A small dose of dezocine suppresses remifentanil-induced cough in general anesthesia induction: a prospective, randomized, controlled study

Rui Ma, Yu Wei and Zifeng Xu

Abstract

Background: The aim of this prospective randomized controlled study was to evaluate whether pretreatment with a small dose of dezocine could prevent remifentanil-induced cough in general anesthesia induction.

Trial design: A total of 210 patients receiving elective operative hysteroscopy from December 2018 to April 2019 were enrolled in the present study. They were randomly equally separated into dezocine group (n = 105) and control group (n = 105). Patients were intravenously pre-administrated with dezocine 0.03 mg/kg (diluted to 5 mL) or the same volume of normal saline 1 min prior to remifentanil infusion. One minute later, intravenous injection of propofol 1.5 mg/kg and cisatracurium 0.1 mg/kg were given to all patients for induction of general anesthesia. The counts of coughs occurred during the anesthesia induction period were recorded and the severity of cough was scaled.

Results: There were 7 cases of mild cough in dezocine group and 18 cases of mild cough, 12 cases of moderate cough and 4 cases of severe cough in control group. The incidence rate of cough was significantly lower and the severity of cough was obviously relieved in dezocine group compared to control group (6.67% vs. 32.38%, P < 0.001).

The two groups were not significantly different in heart rate and mean arterial pressure before the induction, before and after the intubation, and in operating time and postoperative visual analog scale pain scores.

Conclusion: This study recommends the efficacy and safety of a pretreatment with a small dose of dezocine in reducing remifentanil-induced cough during general anesthesia.

Trial Registration: ChiCTR2000032035.
Date of registration: Retrospectively registered on 2020/04/18.

Keywords: Opioids, Cough, General anesthesia, Dezocine, Remifentanil
Background
Opioids are conventionally used as adjunct drugs for induction of general anesthesia [1]. Application of opioids such as fentanyl [2] and sufentanil [3] often elicits cough during induction of general anesthesia. This adverse effect may lead to increased intracranial pressure and intraocular pressure and is extraordinarily dangerous for patients with diseases such as cerebral aneurysm, open eye injury and airway [4]. Remifentanil is a fentanyl congener characterized by short onset and short action time, and has been widely applied for induction of general anesthesia [5]. Remifentanil shows an antitussive effect on brainstem μ-opioid receptors [6]; however, some studies reported it also causes coughing just like fentanyl with an incidence rate varies from 26 to 57% during general anesthesia [7–10].

There is a growing interest in suitable agents and methods to prevent remifentanil-induced cough. For instance, Kim et al. suggests that elongating injection time over than 60 s could inhibit remifentanil-cough during anesthesia in children [7]. Limited maximal infusion rate appears to alleviate remifentanil-induced cough as well [11]. Moreover, there is evidence that pretreatment of several agents such as dexamethasone [12], ketamine or their combination [13] and propofol [14] has been reported to be useful for suppressing cough provoked by remifentanil. Dezocine is a mixed agonist-antagonist opioid analgesic [15]. It was initially identified as a full agonist of κ-receptor and partial agonist/antagonist of μ-receptor [15]. Later study suggested it is a κ-receptor antagonist [15, 16]. Increasing studies have demonstrated that dezocine administration is effective and feasible in preventing the occurrence of sufentanil-induced cough during the induction of general anesthesia [17, 18]. Nevertheless, few studies are focused on the effect of dezocine on remifentanil-induced cough.

Our study pretreated the patients undergoing elective hysteroscopic surgery with a small dose of dezocine prior to remifentanil infusion with a view to investigating whether dezocine pretreatment is a reliable strategy to relieve the incidence and severity of remifentanil-induced cough. This prospective randomized controlled trial would provide some useful clues for further development of anesthesia management.

Methods
Study design
This study was approved by the National science and technology ethics committee (approval number: 2017–101) and registered in the Chinese Clinical Trial Register (registration number: ChiCTR2000032035). A total of 210 patients with ASA physical status I–II who received elective hysteroscopic surgery in our hospital from December 2018 to April 2019 were enrolled in this study. Exclusion criteria were: known hypersensitivity to the drugs used in this study; body mass index > 30 kg/m²; a history of hypertension; severe arrhythmias; chronic bronchitis, asthma, or other respiratory diseases; increased intraocular pressure, intrathoracic pressure or intracranial pressure before surgery. Written informed consent was obtained from each participant.

