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Original Article

Comparison of intubation conditions and apnea time after anesthesia induction with propofol/remifentanil combined with or without small dose of succinylcholine

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Abstract: Background: Many scholars are seeking for an anesthesia induction regimen to meet the requirements of both intubation and instant recovery of spontaneous breathing in case of "cannot intubate, cannot ventilate" to prevent severe consequences. This study aims to investigate whether the combination use of remifentanil 1 μg/kg and small dose of succinylcholine (0.6 mg/kg) is superior to single use of remifentanil 1.5 μg/kg in improving intubation conditions and shortening apnea time under anesthesia induction with propofol. Methods: Sixty patients undergoing selective gynecological laparoscopic operation under general anesthesia were included into the prospective randomized controlled trial. After sufficient preoxygenation, all patients received propofol for anesthesia induction, and patients in group S were managed with remifentanil 1 μg/kg and succinylcholine 0.6 mg/kg, while those in group C were treated with remifentanil 1.5 μg/kg and normal saline. Tracheal intubation was conducted 60 s later, and mechanical ventilation was not performed until spontaneous breathing emerged. The intubation conditions were evaluated, and the apnea time between induction and breathing recovery was recorded. Results: One patient (3.70%) in group S was graded as poor in intubation conditions, which was significantly fewer than 12 patients in group C ($P<0.001$). There was no significant difference in apnea time between two groups (245.50 ± 53.71 vs 251.12 ± 70.71, $P=0.750$). No patient experienced hypoxic event with $SpO_2<90\%$ before recovery of spontaneous breathing. Conclusions: Compared with single use of remifentanil 1.5 μg/kg, the combination use of remifentanil 1 μg/kg and succinylcholine 0.6 mg/kg may offer better intubation conditions and may not prolong apnea time under anesthesia induction with propofol 2 mg/kg.

Keywords: Endotracheal intubation, apnea time, small-dose succinylcholine, remifentanil

Introduction

Difficult airway has long been a focus in anesthesiology research. "Cannot intubate, cannot ventilate" (CICV) after general anesthesia induction may be the real difficult airway. In case of CICV, the recovery of spontaneous breathing before hypoxemia can avoid the severe consequences and allow for other countermeasures such as conscious intubation to solve the airway problem. Therefore, scholars are seeking for an anesthesia induction regimen to meet the requirements of both intubation and instant recovery of spontaneous breathing before the occurrence of hypoxemia.

Stefanutto et al [1] believed that regular dose (1 mg/kg) of succinylcholine, a muscle relaxant, might increase apnea time, while small dose of succinylcholine would not provide favorable intubation conditions, and anesthesia induction with proper doses of remifentanil and propofol excluding muscle relaxants, could avoid the prolongation of respiratory depression. However, though remifentanil 2 μg/kg may offer better intubation conditions, the apnea time is longer [1], which may easily risk the patients in hypoxia. While the intubation conditions with remifentanil 1.5 μg/kg are not ideal, and the risk of hypoxia can not be completely avoided in spite that the apnea time is shortened [1]. Can the anesthesia induction regimen be optimized as combined administration of decreased dose of remifentanil and small dose of succinylcholine? The study of El-Orbany et al [2] revealed that the minimum

Table 1. Assessment of intubation conditions

Criteria	Clinically acceptable		Clinically unacceptable
	Excellent	Good	Poor
Before intubation:			
Ease of laryngoscopy (jaw relaxation)	Easy	Fair	Difficult
Vocal cord position	Abducted	Intermediate	Closed
Vocal cord movement	None	Moving	Closing
Post intubation:			
Airway reaction	None	Diaphragm	Sustained
Movement of limbs	None	Slight	Vigorous

a Intubation conditions: Excellent = all criterion are excellent; Good = all criterion are either excellent or good; Poor = the presence of a single criterion graded as poor.

effective dose of succinylcholine was 0.6 mg/kg, which would yield similar intubation conditions and significantly shorter apnea time in comparison with succinylcholine 1 mg/kg. In their study [2], fentanyl combined with propofol was used in anesthesia induction. What if fentanyl is substituted by remifentanil which is more short-acting? This study aims to investigate whether the combination use of regular dose of remifentanil (1 μg/kg) and small dose of succinylcholine (0.6 mg/kg) is superior to single use of remifentanil 1.5 μg/kg in improving intubation conditions and shortening apnea time under anesthesia induction with propofol.

