



The effect of tulobuterol patches on the respiratory system after endotracheal intubation

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Background: Endotracheal intubation during anesthesia induction may increase airway resistance (R_{aw}) and decrease dynamic lung compliance (C_{dyn}). We hypothesized that prophylactic treatment with a transdermal β_2 -agonist tulobuterol patch (TP) would help to reduce the risk of bronchospasm after placement of the endotracheal tube.

Methods: Eighty-two American Society of Anesthesiologists (ASA) category I or II adult patients showing obstructive patterns were divided randomly into a control and a TP group ($n = 41$ each). The night before surgery, a 2-mg TP was applied to patients in the TP group. Standard monitors were recorded, and target controlled infusion (TCI) with propofol and remifentanyl was used for anesthesia induction and maintenance. Simultaneously, end-tidal carbon dioxide, R_{aw} , and C_{dyn} were determined at 5, 10, and 15 min intervals after endotracheal intubation.

Results: There was no significant difference in demographic data between the two groups. The TP group was associated with a lower R_{aw} and a higher C_{dyn} , as compared to the control group. R_{aw} was significantly lower at 10 min ($P < 0.05$) and 15 min ($P < 0.01$), and C_{dyn} was significantly higher at 5 min ($P < 0.05$) and 15 min ($P < 0.01$) in the TP group. A trend towards a lower R_{aw} was observed showing a statistically significant difference 5 min after endotracheal intubation ($P < 0.01$) in each group.

Conclusions: Prophylactic treatment with TP showed a bronchodilatory effect through suppressing an increase in R_{aw} and a decrease in C_{dyn} after anesthesia induction without severe adverse effects.

Keywords: Bronchospasm; Endotracheal Intubation; Tulobuterol Patch.



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INTRODUCTION

Bronchospasm is a rare but serious complication in patients undergoing endotracheal intubation for general anesthesia [1,2]. This response is likely due to a neural reflex constriction in the airway smooth muscle [3]. Bronchospasm causes an increase in lung resistance and a decrease in lung compliance [3-5], eventually making

it difficult to provide effective mechanical ventilation.

Efforts to minimize the incidence of bronchospasm and peripheral airway constriction after endotracheal intubation are important, especially in patients with chronic airflow obstruction, including asthma and chronic obstructive pulmonary disease (COPD), because they are particularly at risk for bronchospasm under general anesthesia.

Tulobuterol patches (TPs) are transdermal β_2 -agonists

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useful for asthma and COPD patients [6-9]. Although tulobuterol is a short acting β_2 -agonist, a TP exerts continuous bronchodilatory effects with a sustained serum concentration elevation for 24 h [10,11].

We hypothesized that the use of a TP prior to general anesthesia would help to reduce the risk of bronchospasm after endotracheal tube placement in patients showing preoperative chronic airflow obstruction. The purpose of the present study was to determine the bronchodilatory effect of a TP for the prevention of bronchospasm during the induction of general anesthesia.

METHODS

This study was approved by the Institutional Review Board of the hospital and was registered with the Clinical Research Informational Service (KCT0001152, <http://cris.nih.go.kr>). Written informed consent was obtained from all patients.

Eighty-two American Society of Anesthesiologists (ASA) category I or II non-smoking adult patients undergoing minor elective surgery were enrolled in this prospective randomized study. They showed a forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) ratio < 70% in preoperative pulmonary function tests, suggesting chronic airflow obstruction [12]. Patients who used β -blockers, β_2 -agonists, steroids, and other bronchodilatory treatment, or who had a history of COPD exacerbation in the previous 4 weeks, were excluded. The sample size was estimated from preliminary data from ten patients. Power analysis suggested 34 patients per group with a power of 80% at α -error of 0.05 to detect a difference in airway resistance (R_{aw}) at 5 min after endotracheal intubation for 2 cmH₂O/L/sec. To compensate for potential dropout, we recruited 41 patients per group. Patients were randomly assigned to one of two groups using computer-generated random numbers. The tulobuterol patch group patients (TP group, n = 41) received a 2 mg tulobuterol patch applied to the skin of the chest on the night before surgery. The patients in the

control group (n = 41) did not receive a drug-containing patch.

