cough suppression in bronchoscopy procedures. Depth of sedation was assessed according to scales in the Ramsay sedation score from the time of induction. The cough suppression was assessed as how many minutes from the starting time of the bronchoscope entering through the vocal folds until the cough reflex appeared during the procedure. We also planned to observe if there is a significant difference in blood pressure, heart rate, and oxygen saturation measurements between administration of fentanyl in a dose of 1 microgram per kilogram of body weight (μg / kgBW) and fentanyl in a dose of 1.5 micrograms per kilogram of body weight (μg / kgBW) in bronchoscopy patients. Our major hypothesis was administration of fentanyl 1 microgram per kilogram of body weight (μg / kgBW) and fentanyl 1.5 micrograms per kilogram of body weight (μg / kgBW) would produce moderate sedation and cough suppression in bronchoscopy procedures, and a minor hypotheses that there would be a reduction in blood pressure, heart rate and oxygen saturation when fentanyl was administered either at a dose of 1 microgram per kilogram of body weight as well as at the dose of 1.5 Micrograms per kilogram of body weight.

To achieve the research objective, the authors designed this study as an analytical comparative test with three unpaired groups (**see Figure 4**).

Figure 4. Research scheme



The study sample was patients who underwent bronchoscopy procedures during the research period who met the following inclusion criteria: patients for bronchoscopy procedure, with ASA criteria I or II, and aged 18 – 65 years old; and not patients who were left out in in the exclusion criteria: refusal to take part in the research, pregnant patients, patients with history of opioid dependence or mental disorders, patients with allergies to drugs, and patients with impaired liver and kidney function.

Selection of research subjects was carried out with a consecutive sampling method, based on the bronchoscopy scheduled procedures in our unit. Patients who met the research criteria were eligible as research subjects. We determined sample size using formula for hypothesis testing with three or more population means:

$$n1 = n2 = \frac{6(Z\alpha + Z\beta)^2}{ln(OR)^2\left(1 - (P1^3 + P2^3 + P3^3)\right)}$$

Where:
Zα : Z value if type I of error rate (α) = 0.05; which is 1.96
Zβ : Z value if type II of error rate (β) = 0.2; which is 0.842.
Power of research = 1 - β = 1 – 0.2 = 0,8 (Power of research = 80%)
OR : odds ratio
P1 : mean proportion of variables subject group given fentanyl 1 µg / kgBW
P2 : mean proportion of variable subject group given fentanyl 1.5 µg / kgBW
P3 : mean proportion of variable control group

With the number of samples (n) is 16 for each group, and the probability of drop out is 10% (do = 0.1), the sample size with drop out adjustment is:

$$n_{do} = \frac{n}{1 - do} = \frac{16}{1 - 0,1} = 17,7 = 18$$

Based on the calculation of sample size with drop out adjustment, the total sample size was 54 subjects, of whom 18 subjects receiving fentanyl 1 µg / kgBW, 18 subjects receiving fentanyl 1.5 µg / kgBW, and 18 people in the control group. Subjects were collected from bronchoscopy patients in Dr. Kariadi Central Hospital Semarang from September 2020 to January 2021. After informing the research subjects of the details in the research and asking for consent and approval, we took subjects' initial data through history taking and medical records to obtain demographic data (age, gender, weight, height, ASA status, and previous disease history).

All bronchoscopy procedures are performed by experienced experts. Patients were randomly allocated to a group that would receive fentanyl 1 µg / kgBW, a group that would receive fentanyl 1.5 µg / kgBW and a control group that would receive a combination of midazolam and propofol. The randomization method and the fentanyl substance were disguised from the patients. On the day of the bronchoscopy procedure, each subject came to the operating room, then received a nebulizing preparation of 0.2% Lidocaine, and checked the initial vital signs before receiving a premedication of 2 mg of intravenous midazolam. Subjects then received 2 mg / kgBW of propofol in intravenous bolus, before continuing to particular treatment according to the group where he/she belonged. A member of fentanyl treatment would receive fentanyl 1 µg / kgBW or 1.5 µg / kgBW as intravenous bolus of a quarter dose given intermittently and repeatedly every 3 minutes until the target dose was reached. After the target dose of fentanyl was reached, we would continue to a 10 minute of assessing the vital signs and depth of sedation accordingly to the Ramsay sedation scale. A member of control group would receive no additional medication after propofol and go straight to the 10 minute assessment of vital signs and depth of sedation. After 10 minutes, operator could proceed to the bronchoscopy procedure and we assessed how many minutes from the starting time of the bronchoscopy insertion through the vocal folds until the cough reflex appeared during the procedure. The subject would receive 2 mg / kgBW of propofol in slow intravenous bolus to achieve depth of sedation.

After the bronchoscopy procedure was concluded, the subject had further observation in the recovery room and his physiological parameters including blood pressure, respiratory rate and oxygen saturation were evaluated and recorded from the time he/she arrived in the recovery room and repeated every 5 minutes.