Material and methods

The study was approved by the Medical Ethics Committee of Obstetrics and Gynecology Hospital of Fudan University, and informed consent was obtained from each patient. Sixty female patients with ASA I or II aged between 18 and 60 years undergoing selective gynecological laparoscopic operation under general anesthesia were included. Exclusion criteria were body mass index >30; Mallampati airway grade 2 to 4; known allergy to propofol, egg, or opioids; alcohol or drug abuse; history of gastroesophageal reflux disease or neuromuscular disease; and history of upper respiratory tract infection or other airway hyperactivity diseases in the recent two weeks.

With random number table, patients were divided into succinylcholine group (group S: propofol 2 mg/kg, remifentanil 1 μg/kg and succinylcholine 0.6 mg/kg) and control group (group C: propofol 2 mg/kg, remifentanil 1.5 μg/kg and normal saline) according to anesthesia induction drugs. All drugs were prepared by one investigator. Remifentanil in each group was diluted with normal saline to 10 ml, and the injectors were labeled with "2". The injectors infused with succinylcholine (diluted with normal saline to 10 ml) in group S and normal saline 10 ml in group C were labeled with "3".

After entering the operation room, all patients received routine monitoring of BP, HR and SpO_2, and BP was monitored once per minute. An 18-gauge IV catheter was inserted on the upper limb for administration of lactated Ringer's solution. Before anesthesia induction, the patients breathed 100% oxygen, fresh gas flow 10 L/min, through a tight-fitting facemask for a minimum of 3 min and until end-expired oxygen concentration was 90%. Then, propofol 2 mg/kg, drugs labeled with "2" and "3" were injected sequentially. The injection of propofol lasted for about 10 s, so did remifentanil injection. After loss of eyelash reflex, drugs labeled with "3" were injected within 5 s. Time recording commenced after injection. Sixty seconds after administration of drugs labeled with "3", tracheal intubation was attempted by an experienced anesthesiologist blinded to the grouping of the study, and the intubation conditions were graded using the Copenhagen Consensus Conference criteria (**Table 1**) [3]. Breathing circuit of anesthesia machine was connected after intubation, while mechanical ventilation was not done, and there was no fresh airflow in circuit. Patients were patted on the shoulder and called by name every 10 s, and the breathing activity was intensively monitored. If the well-formed wave form emerged on capnogram or the patient opened eyes, time recording ceased, and the duration was defined as apnea time. Meanwhile, intravenous injection of propofol 1 mg/kg, sufentanil 0.5 μg/kg and

