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The Effect of Glycopyrrolate to Support Fentanyl on Reducing Airway Irritation during Inhalation Induction with Desflurane and Nitrous Oxide in Adult Patients

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ABSTRACT

Introduction: Inhalational induction of anesthesia is occasionally used in adults. Desflurane is not used for the induction of anesthesia despite its favorable pharmacokinetic characteristics as it causes airway irritation. This study aims to identify a reduction of airway irritation with pretreatment using fentanyl and glycopyrrolate. **Methods:** A total of 80 adults were randomized into two groups to receive fentanyl and glycopyrrolate (FG group) or fentanyl only (FS group) prior to desflurane administration. Time between desflurane administration and loss of consciousness was recorded as well as expired desflurane concentration. Signs of airway irritation including coughing, apnea, laryngospasm, and excitatory movements at time of induction was also recorded. Unpaired *t* test, Fisher's Exact test, and Chi-square test were used to analyze parametric data and all non-parametric data was analyzed using the Mann–Whitney test. **Results:** This study found time to loss of consciousness was 4 minutes. Incidence of airway irritation in Group FS vs FG including cough, apnea, excitatory movements, and laryngospasm was (20% vs 2.5%), (0% vs 0%), (5% vs 5%), and (7.5% vs 0%) respectively. Total airway irritation was 32.5% in FS compared to 7.5% in FG, with *P* value 0.0103. **Conclusion:** Use of fentanyl and glycopyrrolate decreases airway irritation incidence caused by desflurane in comparison to use of fentanyl alone. This opens the possibility to commonly use desflurane as inhalation induction of anesthesia as its favorable pharmacokinetics may be utilized whilst limiting the adverse effects it causes.

Key words: Glycopyrrolate; Fentanyl; Airway Irritation; Desflurane

INTRODUCTION

Desflurane is an inhalational anesthetic often associated with airway irritation including coughing, apnea, laryngospasm, copious secretion, and excitatory movements.[1] Respiratory irritation is absent when one MAC or below of desflurane is used instead of two MAC. This threshold is determined experimentally by investigating the concentration at which desflurane causes airway irritation. Threshold for desflurane is one MAC or 6%.[2]

This inhalational gas, however, has been shown to have beneficial pharmacokinetics. Due to its low solubility, desflurane allows rapid induction and emergence from anesthesia in comparison to other inhalational agents.[3] Desflurane is also stable in soda lime and does not produce toxic metabolites, thus has low renal and hepatic toxicity.[4]

Opioids have been shown to decrease respiratory irritation caused by use of inhaled anesthetics. A randomized study conducted by Kong et al done on 180 participants receiving desflurane for induction of anesthesia showed that incidence of coughing was 75-80% less in patients pretreated with small doses of opioid agonist fentanyl (5%) or morphine (8%) than in a control group with IV saline.[5]

Glycopyrrolate is an anticholinergic agent which also inhibits salivary gland and respiratory tract secretions.[6-7] This effect is the primary rationale for glycopyrrolate to be used as a premedication with opioids to counteract effects of desflurane. In comparison to atropine, glycopyrrolate is twice as potent and has longer duration of action.[8] This study aims to investigate the effect of glycopyrrolate as an anti-sialagogue with fentanyl to decrease airway irritation caused by use of desflurane.

MATERIALS AND METHODS

This prospective and double-blind randomized clinical study was reviewed and approved by Institutional Research Ethics (approval number: 092/K-LKJ/ETIK/I/2021) on January 15, 2021. This study is a single-center trial conducted in a tertiary hospital in Tangerang, Indonesia from February-June 2021. Written and verbal consent was obtained from all participants. This study was conducted in accordance with ethical standards as written in the Declaration of Helsinski.

Eighty patients who were scheduled to undergo elective surgery were included in this study. Inclusion criteria included (1) had ASA score of I or II and was (2) aged 18-60 years. Patients were excluded if they had (1) history of pulmonary disease or had chronic cough, (2) a history of malignant hyperthermia, (3) family history of anesthetic complications, (4) anemia, (5) obese, (6) had previous exposure to desflurane, (7) consumed medication which may cause interference with the study, (9) smokes, and (10) had history of upper respiratory tract infection one month prior to surgery.