All patients were pre-medicated with midazolam 0.04 mg/kg intramuscularly 1 h before anesthesia induction. In the operating room, after confirming the TP attachment, standard monitors were attached. Anesthesia was induced and maintained using a target-controlled infusion device (Orchestra; Fresenius Kabi, Bad Homburg, Germany) with propofol (target effect site concentration, 4 μ g/ml) and remifentanyl (target effect site concentration, 2 ng/ml). Endotracheal intubation was performed using a 7.5-8 mm diameter cuffed tube with rocuronium 0.6 mg/kg for muscle relaxation. Mechanical ventilation was started as quickly as possible. The ventilator was set to maintain a tidal volume of 8 ml/kg, 10 breath/min, fresh gas flow 4 l/min, oxygen-air (fraction of inspired oxygen, 0.5), and an inspiratory to expiratory ratio of 1:2.

Mean arterial blood pressure (MAP), heart rate (HR), and SaO₂ were recorded before induction and three times every 5 min after endotracheal intubation. Simultaneously, end-tidal carbon dioxide (EtCO₂), airway resistance (R_{aw}), and dynamic lung compliance (C_{dyn}) were determined 5, 10, and 15 min after intubation. These two respiratory variables were measured using a non-invasive cardiac output (NICO) monitor (Respironics-Novametrics, Wallingford, CT, USA) which was placed between the endotracheal tube and the corrugating tube. SPSS 17.0 (SPSS, Chicago, IL, USA) was used for statistical analyses. Data were expressed as the mean \pm SD. The demographic data were compared using the student's t-test and the chi-square test. All continuous variables were checked for normal distribution with the Q-Q plot and the Kolmogorov-Smirnov test. Two-way analysis of variance (ANOVA) for repeated measures was used to analyze the effect of time and group. If significance was detected, multiple comparisons were evaluated using the Bonferroni correction. Statistical significance was set at 0.05.

RESULTS

Throughout the study, neither group demonstrated any serious adverse cardiovascular side effects (palpitations or tachycardia), and all anesthetic inductions were performed safely, without any serious events. (Fig. 1) There were no differences in demographics, including sex, age, weight, height, and ASA physical status between the groups. No significant difference was observed between the groups in the preoperative pulmonary function tests (Table 1).

There was no difference in MAP, HR, SaO₂, or EtCO₂ between the two groups at any measurement points (Fig. 2). Within each group, the HR and SaO₂ showed no significant change during the observational period. However, MAP was significantly different at 5, 10, and

15 min intervals after endotracheal intubation compared to before anesthesia induction ($P < 0.01$) in both groups (Fig. 2a). EtCO₂ also showed a statistically significant difference at 10 min and 15 min, as compared to 5 min after endotracheal intubation ($P < 0.01$) in both groups (Fig. 2c).

The TP group was associated with a lower R_{aw} and a higher C_{dyn}, as compared to the control group. R_{aw} was significantly lower at 10 min ($P < 0.05$) and 15 min ($P < 0.01$), and C_{dyn} was significantly higher at 5 min ($P < 0.05$) and at 15 min ($P < 0.01$) in the TP group (Fig.

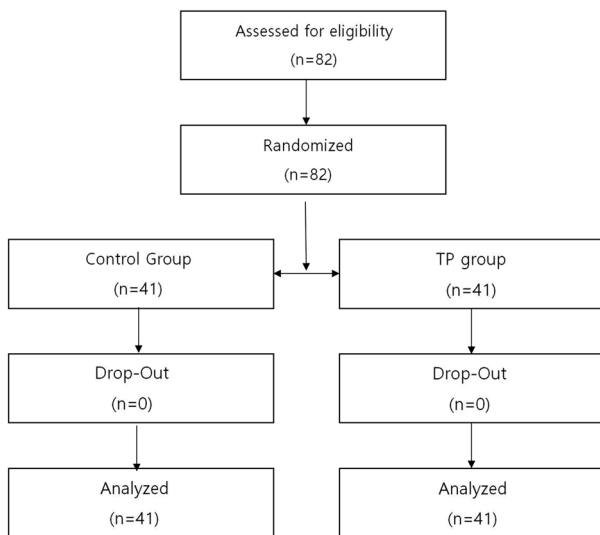


Fig. 1. CONSORT flow diagram.