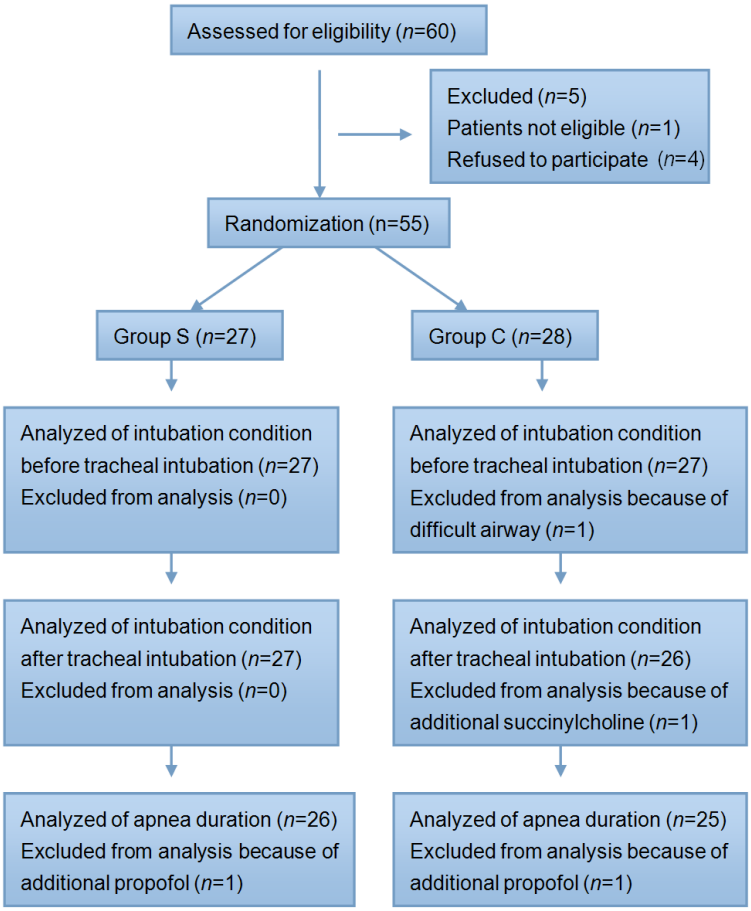

Figure 1. Flow chart showing the flow of subjects through the trial.

rocuronium bromide 0.6 mg/kg was performed by another anesthesiologist immediately, and anesthesia machine was switched on for mechanical ventilation.

No positive pressure ventilation was conducted during observation after induction and intubation. The changes of SpO_2 were monitored, and positive pressure ventilation commenced only if SpO_2 decreased to 90% and spontaneous breathing was not recovered, then observation ceased. The number of hypoxic events in each group was recorded.

An additional injection of succinylcholine 1 mg/kg was performed in case of intubation failure due to unfavorable muscle relaxation, and intubation was attempted again 1 min later, while such a patient was not included in observation of apnea time. Severe cough after intubation should be managed with additional dose of propofol, and such a patient was also withdrawn from recording of apnea time. If Cormach-Lehane grade [4] 3 to 4 was found at laryngoscopic exposure, and laryngeal exposure was not improved after supplementation of succinylcholine 1 mg/kg, then video laryngoscopic intubation was carried out, and such a patient was confirmed as difficult airway and excluded from the study.

HR and BP were recorded before anesthesia (T0), the moment before intubation (T1) and 1 min after intubation (T2), and all patients were followed up after operation for intraoperative awareness and hoarseness.

In the study of Stefanutto et al [1], the prevalence of unaccepted intubation conditions was 33.3% under anesthesia induction with remifentanil 1.5 μg/kg combined with propofol. We assumed that the application of small dose of succinylcholine would improve the intubation conditions, therefore, there would be small possibility for unaccepted intubation conditions, the prevalence of which might not surpass 5%. In this way, with a=0.05 (one-tailed test), in order to achieve differences between two groups, the sample size was supposed to be at least 21 in each group to attain a power of 80%. Considering the potential exclusion or withdraw, a total of 60 patients were included in this study ultimately.

The normal distribution test was performed for continuous variables and data were presented as mean ± SD. Differences between two groups were analyzed using Student's t test for continuous variables or Chi-square test (Fisher's exact test) for categorical variables. Changes in cardiovascular variables from baseline were analyzed by paired t tests. Statistical analysis was performed using SPSS version 21 (SPSS, Inc., Chicago, IL, USA). $P<0.05$ was considered statistically significant.

Results

Among all the 60 patients, 5 patients were withdrawn before anesthesia. After anesthesia

Table 2. Comparison of demographic data

	Group S (n=27)	Group C (n=27)	*P* value
Age (years)	38.41 ± 10.90	36.26 ± 9.90	0.452
Weight (kg)	58.07 ± 7.01	58.22 ± 7.88	0.942
Height (cm)	161.30 ± 4.65	161.85 ± 4.38	0.653
ASA score (I/II)	16/11	14/13	0.784

Values are mean ± SD or number.

Table 3. Comparison of intubation conditions

	Group S				Group C				*P* value
	n	Excellent	Good	Poor	n	Excellent	Good	Poor	
Before intubation	27	24	3	0	27	19	7	1	0.175
Post intubation	27	24	2	1	26	5	10	11	0.000

Values are number.