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Patients who fulfilled the criteria was then randomized into two groups to receive fentanyl and glycopyrrolate (FG group) or fentanyl only (FS group). Randomization was conducted using a computer-generated assignment table. Medications were given using a syringe, which was prepared by a nurse who was not involved in the study. Patients were given either fentanyl 1 µg/kg with glycopyrrolate 5 µg/kg (FG group) or fentanyl 1 µg/kg with saline (FS group) with a total of 10 mL. Medications were then administered within one minute by an anesthesiologist who was not aware of the syringe contents. Preoxygenation was then given with 100% oxygen at six lpm for three minutes. Oxygen flow was then reduced to three lpm with nitrous oxide of three lpm (FiO2 of 50%). One percent desflurane was then administered and increased gradually by 1% for every six breaths. Induction time was defined as complete at which there was loss of verbal contact and loss of eyelash reflex.

Monitoring conducted during anesthesia in this study included pulse oximetry, non-invasive blood pressure, ECG, end-tidal CO2, and expired desflurane concentration using CSI Criticare Poet Plus 8100 anesthetic and respiratory gas monitor.

Age, weight, gender, ASA, diagnosis, type of surgery for each patient was noted. Readings of pulse oximeter prior and during induction, time recorded between desflurane administration and indication time, and expired desflurane concentration was also recorded. Signs of airway irritation including coughing, apnea, laryngospasm, and excitatory movements at time of induction was also recorded. If patients experienced coughing, coughing was then graded into mild (1-3), moderate (4-7), and severe (8 or more). Apnea was defined as loss or no breathing movements for more than 30 seconds.

Patients who experienced laryngospasm was given propofol 2 mg/kg IV with succinylcholine of 1.5 mg/kg if deemed necessary. Ventilation using 100% oxygen via mask was also provided until saturation improved.

Unpaired *t* test, Fisher's Exact test, and Chi-square test were used to analyze parametric data and all non-parametric data was analyzed using the Mann–Whitney test. *P* value of <0.05 was considered significant. Time required for induction, expired desflurane concentration at induction, arterial pressure, and heart rate before and after induction were analyzed using unpaired *t* test. *P* value of <0.05 was considered significant. Incidence of airway irritation was analyzed using Fisher's exact test and Chi-square test. *P* value of <0.05 was considered significant.

RESULTS

A total of 80 subjects were studied. The summary statistics for patient demographics are shown in table 1.

Table 2 shows the induction times for the two study groups. Induction times were not significantly different with *P* value of 0.4795. The expired desflurane concentrations at loss of consciousness are shown in table 2 and were not significantly different between the two groups with *P* value of 0.6987.

The incidence of airway irritation are shown in table 3. Airway irritation between FS and FG group was significantly different, with *P* value of 0.0103. Coughing was significantly higher in FS in comparison to FG, with *P* value of 0.0289. Incidence of apnea between FS and FG group were not statistically significant, with *P* value of 1.0000. Laryngospasm occurred in three patients in FS group. In one patient, desaturation occurred where oxygen saturation reached 94%. Two other patients had laryngospasm without oxygen desaturation. There was no significant difference between the FS and FG groups with *P* value of 0.2392. Even though there was no significant difference noted, the incidence of 3 patients who developed laryngospasm cannot be disregarded. The incidence of excitatory movements in both groups were equal with *P* value of 1.000. The significant differences in total airway irritation as shown in table 3 showed that combination of fentanyl-glycopyrrolate were effective to reduce airway irritation to as low as 7.5% during induction with desflurane in 50% nitrous oxide.

Table 1: Patient Demographics.

	Group FS (N=40)	Group FG (N=40)
Age (year, mean (range))	43 (21–65)	45(22–65)
Weight (kg, mean (SD))	56 (10)	55 (9.6)
ASA status		
I	52	56
II	8	4
Gender		
Male	25	19
Female	35	41

Values are not significantly different (*P*>0.05) ***(Mann-Whitney test)***

Table 2: Time to Loss of Consciousness and the Expired Desflurane Concentration.

	Group FS	Group FG	P Value
Time to loss of consciousness (min, mean (SD) median)	4.0(1.1); 4.0	3.8(1.4); 3.1	0.4795
Expired desflurane concentration at loss of consciousness (%, mean (SD) median)	3.8(1.1); 3.6	3.9 (1.2); 3.8	0.6987

Values are not significantly different (*P*>0.05) ***(Unpaired t test)***

Table 3: Incidence Airway Irritation during Induction.