Table 1. Demographic data

	Control group	TP group
Sex (M/F)	33/8	30/11
Age (years)	67.7 ± 7.5	69.8 ± 8.4
Height (cm)	166.1 ± 8.4	162.4 ± 8.9
Body weight (kg)	63.2 ± 8.3	60.0 ± 8.5
ASA physical status (I/II)	3/38	5/36
FEV ₁ /FVC	61.3 ± 7.8	60.2 ± 8.9

Values are represented as mean ± SD.

M: male, F: female, TP: tulobuterol patch, FEV₁: forced expiratory volume in 1 sec, FVC: forced vital capacity.

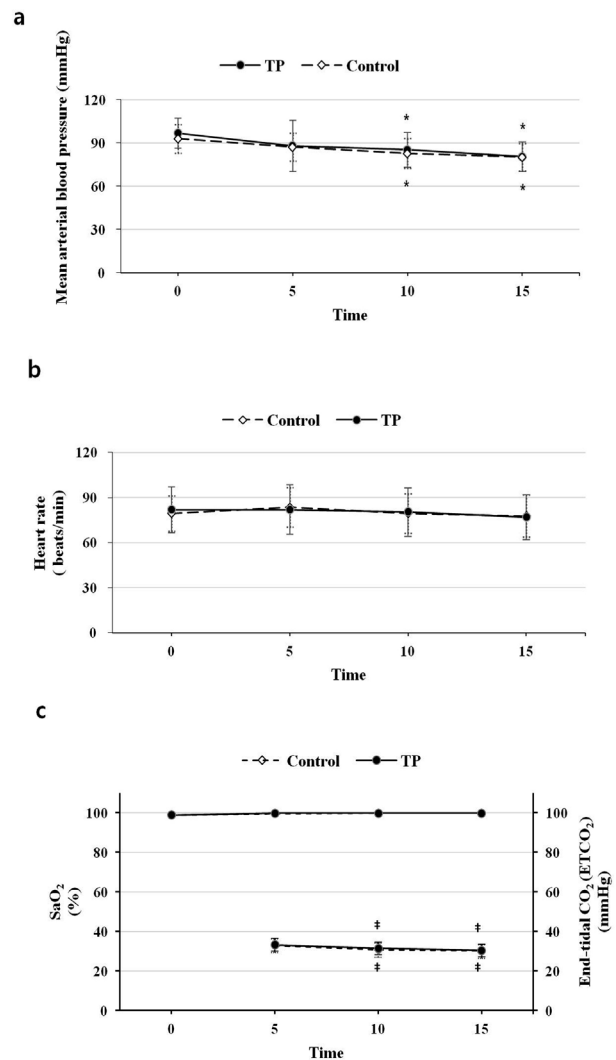


Fig. 2. Time numbers on the abscissas indicate the following: 0, before induction, and 5, 10, 15, 5 min, 10 min, 15 min after endotracheal intubation. Values are shown as the mean ± standard deviation. * $P < 0.01$ vs before induction within the group. † $P < 0.01$ vs 5 min after endotracheal intubation within the group.