The incidence of remifentanil (1.5 μg/kg)-induced cough in control group was around 30% in our early study (unpublished). We hypothesized that the incidence rate of cough in dezocine group was lower than 10%. Based on α = 0.05 (two-sided) and power = 0.95 (β = 0.05), a medium effect size (Cohen’s f = 0.25), the estimated sample size was 104. Taking the dropout into account, the sample size was set at 105 in each group.

The 210 patients were randomly and equally divided into two groups: dezocine group and control group by a computer-generated allocation program.

Anesthesia and monitoring
In brief, all patients of the two groups were fasted for 8 h. Peripheral venous access was established using a 20-gauge cannula on the dorsal hand in the operating room. Heart rate (HR) and blood pressure were monitored. Two minutes prior to induction of general anesthesia, patients of the dezocine group received intravenous infusion of dezocine 0.03 mg/kg (diluted to 5 mL), while patients of the control group received an injection of 5 mL normal saline.

One minute later, remifentanil 1.5 μg/kg (1 mg remifentanil diluted with normal saline in a 50 mL syringe; Yichang Humanwell Pharmaceutical Co., LTD, Yichang, Hubei Province, China) was administrated to all patients of the two groups by a syringe pump at a rate of 600 mL/h, followed by intravenous injection of propofol 1.5 mg/kg and cisatracurium 0.1 mg/kg (Hengrui Pharmaceutical Co., LTD, Shanghai, China) 1 min later to induce general anesthesia. Endotracheal intubation was then conducted and the patients were ventilated mechanically.

HR and mean arterial pressure (MAP) before the anesthesia induction, immediately before and 1 min after intubation were recorded. Side effects such as vomiting [19], hypoxemia (SpO₂ < 90%) [20] or other intended effects during the induction period were also recorded. The number of coughs of the two groups was recorded and the severity of cough was defined as follows: mild, 1–2; moderate, 3–4; severe, 5 or more [21, 22]. In addition, operative time and visual analog scale (VAS) pain score 30 mins and 60 mins postoperatively were recorded and analyzed as well.

Statistical analysis
The primary endpoint was the incidence of cough in different groups. All statistical analyses were done by SPSS.
Intraoperative oxygen saturation (SpO$_2$) of each patient class:

$P$ (58.82 ± 7.92 kg vs. 59.50 ± 9.93 kg, 41.99 ± 10.43 years vs. 42.61 ± 11.26 years, $P$). Differences between the two groups in age (41.99 ± 10.43 years vs. 42.61 ± 11.26 years, $P$) were analyzed by repeated measure ANOVA with Bonferroni correction.

Weight of patients in control group were 22–89 kg, and in dozocine group was 25–73 years and body weight range was 43–80 kg. There was no significant difference between the two groups in age (41.99 ± 10.43 years vs. 42.61 ± 11.26 years, $P$ = 0.680), body weight (58.82 ± 7.92 kg vs. 59.50 ± 9.93 kg, $P$ = 0.586) and ASA class (78/27 vs. 74/31, $P$ = 0.644) (Table 1).

Hysteroscopy is an established endoscopic surgical procedure in obstetrics and gynecology practice for diagnosis and management of endometrial problems, with advantages of fewer complications, shorter recovery time and lower costs [23, 24]. However, pain is the most common complication of hysteroscopy because of several procedures such as cervical dilatation, uterine distension and peritoneal irritation [25]. Application of appropriate anesthetic agents for maximal anesthetic effect is a critical issue for hysteroscopy [26]. Remifentanil is a short-acting anilidopiperidine opioid with unique pharmacokinetic characteristics, facilitating fast and efficient analgesia. It is metabolized by esterases independently of hepatic and renal functions, and was therefore eliminated at a more rapid speed than other anilidopiperidine opioids [27]. Remifentanil alone or in combination with

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### Table 1: Demographic characteristics of patients in two groups

| Group                  | Control group | Dezocine group | $P$ |
|------------------------|---------------|----------------|-----|
| n                       | 105           | 105            |     |
| Age (year)             | 41.99 ± 10.43 | 42.61 ± 11.26  | 0.680|
| Body weight (kg)       | 58.82 ± 7.92  | 59.50 ± 9.93   | 0.586|
| ASA class (I/II)       | 78/27         | 74/31          | 0.644|

Data represent mean ± SD or numbers. Difference between groups were compared by students’ t test or chi-square test.