In testing the hypothesis, we assessed the difference in the mean of the ratio-scaled variables between the group with Fentanyl of 1 µg / kgBW, the group with Fentanyl of 1.5 µg / kgBW, and control group using the one way Anova and Post Hoc Bonferroni tests if the data was well-modelled by a normal distribution or the Kruskall-Wallis and Post Hoc Mann-Whitney tests if the data was not well-modelled by a

normal distribution. We assessed the difference in the proportion of the nominal-scaled or ordinal-scaled variables between the group with Fentanyl treatment and control group using the *Chi* square post hoc test or Fisher's exact test if more than 20% of cells with an expected frequency of <5 were found.

RESULTS

We managed to include a total of 54 patients as the study samples, all voluntarily participated in the research after signing the informed consent. Firstly, we collected and documented initial data including gender, age, body weight, height, ASA status, and then we divided the research subjects into three groups

Table 3. Basic data of research subjects.

Variables	F	%	Mean ± SD	Median (min – max)
Group				
Control	18	33.3		
Fentanyl 1 µg / kgBW	18	33.3		
Fentanyl 1.5 µg / kgBW	18	33.3		
Cough-free duration (minutes)			4,41 ± 2,73	5 (0 – 8)
Initial systolic pressure (mmHg)			126,26 ± 11,24	156 (101 – 152)
Initial diastolic pressure (mmHg)			73,67 ± 7,60	73,5 (62 – 94)
Initial heart rate (times per minute)			96,00 ± 6,75	95,5 (83 – 110)
Initial respiratory rate (times per minute)			22,44 ± 2,59	23 (18 – 27)
Initial oxygen saturation (%)			97,94 ± 1,14	98 (95 – 99)
Ramsey Sedation Scale			2,81 ± 1,03	2 (2 – 5)

Table 3 displayed basic data of our research subjects. Initial data for assessment included the initial vital signs, such as systolic and diastolic blood pressure, heart rate, respiratory rate and subjects' oxygen saturation. After administration of fentanyl in a dose of 1 microgram per kilogram of body weight or fentanyl in a dose of 1.5 micrograms per kilogram of body weight, we assessed our research subjects' sedation depth using the Ramsay sedation scale, then assessed the length of time each subject is cough-free during bronchoscopy insertion through the vocal folds.

Table 4. Descriptive table of Ramsay sedation scale.

Groups	Mean ± SD	Median (min – max)	p£
Control group	4.11 ± 0.58	4 (3 – 5)	0.000
Fentanyl 1 µg/kgBW	2.00 ± 0.00	2 (2 – 2)	–
Fentanyl 1.5 µg/kgBW	2.33 ± 0.49	2 (2 – 3)	0.000

* Normal ($p > 0.05$); £ Shapiro-wilk

Considering the data in table 4 was not well-modelled by a normal distribution according to results of the normality test, we proceeded to use the *Kruskal-Wallis* test to find out the difference in the Ramsay sedation scale

Table 5. The *Kruskal-Wallis* test result of Ramsay sedation scale.

Groups	Median (min – max)	p
Control group	4 (3 – 5)	0.000*
Fentanyl 1 µg/kgBW	2 (2 – 2)	
Fentanyl 1,5 µg/kgBW	2 (2 – 3)	

*Significant ($p < 0.05$)

After the p value of the *Kruskal-Wallis* test < 0.05 confirmed significant difference in the Ramsay sedation scale, we proceeded to do the *Mann-Whitney* test to determine the difference in the Ramsay sedation scale between treatment groups.

Table 6. The *Mann Whitney* test result of Ramsay sedation scale between treatment groups.

Groups		P
I	II	
Control group	Fentanyl 1 µg/kgBW	0.000*
	Fentanyl 1.5 µg/kgBW	0.000*
Fentanyl 1 µg/kgBW	Fentanyl 1.5 µg/kgBW	0.058

*Significant ($p < 0.05$)

From table 6, we observed that the Ramsay sedation scale showings of the control group compared to the Ramsay sedation scale from the groups receiving fentanyl treatments of 1 µg / kgBW or 1.5 µg / kgBW were significant. However there was no significant difference in the Ramsay sedation scale between the group receiving fentanyl treatment of 1 µg / kgBW and the group receiving fentanyl treatment of 1.5 µg / kgBW. The results explained that there was a significant difference in the depth of patient sedation between the control group and the treatment groups; as patients without fentanyl treatment were sedated deeper on the Ramsay 4 scale, patients in the treatment groups with either fentanyl of 1 µg / kgBW or 1.5 µg / kgBW had the depth of sedation on the Ramsay 2 scale and unable to reach moderate sedation as expected. In that circumstances, anaesthesiologists added propofol in combination with fentanyl to achieve moderate sedation.

Table 7. Descriptive table of cough suppression effects.