	Group FS	Group FG	P Value
Cough	(8/40) 20%	(1/40) 2.5%	0.0289
Apnea	(0/40) 0%	(0/40) 0%	1.0000
Excitatory movements	(2/40) 5%	(2/40) 5%	1.0000
Laryngospasm	(3/40) 7.5%	(0/40) 0%	0.2392
Total Airway Irritation	(13/40) 32.5%	(3/40) 7.5%	0.0103

Statistical significance accepted at *P* < 0.05 ***(Fisher's exact test and Chi-square test)***

Changes in blood pressure and heart rate in the two groups are shown in table 4.

DISCUSSION

Desflurane is often associated with airway irritation due to its odor, thus rarely used for induction. Airway irritation include airway reactivity and hypersecretion causing coughing, apnea, laryngospasm, and excitatory movements at induction.[1] One MAC or lower of desflurane was shown to cause lower airway irritation in comparison to two MAC.[2] However, its other properties including having low solubility allows rapid induction and emergence in anesthesia. Furthermore, it has low hepatic and renal toxicity.[3-4]

Nitrous oxide is a weak anesthetic, which is commonly used in combination to other gases. Use of nitrous oxide in high concentrations will also increase alveolar concentration of second gas. This effect is known as the "second gas" effect.[9] When nitrous oxide is used in conjunction with desflurane, this reduces MAC value. In this study, desflurane was used in a mixture of 50% nitrous oxide for induction. The mean expired desflurane concentration at induction time in the FS and FG group was 3.9% and 4.4% respectively. No differences in time

Table 4: Arterial Pressure and Heart Rate (Before and After Induction).

	Group FS		P Value	Group FG		P Value
	Before	After		Before	After	
Systolic pressure (mmHg, mean (SD))	134 (21.3)	131 (23.7)	0.5533	140 (21.6)	131 (28.9)	0.1187
Diastolic pressure (mmHg, mean (SD))	70 (12.0)	67 (14.6)	0.3185	75 (12.4)	73 (14.0)	0.5008
Mean arterial pressure (mmHg, mean (SD))	91 (13.4)	90 (16.5)	0.7668	99 (12.3)	95 (12.8)	0.1581
Heart rate (beats min^{-1}, mean (SD))	73 (13.3)	64 (12.7)	0.0257	80 (16.1)	89 (11.6)	0.0053

Statistical significance accepted at $P < 0.05$ ***(Unpaired t test)***

to induction and expired desflurane concentration between FS and FG group were found.

Opioids markedly decrease the potential for respiratory irritation from inhaled anesthetic agents.[5] Glycopyrrolate is an anticholinergic agent with a quaternary ammonium compound.[10] As an antisialagogue, glycopyrrolate is about twice as potent as atropine and has a longer duration of action in the absence of sedation. Its potent inhibition effect of salivary gland and respiratory tract secretions is the primary rationale for using this medication as a premedication for inhalational induction with desflurane.[11-12]

Fentanyl as a rapid acting opioid was proven to be effective as an agent to suppress airway reflex during induction with desflurane.[13] Meanwhile glycopyrrolate with its potency will reduce respiratory tract secretion.[11] Combination of both together with nitrous oxide will provide satisfactory inhalational induction with desflurane and will lessen the incidence of airway irritation.

Prior research conducted by Kong et al has shown that airway irritation was associated with use of desflurane, including coughing (26-59%), apnea (13-35%), excitation (24-43%), and laryngospasm.[5] This incidence was shown to decrease when opioids (such as fentanyl and morphine) was used. This finding was supported by our results. Incidence of airway irritation in Group FS vs FG including cough, apnea, excitatory movements, and laryngospasm was (20% vs 2.5%), (0% vs 0%), (5% vs 5%), and (7.5% vs 0%) respectively. Total airway irritation was 32.5% in FS compared to 7.5% in FG, with *P* value 0.0103. Incidence of apnea and excitatory movements decreased to a figure similar to use of sevoflurane for induction when pretreatment with fentanyl was utilized.[14-15]

The changes in blood pressure before and after induction were comparable in both groups. Meanwhile the changes in heart rate before and after induction were significantly different with *P* value of 0.0257 in FS group and *P* value of 0.0053 in FG group. Decrease of heart rate after induction in FS group was most likely because of fentanyl property on diminishing the sympathomimetic effect of desflurane.[16] Meanwhile increase of heart rate after induction in FG group was most likely because of the anti-muscarinic properties of glycopyrrolate.