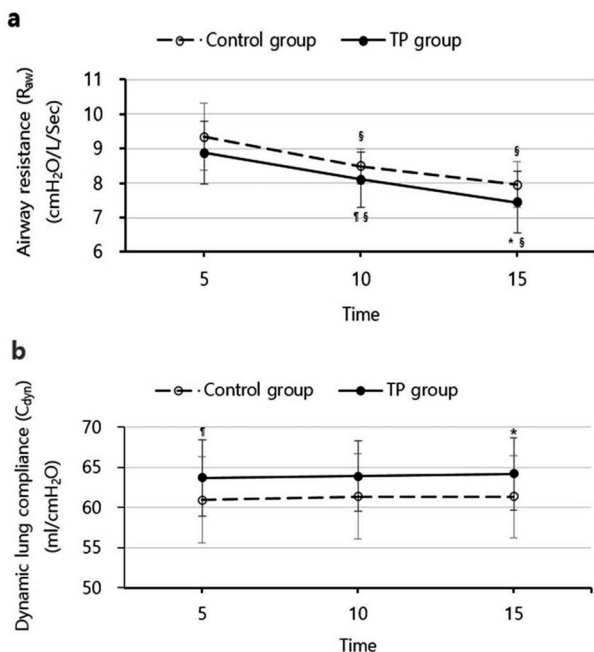


Fig. 3. Time numbers on the abscissas indicate the following: 5, 10, 15, 5 min, 10 min, 15 min after endotracheal intubation. Values are shown as the mean \pm standard deviation. * $P < 0.01$ vs control group, [†] $P < 0.05$ vs control group. [§] $P < 0.01$ vs 5 min after endotracheal intubation within the group.

3). A trend towards a lower R_{aw} was observed and showed a statistically significant difference 5 min after endotracheal intubation ($P < 0.01$) in each group (Fig. 3a). In contrast, C_{dyn} showed no change 5 min after endotracheal intubation in either group (Fig. 3b).

DISCUSSION

This study investigated the bronchodilatory effect of TPs for the prevention of bronchospasm after endotracheal intubation. Our hypothesis was that the bronchodilatory effect of a TP might affect airway resistance (R_{aw}) and dynamic lung compliance (C_{dyn}), consequently reducing the risk of bronchospasm after anesthesia induction.

Numerous factors, including cold air, allergens, stress, and invasive ventilator devices, may cause bronchial smooth muscle contraction and eventually lead to bronchospasm [13]. In patients undergoing general anesthesia, cold inspired gases, laryngoscopy, and

endotracheal intubation can provoke bronchospasm. Importantly, intraoperative bronchospasm is a rare but serious complication [1,2]. In this study, we enrolled patients showing an obstructive pattern in preoperative pulmonary function tests on the assumption that they had a bronchial hyperresponsiveness, such as asthma or COPD [14]. In these patients, the risk of bronchospasm increases with endotracheal intubation, as compared to normal patients. We measured two respiratory variables, R_{aw} and C_{dyn} . An increase in R_{aw} and a decrease in C_{dyn} could increase the possibility of bronchospasm and it has been reported that R_{aw} is more sensitive than C_{dyn} to bronchospasm [15].

We used target-controlled infusion with propofol and remifentanyl, instead of a volatile agent for anesthesia induction and maintenance, to minimize the influence of anesthetics on airway resistance. The bronchodilatory effect of a volatile agent, such as isoflurane or sevoflurane, may affect airway resistance [16], and there have been reports that desflurane may provoke bronchoconstriction in smokers [17]. For anesthesia induction, thiopental or etomidate may also be used. Although the possibility of bronchospasm cannot be precluded when using propofol, propofol is more effective in constraining increases in airway resistance [2,3,18,19]. Simultaneously, we used rocuronium as a muscle relaxant, which is useful in asthma patients for rapid sequence induction, because some neuromuscular blocking agents, such as mivacurium and atracurium, have a histamine-releasing effect and may cause bronchospasm [20].