Groups	Mean ± SD	Median (min – max)	p£
Control group	1.00 ± 1.03	1 (0 – 3)	0.002
Fentanyl 1 µg/kgBW	5.50 ± 1.38	5 (3 – 8)	0.299*
Fentanyl 1.5 µg/kgBW	6.72 ± 1.02	7 (5 – 8)	0.023

* Normal ($p > 0.05$); £ Shapiro-wilk

Considering the data in table 4 was not well-modelled by a normal distribution according to results of the normality test, we proceeded to use the *Kruskal-Wallis* test to find out the difference in the cough suppression effects.

Table 8. The *Kruskal-Wallis* test result of cough suppression effects.

Groups	Median (min – max)	p
Control group	1 (0 – 3)	0.000*
Fentanyl 1 µg/kgBW	5 (3 – 8)	
Fentanyl 1.5 µg/kgBW	7 (5 – 8)	

Keterangan : *Significant($p < 0.05$)

After the p value of the *Kruskal-Wallis* test < 0.05 confirmed significant difference in the cough suppression effects, we proceeded to do the *Mann-Whitney* test to determine the difference in the cough suppression effects between treatment groups.

Table 9. The *Mann-Whitney* test result of cough suppression effects between treatment groups.

Groups		p
I	II	
Control group	Fentanyl 1 µg/kgBW	0.000*
	Fentanyl 1.5 µg/kgBW	0.000*
Fentanyl 1 µg/kgBW	Fentanyl 1.5 µg/kgBW	0.006*

*Significant ($p < 0.05$)

From table 9, we observed that the cough suppression effects of the control group compared to the cough suppression effects from the groups receiving fentanyl treatments of 1 µg / kgBW or 1.5 µg / kgBW were significant. There was also significant difference in the cough suppression effects between the group receiving fentanyl treatment of 1 µg / kgBW and the group receiving fentanyl treatment of 1.5 µg / kgBW. The results explained that subjects with fentanyl treatments showed significantly better suppression effects for coughing compared to control group patients. As there also was a significance difference in suppression effects for coughing between the group receiving fentanyl treatment of 1 µg / kgBW and the group receiving fentanyl treatment of 1.5 µg / kgBW, we could summarize that a fentanyl treatment of 1 µg / kgBW was adequate to suppress cough although a dose of 1.5 µg / kgBW would show better cough suppression effect.

Table 10. Descriptive table of systolic pressure before the procedure, after the procedure and the difference between before and after.

Systolic	Groups	Mean ± SD	Median (min – max)	p¿
Before	Control group	122.00 ± 11.90	124.5 (101 – 143)	0.685*
	Fentanyl 1 µg/kgBB	128.11 ± 10.81	127.5 (112 – 152)	0.658*
	Fentanyl 1.5 µg/kgBB	128.67 ± 10.32	127.5 (113 – 150)	0.725*
After	Control group	98.06 ± 10.39	98 (79 – 116)	0.715*
	Fentanyl 1 µg/kgBB	122.00 ± 11.90	124.5 (101 – 143)	0.685*
	Fentanyl 1.5 µg/kgBB	121.33 ± 11.75	124 (101 – 140)	0.466*
Delta	Control group	-23.94 ± 7.30	-21.5 (-38 – (-12))	0.675*
	Fentanyl 1 µg/kgBB	-6.11 ± 4.03	-4.5 (-15 – (-1))	0.058*
	Fentanyl 1.5 µg/kgBB	-7.33 ± 4.51	-6 (-15 – (-1))	0.144*

* Normal (p > 0.05); ¿ Shapiro-wilk

Table 11. The difference in systolic pressure before the procedure and after the procedure between each treatment groups and control group.

Groups	Systolic		p	Delta
	Before	After		
Control group	122.00 ± 11.90	98.06 ± 10.39	0.000¶*	-23.94 ± 7.30
Fentanyl 1 µg/kgBW	128.11 ± 10.81	122.00 ± 11.90	0.000¶*	-6.11 ± 4.03
Fentanyl 1.5 µg/kgBW	128.67 ± 10.32	121.33 ± 11.75	0.000¶*	-7.33 ± 4.51
p	0.143§	0.000§*		0.000§*
Levene	0.719**	0.588**		0.007

* Significant (p < 0.05); ** Homogen (p > 0.05); § One Way Anova; ¶ Paired t

Table 12. Post-hoc test results of the systolic pressure after the procedure and the difference before-and-after the procedure.

Groups		Systolic	
I	II	After[1)]	Delta[2)]
Control group	Fentanyl 1 µg/kgBW	0.000*	0.000*
	Fentanyl 1.5 µg/kgBW	0.000*	0.000*
Fentanyl 1 µg/kgBW	Fentanyl 1.5 µg/kgBW	1.000	0.670

* Significant (p < 0.05); 1) Bonferroni; 2) Games-Howell

Figure 5. Diagram of post-hoc test results of the systolic pressure after the procedure and the difference (delta) between before-and-after the procedure.