Sevoflurane is more commonly used for inhalational induction as it has been shown to have lower occurrence of adverse respiratory events (12.8% vs 20.0%).[17] Pretreatment with fentanyl and glycopyrrolate shows that 7.5% patients experience adverse respiratory effects. This shows that fentanyl and glycopyrrolate during desflurane induction reduces the incidence of adverse respiratory effect comparable with sevoflurane.

CONCLUSION

This study concludes that use of fentanyl and glycopyrrolate decreases airway irritation incidence caused by desflurane in comparison to use of fentanyl alone. This opens the possibility to commonly use desflurane as inhalation induction of anesthesia as its favorable pharmacokinetics may be utilized whilst limiting the adverse effects it causes.

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Conflict of Interest: Authors declare no conflict of interest.

Ethical Approval and Consent to Participate: This study has been approved by Institution Ethical Committee with registration number 092/K-LKJ/ETIK/I/2021 on January 15, 2021. Written and verbal consent have been obtained from participants in this study.

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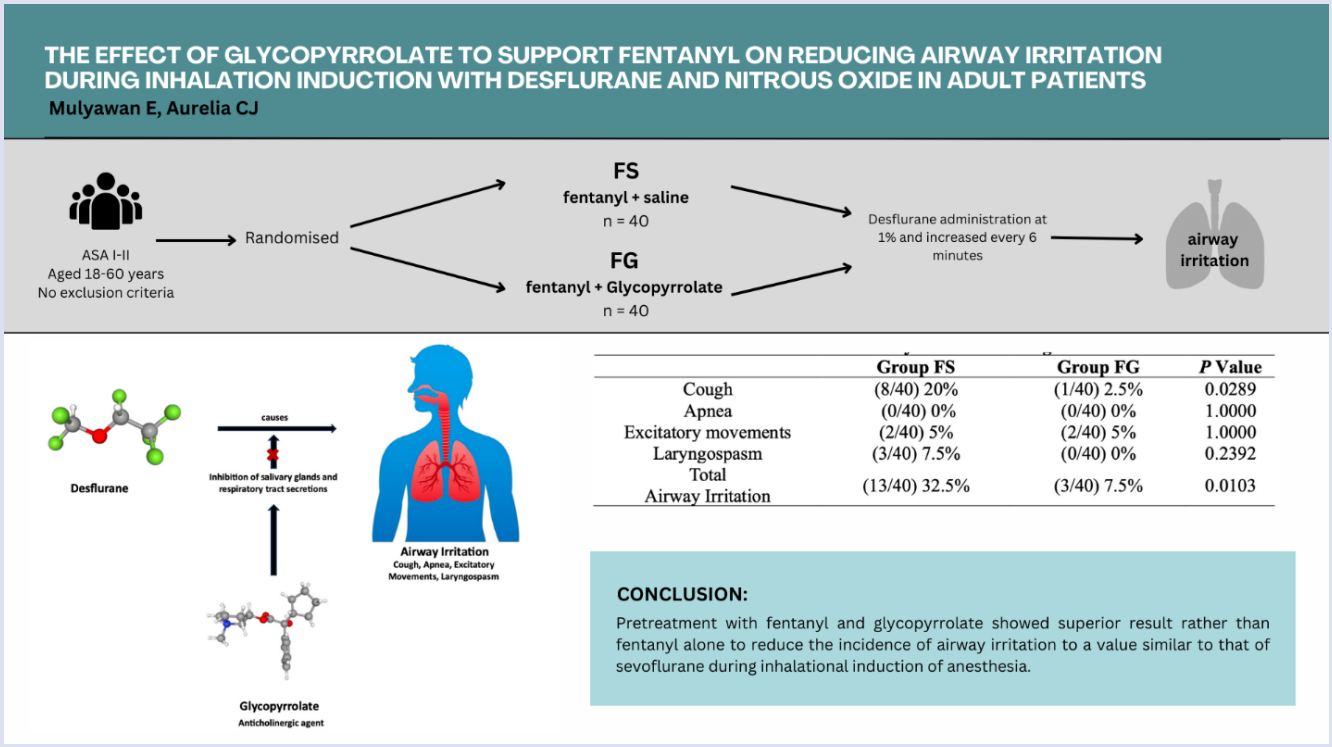
GRAPHICAL ABSTRACT



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