Table 4. Comparison of ventilatory variables

	Group S (n=26)	Group C (n=25)	*P* value
SpO_2<95%	2 (7.69%)	1 (4.0%)	1.000
SpO_2<99%	3 (11.54%)	2 (8.0%)	1.000
Apnea time (s)	245.50 ± 53.71 (113-321)	251.12 ± 70.71 (135-375)	0.750

Values are mean ± SD (range) or number (%).

Table 5. Comparison of hemodynamic data

		Group S (n=27)	Group C (n=26)	*P* value (between groups)
HR	T0	79.2 ± 12.5	77.2 ± 11.7	0.567
	T1	76.8 ± 12.7	67.5 ± 11.8	0.010
	T2	81.4 ± 12.4	79.0 ± 15.1	0.533
SBP	T0	115.8 ± 13.2	117.4 ±10.9	0.634
	T1	100.8 ± 10.1	100.4 ± 12.7	0.909
	T2	105.6 ± 13.6	103.6 ± 13.2	0.586
DBP	T0	66.9 ± 8.1	68.6 ± 8.6	0.466
	T1	58.3 ± 10.6	56.1 ± 11.4	0.490
	T2	59.5 ± 9.7	59.3 ± 11.5	0.962

T0: the moment before anesthesia; T1: the moment before intubation; T2: 1 min after intubation. Data are mean ± SD. HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure.

induction, 1 patient in group C was graded as 4 in Cormach-Lehane grading, and was not improved in laryngeal exposure after addition of succinylcholine, then was transferred for video laryngoscopic intubation. This patient was also excluded from the study. Ultimately, 27 patients in each group completed the study and entered statistical analysis (**Figure 1**).

There was no significant difference in demographic data such as age and body weight between two groups (**Table 2**).

The intubation conditions of 1 patient (3.70%) in group S were graded as poor, and the percent was significantly lower than that in group C (n=12, 44.4-4%) (P<0.001). **Table 3** demonstrated a further evaluation on intubation conditions of two groups, with "Ease of laryngoscopy", "Vocal cord position" and "Vocal cord movement" as pre-intubation conditions and "Airway reaction" and "Movement of limbs" as post-intubation conditions. Glottal closure was observed by laryngoscope in 1 patient in group C, and succinylcholine 1 mg/kg was supplemented, then intubation was successfully performed. The pre-intubation conditions of this patient were graded as poor, and post-intubation evaluation was not carried out, therefore, a total of 26 patients participated in the evaluation of post-intubation conditions in group C. As revealed by **Table 3**, the pre-intubation conditions were similar between two groups, while significantly more patients in group C were graded as poor in post-intubation conditions. The intubation conditions in group C, which were characterized by obvious cough and limb movement after intubation in more than 40% of patients, were poorer than those in group S.

Additional succinylcholine was administered for 1 patient in group C before intubation, and propofol was supplemented to control cough after intubation in 1 patient in group S and another patient in group C. These three patients were excluded from apnea time analysis. There was no significant difference in apnea time after

induction between two groups (**Table 4**). No hypoxic event with SpO_2<90% before recovery of spontaneous breathing was observed in all patients (**Table 4**).

There was no significant difference in baseline HR, SBP and DBP between two groups. In group C, HR was significantly decreased at T1 time point, and recovered to baseline level at T2 time point. There was no significant change in HR among different time points in groups S. HR at T1 time point in group C was lower than that in group S. SBP and DBP at T1 and T2 time points in both groups were moderately decreased, while there was no significant difference between two groups at each time point (**Table 5**).

Post-operative follow-up revealed that there was no incidence of intraoperative awareness and hoarseness in both groups.