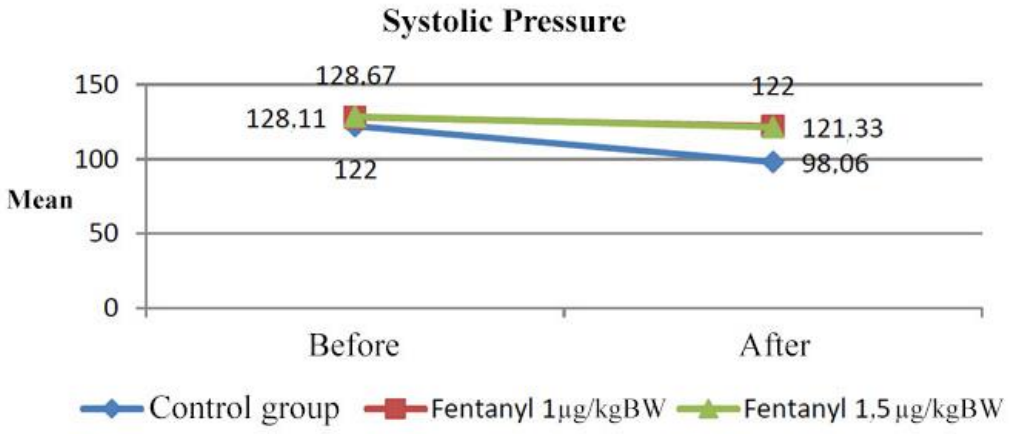


Table 13. Descriptive table of diastolic pressure before the procedure, after the procedure and the difference between before and after.

Diastolic	Groups	Mean ± SD	Median (min – max)	p¿
Before	Control group	73.67 ± 7.75	73.5 (62 – 94)	0,348*
	Fentanyl 1 µg/kgBW	73.67 ± 7.75	73.5 (62 – 94)	0,348*
	Fentanyl 1.5 µg/kgBW	73.67 ± 7.75	73.5 (62 – 94)	0,348*
After	Control group	61.17 ± 4.90	61 (52 – 71)	0,326*
	Fentanyl 1 µg/kgBW	71.06 ± 7.41	70 (60 – 90)	0,407*
	Fentanyl 1.5 µg/kgBW	70.67 ± 7.15	69.5 (61 – 88)	0,312*
Delta	Control group	-12.50 ± 4.22	-12 (-23 – (-7))	0,226*
	Fentanyl 1 µg/kgBW	-2.61 ± 1.29	-2 (-5 – (-1))	0,028
	Fentanyl 1.5 µg/kgBW	-3.00 ± 1.75	-3 (-6 – (-1))	0,053*

* Normal (p > 0,05); ¿ Shapiro-wilk

Table 14. The difference in diastolic pressure before the procedure and after the procedure between each treatment groups and control group.

Groups	Diastolic		p	Delta
	Before	After		
Control group	73.67 ± 7.75	61.17 ± 4.90	0.000¶*	-12.50 ± 4.22
Fentanyl 1 µg/kgBW	73.67 ± 7.75	71.06 ± 7.41	0.000¶*	-2.61 ± 1.29
Fentanyl 1.5 µg/kgBW	73.67 ± 7.75	70.67 ± 7.15	0.000¶*	-3.00 ± 1.75
p	1.000§	0.000§*		0.000‡*
Levene	1.000**	0.120**		–

* Significant (p < 0.05); ** Homogen (p > 0.05); § One Way Anova; ¶ Paired t

Table 15. Post-hoc test results of the diastolic pressure after the procedure and the difference before-and-after the procedure.

Groups		Diastolic	
I	II	After[1)]	Delta[2)]
Control group	Fentanyl 1 µg/kgBW	0.000*	0.000*
	Fentanyl 1.5 µg/kgBW	0.000*	0.000*
Fentanyl 1 µg/kgBW	Fentanyl 1.5 µg/kgBW	1.000	0.593

* Significant ($p < 0.05$); [1)] Bonferroni; [2)] Games-Howell

Figure 6. Post-hoc test results of the diastolic pressure after the procedure and the difference (delta) between before-and-after the procedure.