A TP is categorized as a long-acting β_2 -agonist and shows continuous bronchodilatory effects for 24 h with a low incidence of adverse effects [10,11]. It has been used for the long-term treatment of asthma and COPD, and its benefits have been previously demonstrated [11,21]. Compared to oral or inhaled tulobuterol, TPs maintain a stable serum tulobuterol concentration for a prolonged period [10,22] and are simpler to administer. Nevertheless, transdermal absorption of the TP is slower than when tulobuterol is administered orally or inhaled. The time to maximum TP plasma concentration (T_{max})

is between 9 h and 12 h, whereas the T_{max} of inhaled tulobuterol is between 0.8 h and 1.5 h. At the dose used in our study (2 mg), T_{max} was 11.8 h and the maximum plasma concentration (C_{max}) was 1.4 ng/ml [10]. Considering the T_{max} , we applied a TP on the night before surgery, because it was the optimal time to obtain a sufficient TP effect for all patients enrolled in the study. We hypothesized that a single TP application could attenuate the response to endotracheal intubation and improve airway obstruction in anesthetized patients, similar to other inhaled β_2 -agonists [4]. There are potential side-effects of β_2 -agonists, including hypokalemia, arrhythmia, and tachycardia, especially in elderly patients [23-25]. However, at standard TP doses, such adverse effects are rare [8,21].

According to our results, R_{aw} was lower at all measurement points in the TP group. However, R_{aw} at 5 min after endotracheal intubation showed no statistically significant difference compared to the control group. It is possible that a 2 mg TP may not be sufficient to attenuate the response after endotracheal intubation completely. Alternatively, a TP may fail to reach C_{max} in some patients. If we had applied a TP earlier, almost all patients would have been exposed for 12 h, reaching C_{max} . However, earlier TP administration was not optimal in our hospital. In both groups, R_{aw} at 10 min and 15 min was lower, as compared to 5 min after endotracheal intubation. This is likely due to the decrease in bronchial hyperresponsiveness rather than the TP. Overall, even though a high C_{dyn} value was recorded at all measurement points in the TP group, there was no statistically significant difference in C_{dyn} 10 min after endotracheal intubation. This may have been due to an unrecognized error.

In summary, our results suggest that a single TP application effectively suppressed the increase in R_{aw} and the decrease in C_{dyn} without any severe adverse effects after anesthesia induction. The bronchodilatory effect of the TP may be helpful to reduce the risk of bronchospasm after endotracheal intubation.

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REFERENCES

1. Olsson GL. Bronchospasm during anaesthesia. A computer-aided incidence study of 136,929 patients. *Acta Anaesthesiol Scand* 1987; 31: 244-52.
2. Pizov R, Brown RH, Weiss YS, Baranov D, Hennes H, Baker S, et al. Wheezing during induction of general anesthesia in patients with and without asthma. A randomized, blinded trial. *Anesthesiology* 1995; 82: 1111-6.
3. Eames WO, Rooke GA, Wu RS, Bishop MJ. Comparison of the effects of etomidate, propofol, and thiopental on respiratory resistance after tracheal intubation. *Anesthesiology* 1996; 84: 1307-11.
4. Kil HK, Rooke GA, Ryan-Dykes MA, Bishop MJ. Effect of prophylactic bronchodilator treatment on lung resistance after tracheal intubation. *Anesthesiology* 1994; 81: 43-8.
5. Kim ES, Bishop MJ. Endotracheal intubation, but not laryngeal mask airway insertion, produces reversible bronchoconstriction. *Anesthesiology* 1999; 90: 391-4.
6. Fukuchi Y, Nagai A, Seyama K, Nishimura M, Hirata K, Kubo K, et al. Clinical efficacy and safety of transdermal tulobuterol in the treatment of stable COPD: an open-label comparison with inhaled salmeterol. *Treat Respir Med* 2005; 4: 447-55.
7. Yoshihara S, Yamada Y, Abe T, Arisaka O. The use of patch formulation of tulobuterol, a long-acting beta2-