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### Table 2: Observations of MAP and HR

| Variable       | Group          | Before induction | 1 min before intubation | 1 min after intubation |
|----------------|----------------|------------------|-------------------------|------------------------|
| (mmHg)         | Control group  | 85.64 ± 8.32     | 70.26 ± 7.47*           | 69.79 ± 6.19*          |
|                | Dezocine group | 88.03 ± 14.91    | 70.06 ± 8.24*           | 70.07 ± 7.94*          |
| HR (beats/min) | Control group  | 81.77 ± 13.04    | 60.86 ± 8.04*           | 60.28 ± 7.81*          |
|                | Dezocine group | 79.58 ± 13.71    | 60.89 ± 7.55*           | 60.19 ± 6.69*          |

Difference between groups at same time point was compared by Student’s t test. Difference among different time points in the same group was compared by repeated measure ANOVA. *$P$ < 0.05 vs. before anesthesia induction. MAP, mean arterial pressure; HR, heart rate.

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### Results

#### Demographic characteristics

Total 210 ASA I and II patients were included in this study. They were randomly assigned to dozocine group ($n$ = 105) or control group ($n$ = 105). The age range of patients in dozocine group was 25–73 years and body weight range was 43–80 kg. The age range and body weight of patients in control group were 22–75 years and 42–89 kg, respectively. There was no significant difference between the two groups in age (41.99 ± 10.43 years vs. 42.61 ± 11.26 years, $P$ = 0.680), body weight (58.82 ± 7.92 kg vs. 59.50 ± 9.93 kg, $P$ = 0.586) and ASA class ($P$ = 0.644) (Table 1).

Our study enrolled a total of 210 patients scheduled for hysteroscopy who were equally randomized into dozocine group and control group. Patients in these two groups had similar age and body weight. The patients in the dozocine group received a small dose of dozocine prior to remifentanil administration, while patients in control group were given the same volume of normal saline. A pre-emptive administration of dozocine decreased the incidence of cough from 32.38% to 6.67% and relieved the severity of cough. These findings suggest that pretreatment with dozocine could effectively prevent remifentanil-induced cough during general anesthesia induction in patients undergoing operative hysteroscopy.

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### Discussion

Our study enrolled a total of 210 patients scheduled for hysteroscopy who were equally randomized into dozocine group and control group. Patients in these two groups had similar age and body weight. The patients in the dozocine group received a small dose of dozocine prior to remifentanil administration, while patients in control group were given the same volume of normal saline. A pre-emptive administration of dozocine decreased the incidence of cough from 32.38% to 6.67% and relieved the severity of cough. These findings suggest that pretreatment with dozocine could effectively prevent remifentanil-induced cough during general anesthesia induction in patients undergoing operative hysteroscopy.

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As shown in Table 3, mild cough was observed in 7 patients of dozocine group, with an incidence of 6.67%. Control group had 34 patients with cough (32.38%), including 18 patients with mild cough, 12 patients with moderate cough and 4 patients with severe cough. The patients in dozocine group had a significantly lower incidence of cough and improved severity of cough in comparison with those in control group ($P$ < 0.001). Additionally, there were no significant differences in operating time, 30-min and 60-min postoperative VAS pain scores ($P$ > 0.05, Table 4).

**Table 3: Incidence and severity of cough, operating time and VAS pain score**

As shown in Table 3, mild cough was observed in 7 patients of dozocine group, with an incidence of 6.67%. Control group had 34 patients with cough (32.38%), including 18 patients with mild cough, 12 patients with moderate cough and 4 patients with severe cough. The patients in dozocine group had a significantly lower incidence of cough and improved severity of cough in comparison with those in control group ($P$ < 0.001). Additionally, there were no significant differences in operating time, 30-min and 60-min postoperative VAS pain scores ($P$ > 0.05, Table 4).