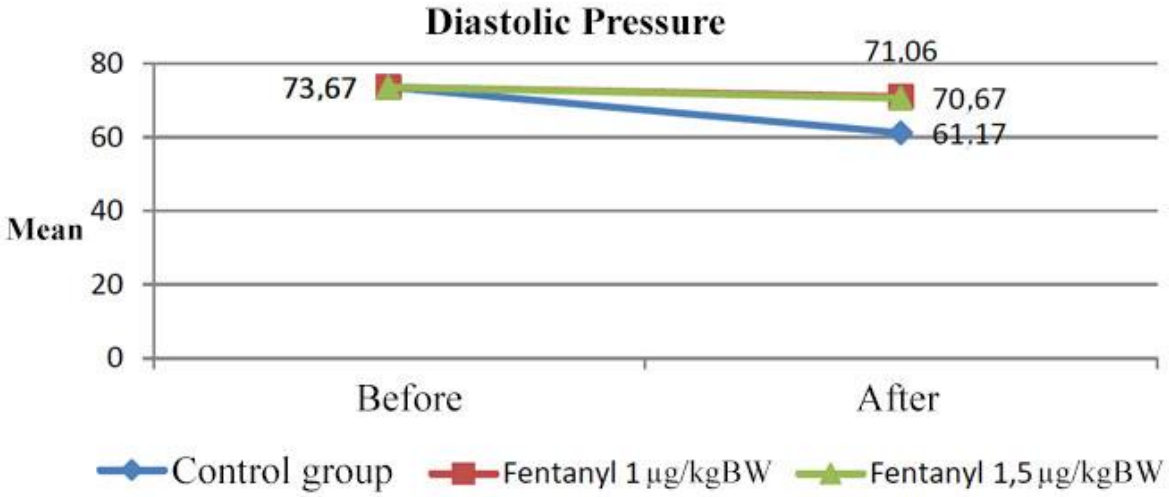


Table 16. Descriptive table of pulse rate before the procedure, after the procedure and the difference between before and after.

Pulse Rate	Groups	Mean ± SD	Median (min – max)	p[¿]
Before	Control group	96.00 ± 6.89	95.5 (83 – 110)	0,786*
	Fentanyl 1 µg/kgBW	96.00 ± 6.89	95.5 (83 – 110)	0,786*
	Fentanyl 1.5 µg/kgBW	96.00 ± 6.89	95.5 (83 – 110)	0,786*
After	Control group	80.50 ± 3.26	81 (74 – 85)	0,119*
	Fentanyl 1 µg/kgBW	90.94 ± 2.07	91 (86 – 94)	0,116*
	Fentanyl 1.5 µg/kgBW	90.94 ± 2.07	91 (86 – 94)	0,116*
Delta	Control group	-15.50 ± 7.77	-14 (-34 – (-4))	0,154*
	Fentanyl 1 µg/kgBW	-5.06 ± 6.82	-4 (-18 – 7)	0,184*
	Fentanyl 1.5 µg/kgBW	-5.06 ± 6.82	-4 (-18 – 7)	0,184*

* Normal ($p > 0.05$); [¿] Shapiro-wilk

Table 17. The difference in pulse rate before the procedure and after the procedure between each treatment groups and control group.

Groups	Pulse Rate		p	Delta
	Before	After		
Control group	96.00 ± 6.89	80.50 ± 3.26	0.000¶*	-15.50 ± 7.77
Fentanyl 1 µg/kgBW	96.00 ± 6.89	90.94 ± 2.07	0.006¶*	-5.06 ± 6.82
Fentanyl 1.5 µg/kgBW	96.00 ± 6.89	90.94 ± 2.07	0.006¶*	-5.06 ± 6.82
p	1.000§	0.000§*		0.000§*
Levene	1.000**	0.083**		0.907**

* Significant ($p < 0.05$); ** Homogen ($p > 0.05$); § One Way Anova; ¶ Paired t

Table 18. Post-hoc test results of the pulse rate after the procedure and the difference before-and-after the procedure.

Groups		Pulse Rate	
I	II	After[1)]	Delta[1)]
Control group	Fentanyl 1 µg/kgBW	0.000*	0.000*
	Fentanyl 1.5 µg/kgBW	0.000*	0.000*
Fentanyl 1 µg/kgBW	Fentanyl 1.5 µg/kgBW	1.000	0.670

* Significant ($p < 0.05$); [1)] Bonferroni

Figure 7. Post-hoc test results of the pulse rate after the procedure and the difference (delta) between before-and-after the procedure.

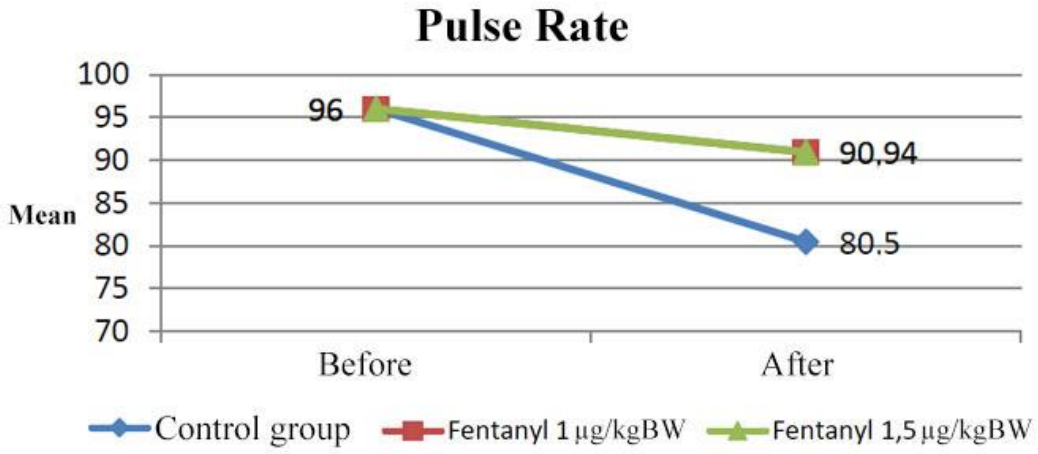


Table 19. Descriptive table of respiratory rate before the procedure, after the procedure and the difference between before and after.