- adrenoreceptor agonist, in the treatment of severe pediatric asthma. *Ann Allergy Asthma Immunol* 2006; 96: 879-80.
8. Horiguchi T, Kondo R, Miyazaki J, Fukumoto K, Torigoe H. Clinical evaluation of a transdermal therapeutic system of the beta2-agonist tulobuterol in patients with mild or moderate persistent bronchial asthma. *Arzneimittelforschung* 2004; 54: 280-5.
 9. Burioka N, Miyata M, Endo M, Fukuoka Y, Suyama H, Nakazaki H, et al. Alteration of the circadian rhythm in peak expiratory flow of nocturnal asthma following nighttime transdermal beta2-adrenoreceptor agonist tulobuterol chronotherapy. *Chronobiol Int* 2005; 22: 383-90.
 10. Uematsu T, Nakano M, Kosuge K, Kanamaru M, Nakashima M. The pharmacokinetics of the beta 2-adrenoreceptor agonist, tulobuterol, given transdermally and by inhalation. *Eur J Clin Pharmacol* 1993; 44: 361-4.
 11. Iikura Y, Uchiyama H, Akimoto K, Ebisawa M, Sakaguchi N, Tsubaki T, et al. Pharmacokinetics and pharmacodynamics of the tulobuterol patch, HN-078, in childhood asthma. *Ann Allergy Asthma Immunol* 1995; 74: 147-51.
 12. Pauwels RA, Buist AS, Calverley PM, Jenkins CR, Hurd SS, GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001; 163: 1256-76.
 13. Hepner DL, Castells MC. Anaphylaxis during the perioperative period. *Anesth Analg* 2003; 97: 1381-95.
 14. Postma DS, Kerstjens HA. Characteristics of airway hyperresponsiveness in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 1998; 158: S187-92.
 15. Wajima Z, Shiga T, Imanaga K, Inoue T, Ogawa R. Effect of prophylactic bronchodilator treatment with i.v. carperitide on airway resistance and lung compliance after tracheal intubation. *Br J Anaesth* 2006; 96: 660-4.
 16. Rooke GA, Choi JH, Bishop MJ. The effect of isoflurane, halothane, sevoflurane, and thiopental/nitrous oxide on respiratory system resistance after tracheal intubation. *Anesthesiology* 1997; 86: 1294-9.
 17. Goff MJ, Arain SR, Ficke DJ, Uhrich TD, Ebert TJ. Absence of bronchodilation during desflurane anesthesia: a comparison to sevoflurane and thiopental. *Anesthesiology* 2000; 93: 404-8.
 18. Kabara S, Hirota K, Yoshioka H, Kudo T, Ishihara H, Matsuki A. Differential effects of thiopental on methacholine- and serotonin-induced bronchoconstriction in dogs. *Br J Anaesth* 2003; 91: 379-84.
 19. Nishiyama T, Hanaoka K. Propofol-induced bronchoconstriction: two case reports. *Anesth Analg* 2001; 93: 645-6.
 20. Sparr HJ, Beaufort TM, Fuchs-Buder T. Newer neuromuscular blocking agents: how do they compare with established agents? *Drugs* 2001; 61: 919-42.
 21. Kume H, Kondo M, Ito Y, Suzuki R, Yamaki K, Takagi K. Effects of sustained-release tulobuterol on asthma control and beta-adrenoreceptor function. *Clin Exp Pharmacol Physiol* 2002; 29: 1076-83.
 22. Musoh K, Kawamura K, Miyake I, Shimada S, Ohashi T, Iwanaga Y, et al. The effect of tulobuterol tape on histamine-induced bronchoconstriction in conscious guinea pigs: long duration of action. *Jpn J Pharmacol* 1999; 79: 401-2.
 23. Leff AR. Identifying patients at risk from the use of beta-adrenergic agonists. *Am J Respir Crit Care Med* 1996; 154: 1593.
 24. Suissa S, Hemmelgarn B, Blais L, Ernst P. Bronchodilators and acute cardiac death. *Am J Respir Crit Care Med* 1996; 154: 1598-602.
 25. Wong CS, Pavord ID, Williams J, Britton JR, Tattersfield AE. Bronchodilator, cardiovascular, and hypokalaemic effects of fenoterol, salbutamol, and terbutaline in asthma. *Lancet* 1990; 336: 1396-9.