**Table 4: Discussion**

Our study enrolled a total of 210 patients scheduled for hysteroscopy who were equally randomized into dozocine group and control group. Patients in these two groups had similar age and body weight. The patients in the dozocine group received a small dose of dozocine prior to remifentanil administration, while patients in control group were given the same volume of normal saline. A pre-emptive administration of dozocine decreased the incidence of cough from 32.38% to 6.67% and relieved the severity of cough. These findings suggest that pretreatment with dozocine could effectively prevent remifentanil-induced cough during general anesthesia induction in patients undergoing operative hysteroscopy.

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adjunct agents has been widely utilized for general anesthesia in hysteroscopy [28]. In the present study, similarly, intravenous infusion of remifentanil 1.5 μg/kg in synergy with propofol 1.5 mg/kg and cisatracurium 0.1 mg/kg 1 min later were used for the induction of general anesthesia in all patients. Cough is often elicited by remifentanil infusion and is a causative factor of undesirable conditions including elevated intracranial, intra-ocular and intra-abdominal pressure [29]. In the present study, the incidence of remifentanil-induced cough without any pretreatment was 32.38% (34/105). Previous studies showed an incidence range of 26–57% during general anesthesia [7, 9–11]. The variance may be possibly attributed to different doses, effect-site concentrations and infusion speeds used in different studies.

The exact mechanisms behind opioid-induced cough remain elusive. One possible mechanism is that opioids cause suppression of central sympathetic outflow and strengthening of the vagus nerve, thus resulting in cough [30]. Pulmonary chemoreflex mediated by irritant receptors or vagal C-fiber receptors close to pulmonary vessels, opioid-induced histamine release from lung mast cells and tracheal smooth muscle constriction may be responsible for occurrence of cough [31]. Control of opioid-induced cough is of paramount clinical significance. Dezocine is a mixed agonist-antagonist opioid and its inhibitory action on opioid-induced cough has been proved in prior studies [17, 32]. In our study, the incidence of remifentanil-induced cough was 32.38% (18 cases of mild cough, 12 cases of moderate cough and 4 cases of severe cough) in the patients pre-administrated with normal saline, and was 6.67% (7 cases of mild cough) in the patients pre-administrated with dezocine. This result revealed that pre-administration of dezocine was effective in suppressing remifentanil-induced cough during general anesthesia induction. In a previous study, no patient pretreated with infusion of dezocine 0.1 mg/kg reports sufentanil-induced cough, in contrast the control patients had a cough incidence of 31.9% [17]. Although dezocine 0.1 mg/kg seems to exert a more potent suppressive effect, higher HR and blood pressure are detected in the patients receiving a pre-emptive infusion of dezocine compared to the control patients in their study. In the current study, 0.03 mg/kg dezocine, a third of an analgesic dose of dezocine was selected. Patients in the dezocine and control groups were not significantly different in HR and MAP before the anesthesia induction, prior to intubation and 1 min after intubation, and in operating time, 30-min and 60-min postoperative VAS pain scores. These observations indicated that pre-administration of dezocine 0.03 mg/kg does not affect hemodynamics, operating time and postoperative pain of patients. Postoperative analgesia demands a larger dose of dezocine.

Dezocine was thought to be a κ opioid receptor agonist, but recent data suggest it could be a κ opioid receptor antagonist [16]. The cough suppression by dezocine may be due to κ receptors antagonism or decreased noradrenaline and serotonin reuptake [33]. Xu et al. speculated that dezocine may reduce fentanyl-induced cough by antagonizing fentanyl-activated μ receptors via activating κ receptors [34]. Our study did not unveil the exact mechanisms underlying the suppression on remifentanil-induced cough by dezocine. More in-depth studies are necessary to decipher the exact mechanisms. Cough suppressing effect of different doses of dezocine was not explored in the present study. These limitations should be addressed in future studies.

**Conclusion**

Our study showed that premedication of a low dose of dezocine was capable of effectively and safely repressing remifentanil-induced cough during general anesthesia in the patients receiving operative hysteroscopy. This study offers more insights concerning alternative regimens to prevent remifentanil-induced cough.

**Abbreviations**

HR: Heart rate; MAP: Mean arterial pressure; VAS: Visual analog scale

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Not applicable.

**Authors’ contributions**

RM designed the project and wrote the manuscript; YW performed the data analysis; ZX collected the data and revised this paper. All authors read and approved the final manuscript.
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