Respiratory Rate	Groups	Mean ± SD	Median (min – max)	p¿
Before	Control group	22.44 ± 2.64	23 (18 – 27)	0.392*
	Fentanyl 1 µg/kgBW	22.44 ± 2.64	23 (18 – 27)	0.392*
	Fentanyl 1.5 µg/kgBW	22.44 ± 2.64	23 (18 – 27)	0.392*
After	Control group	9.56 ± 2,81	10 (4 – 14)	0.612*
	Fentanyl 1 µg/kgBW	16.83 ± 1,10	17 (15 – 19)	0.197*
	Fentanyl 1.5 µg/kgBW	16.83 ± 1,10	17 (15 – 19)	0.197*
Delta	Control group	-12.89 ± 2.93	-12.5 (-18 – (-7))	0.727*
	Fentanyl 1 µg/kgBW	-5.61 ± 2.43	-6 (-10 – (-1))	0.805*
	Fentanyl 1.5 µg/kgBW	-5.61 ± 2.43	-6 (-10 – (-1))	0.805*

* Normal ($p > 0.05$); ¿ Shapiro-wilk

Table 20. The difference in respiratory rate before the procedure and after the procedure between each treatment groups and control group.

Groups	Respiratory Rate		p	Delta
	Before	After		
Control group	22.44 ± 2,64	9,56 ± 2.81	0.000¶*	-12,89 ± 2,93
Fentanyl 1 µg/kgBW	22.44 ± 2,64	16.83 ± 1,10	0.000¶*	-5,61 ± 2,43
Fentanyl 1.5 µg/kgBW	22.44 ± 2,64	16.83 ± 1,10	0.000¶*	-5,61 ± 2,43
p	1,000§	0.000§*		0.000§*
Levene	1.000**	0,000		0.595**

* Significant ($p < 0.05$); ** Homogen ($p > 0.05$); § One Way Anova; ¶ Paired t

Table 21. Post-hoc test results of the pulse rate after the procedure and the difference before-and-after the procedure.

Groups		Respiratory Rate	
I	II	After[2)]	Delta[1)]
Control group	Fentanyl 1 µg/kgBW	0.000*	0.000*
	Fentanyl 1.5 µg/kgBW	0.000*	0.000*
Fentanyl 1 µg/kgBW	Fentanyl 1.5 µg/kgBW	1.000	1.000

* Significant ($p < 0.05$); [1)] Bonferroni [2)] Games-Howell

Figure 8. Diagram of post-hoc test results of the respiratory rate after the procedure and the difference (delta) between before-and-after the procedure.

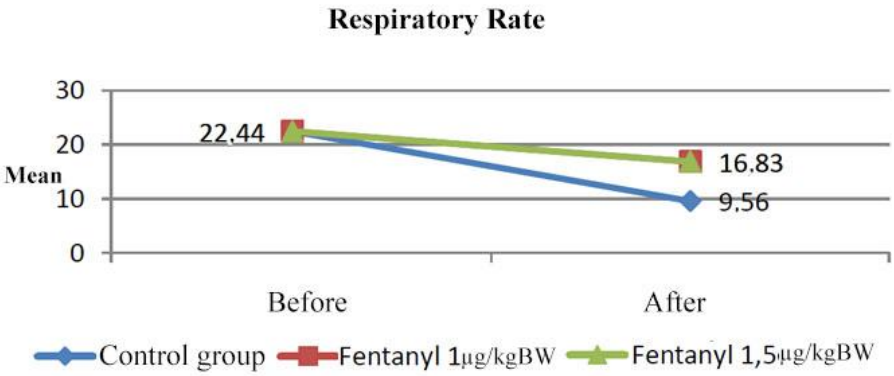


Table 22. Descriptive table of oxygen saturation before the procedure, after the procedure and the difference between before and after.

Saturation	Groups	Mean ± SD	Median (min – max)	p¿
Before	Control group	97.94 ± 1.16	98 (95 – 99)	0.004
	Fentanyl 1 µg/kgBW	97.94 ± 1.16	98 (95 – 99)	0.004
	Fentanyl 1.5 µg/kgBW	97.94 ± 1.16	98 (95 – 99)	0.004
After	Control group	89,11 ± 3,53	89.5 (84 – 94)	0.101 *
	Fentanyl 1 µg/kgBW	96,50 ± 0,79	97 (95 – 98)	0,008
	Fentanyl 1.5 µg/kgBW	96,50 ± 0,79	97 (95 – 98)	0.008
Delta	Control group	-8,83 ± 3,88	-7,5 (-15 – (-2))	0.127 *
	Fentanyl 1 µg/kgBW	-1,44 ± 1,69	-2 (-4 – 3)	0.027
	Fentanyl 1.5 µg/kgBW	-1,44 ± 1,69	-2 (-4 – 3)	0.027

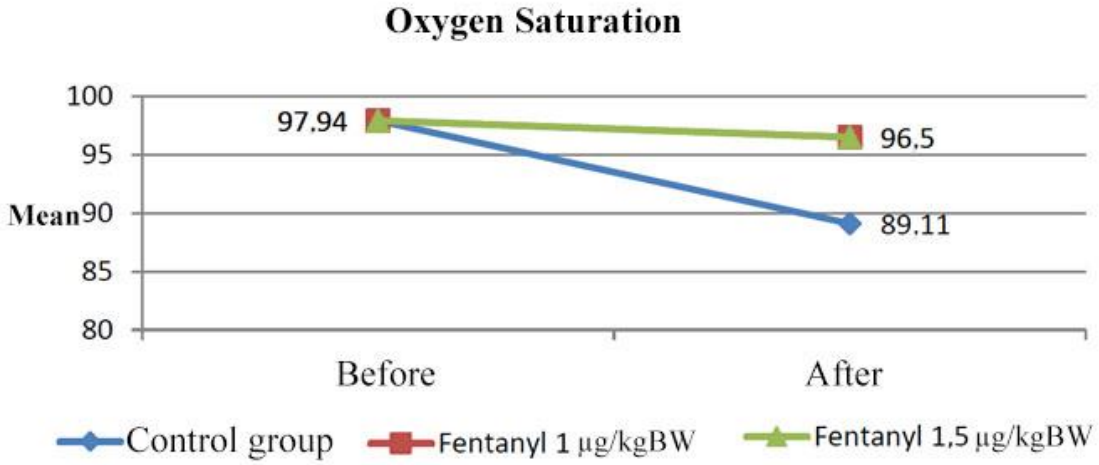
* Normal ($p > 0.05$); ¿ Shapiro-wilk

Table 23. The difference in oxygen saturation before the procedure and after the procedure between each treatment groups and control group.

Groups	Oxygen Saturation		p	Delta
	Before	After		
Control group	97.94 ± 1.16	89.11 ± 3.53	0.000†*	-8.83 ± 3.88
Fentanyl 1 µg/kgBW	97.94 ± 1.16	96.50 ± 0.79	0.008†*	-1.44 ± 1.69
Fentanyl 1.5 µg/kgBW	97.94 ± 1.16	96.50 ± 0.79	0.008†*	-1.44 ± 1.69
p	1.000‡	0.000‡*		0.000‡*

*Significant ($p < 0.05$); §Kruskal-Wallis; †Wilcoxon

Figure 9. Diagram of post-hoc test results of the oxygen saturation after the procedure and the difference (delta) between before-and-after the procedure.



DISCUSSION

Administration of sedative agents achieve the desired depth of sedation without risking airway patency, ventilation function and cardiovascular function.[3] Moderate sedation level provides patients of unconsciousness but still responsive to verbal commands. If a patient is unresponsive to verbal commands and reacts only to the pain stimulus, he or she falls into a deep sedation state and risk his or her airway patency.[3] To achieve the required moderate sedation, the sedative agent of choice should be titrated in incremental doses.[17] This is especially crucial in patients where the arm–brain circulation time (time needed for a drug substance to travel from the injection site to the brain and produce a central nervous system effect) is prolonged (e.g. in heart failure). In elder patients, dose adjustment is mandatory due to comorbid risks of hepatic or renal metabolic impairments, reduced tissue and blood esterases and increased tissue sensitivity to a certain drug.[17] Anaesthesiologists should always monitor the depth of sedation and record them in accordance of the Ramsay sedation scale as shown in **Table 1**. For moderate sedation, the scale should not exceed level 3. Ideal sedative agent should have a rapid onset of action, short duration of action and rapid recovery of cognitive function.[5] In our study, we used three-drug regimens: midazolam as a premedication, propofol for the control group, and fentanyl as the treatment group. Our study used fentanyl as a sedative agent because opioids are also widely chosen because of their analgesic, sedative, and antitussive effects. Fentanyl also has a faster onset of action than morphine. Fentanyl interacts with µ- (mu-) opioid receptors and binds to kappa κ- (kappa-) and δ- (delta-), where receptors function in sedation and respiratory depression together with receptors, and receptors play a role in sedation function.[16]

Subjects in the treatment group receiving either fentanyl of 1 microgram per kilogram of body weight (µg / kgBW) or 1.5 micrograms per kilogram of body weight (µg / kgBW) reached only to the level 2 on the Ramsay scale, while subjects in the control group using propofol of 2 milligrams per kilogram of body weight (mg / kgBW) for induction effectively reached level 4 (as shown in **Table 4)**. We observed that ventilation function and airway patency were somewhat uneasy at the level 4 of sedation. Statistical analysis also revealed the depth of sedation in the control group was significantly different ($p < 0.05$) compared to the treatment groups, while between the two treatment groups, the depth of sedation was not significantly different ($p > 0.05$) (as shown in **Table 6**). The treatment groups did not reach the

expected depth of sedation in the treatment group in all probability due to several factors, like inadequate amount of drug dose, drug administration, or patient factors. One study suggested that anaesthesiologists may use high dose fentanyl in intravenous drip,[18] while our study applied intravenous fentanyl incrementally by giving 1/4 dose every 3 minutes until the target dose based on patient's body weight was reached. We assumed that was the reason behind the sedation threshold with fentanyl not effectively achieved.

Previous studies have shown that fentanyl had an effect on cough suppression because it acts on μ- (mu-) opioid receptors and binds to κ- (kappa-) and δ- (delta-) opioid receptors in the central nervous system with proper dose and route of administration like rapid intravenous bolus administration.[16,19] Our study revealed that the use of fentanyl significantly suppressed cough on bronchoscopy procedures compared to the control group without fentanyl (as shown in **Table 7, Table 8**) and furthermore fentanyl at a dose of 1 μg / kgBW was already sufficient to suppress cough reflex although larger dose would provide longer period of cough suppression (as shown in **Table 7** to **Table 9**).

We administered fentanyl as intermittent boluses to achieve the target dose with an interval of every 3 minutes. After administering the last dose, we waited for 10 minutes for the drug to reach plasma levels and at the same time watchfully anticipating if there were any side effects,[20] then assessed the depth of sedation using the Ramsay sedation scale before proceeded to the bronchoscopy procedure. As we observed the scope passing through the vocal folds, we started measuring the length of time until the first cough reflex occurred. We noticed that in our control group, subjects coughed as soon as the scope entered through the vocal folds, whereas in the treatment groups, there was a longer time period and cough reflex appeared after the scope descended to the carina or the bronchus (as shown in **Table 7**). The mechanism of how fentanyl suppress cough reflex is not clearly understood yet, however a study suggested that the effect depended on its plasma concentration.[20] We did not conduct plasma concentration assessment of fentanyl in this study.

Progressive incremental administration of fentanyl reduces expiratory reflex (forceful expiration without prior inspiration), spasmodic panting (rapid and shallow breathing with respiratory rate exceeding 60 times per minute for more than 10 seconds) and cough reflex, (forceful expiration with a previous inspiration), except for apnea with laryngeal spasm (complete closure of the glottis for more than 10 seconds). This indicates that the administration of a dose of propofol to suppress the upper airway reflex stimulated by bronchoscopy.[21]

We observed and recorded patient's vital signs of systolic and diastolic pressure, pulse rate, respiratory rate, and oxygen saturation at a moment before administering and at the 10th minute after administering the last dose of fentanyl. We noticed decrease of systolic and diastolic pressure, pulse rate, respiratory rate, and oxygen saturation. (as shown in **Table 10** – **Table 23** and **Figure 5** – **Figure 9**) resembling to findings of previous studies.

Subjects' systolic and diastolic blood pressure along with their respiratory rate decreased during bronchoscopy procedures, while pulse rate increased. Statistical analysis, as displayed in **Figure 5** to **Figure 9**, show that the control group with 2 mg / kgBW of propofol in intravenous bolus slowly experienced a more significant alteration in vital signs than the fentanyl group, either with a dose of 1 μg / kgBW or 1.5 μg / kgBW. Propofol, given as an intravenous bolus or as a continuous infusion, is the most common drug used for induction of anaesthesia and acts quickly to achieve appropriate level of sedation within 30 seconds,[22] therefore it is obvious, subjects in the control group who received propofol achieved sedation faster and deeper to level 4 of Ramsay sedation scale. This deeper level of sedation troubled patients' airway patency and manifested clinically as the decrease of oxygen saturation level, of which 11 of 18 patients had their saturation dropped to below 95%, but still above 90%. Comparing and statistically analysing the two treatment groups of different dose of fentanyl, we found no significant difference in vital signs alteration between the two different doses (as shown in **Table 10** – **Table 23**).

We realized that our study had limitations. We believed with a larger number of subjects and a longer period of research would provide better results and conclusion. We also found administering fentanyl to bronchoscopy patients quite a challenge as there was not yet a standard protocol and regulation for that, so our study followed the method of administering fentanyl based on previous studies. We also envisioned the need to assess the plasma concentration level of the drug given, so we could have the safe limit for giving a sedating agent for bronchoscopy. Any similar researches in the future should result in better conclusion if they consider all the aforementioned matters.

CONCLUSION

Our study revealed that as fentanyl significantly suppressed cough reflex and larger dose would provide longer period of suppression. Subjects with fentanyl treatment showed more favourable altercation in systolic and diastolic blood pressure, pulse rate, respiratory rate and oxygen saturation compared to subjects in control group with 2 mg / kgBW of propofol, but comparing and statistically analysing the two groups of different dose of fentanyl, we found no significant difference in vital signs alteration.

CONFLICTS OF INTEREST

Authors declared no conflicts of interest during the research and the writing of article.

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