Discussion

Many studies have indicated that remifentanil combined with propofol for anesthesia induction may achieve tracheal intubation in the absence of muscle relaxants. However, a lot of studies confirmed that only large dose of remifentanil (3 to 4 μg/kg) could lead to satisfactory intubation conditions [5-9]. The velocity of remifentanil injection was lower in all of these studies, and a complete injection took 30 to 90 s. Recently, Stefanutto et al [1] administered the drugs as bolus doses in rapid succession, and both injection of remifentanil and propofol was done in 5 to 10 s. It was concluded that more than 90% volunteers achieved acceptable intubation conditions under anesthesia induction with remifentanil 2 μg/kg and propofol 2 mg/kg, while the mean apnea time was 6.1 min, leading to serious desaturation (SpO_2<80%) in one third of volunteers. Decreasing the remifentanil dose to 1.5 μg/kg decreased, but did not abolish, the risk of desaturation, and the intubation conditions were no longer satisfactory.

In the studies mentioned above, remifentanil was applied before propofol injection. Trabold et al [10] reported that the velocity of remifentanil to reach the effective concentration in brain was significantly higher than that of propofol, and the administration of remifentanil after propofol could improve the intubation conditions. In the study of Trabold et al [10], the dose of remifentanil was only 1 μg/kg, that of propofol was 2.5 mg/kg, and the percent of unacceptable intubation conditions decreased from 40% to 6.7% after changing the order of drug administration.

In this study, we also investigated the intubation conditions after combination use of remifentanil 1.5 μg/kg and propofol 2 mg/kg. However, the sequence of drug administration that remifentanil was given after propofol was different from that of Stefanutto et al [1]. Without considering apnea time, Trabold et al [10] used higher doses of propofol (2.5 mg/kg). However, we tried to both improve the intubation conditions and shorten the apnea time. Based on the pharmacokinetics differences of propofol and remifentanil, we chose the minimum recommended dose of propofol (2 mg/kg) in clinics [11] for anesthesia induction for intubation without muscle relaxation, and 2 mg/kg is also the dose commonly used to facilitate tracheal intubation in combination with the potent opioids.

Previous studies [2, 12, 13] have revealed that 0.6 mg/kg is the minimum effective dose for satisfactory intubation conditions for succinylcholine, which may lead to significantly shorter apnea time than 1 mg/kg. In these studies, fentanyl combined with propofol was adopted for anesthesia induction. It is undetermined whether remifentanil may outperform fentanyl in decreasing apnea time, and it is also unclear whether the adjusted induction regimen is better than single use of propofol/remifentanil for intubation without muscle relaxation in management with CICV scenario.

The intubation conditions in group C in this study were similar with those in the study of Stefanutto et al [1], while the apnea time seemed to be shorter than the latter (251.12 ± 70.71 min vs 282 ± 90 min). More importantly, the prevalence of hypoxic events in the study of Stefanutto et al [1] was significantly higher than that in this study (33% vs 0%), which might be related to the order of drug administration or gender distribution of the study objects. All the study objects in this study were females, while most of the objects in the study of Stefanutto et al [1] were males (11/12). It is known to all that the basic metabolic rate of males is higher than that of females, and the oxygen consumption of

males is larger than that of females, it is assumed that males may be more susceptible to hypoxia in the absence of ventilation.

This study indicated that compared with single use of propofol/remifentanil for anesthesia induction, succinylcholine 0.6 mg/kg significantly improved the intubation conditions, with satisfactory or acceptable intubation conditions in more than 95% patients, and did not increase the apnea time. At about 4 min, the spontaneous breathing recovered in patients in both groups, and no hypoxic events with SpO_2<90% or more severe hypoxemia with SpO_2<80% occurred. Therefore, small dose of succinylcholine combined with propofol and remifentanil can be used for anesthesia induction to provide favorable intubation conditions and help to recover spontaneous breathing in case of CICV scenario to prevent from serious consequences. If more attention is paid to pre-intubation conditions in dealing with difficult airway, propofol/remifentanil for anesthesia induction without muscle relaxation may also be feasible to some extent. Because the poor intubation conditions of this induction regimen are characterized by obvious cough and limb movement in more patients, while the pre-intubation conditions are acceptable in 95% patients, so it is a candidate regimen under some circumstances such as contraindication to succinylcholine. However, cough may result in increased intracranial pressure and intraocular pressure, can cause serious consequences in patients with existing high intracranial pressure and intraocular pressure, and may lead to severe bronchospasm in those with asthma [14], the potential risks should be considered in employment of this regimen. Therefore, the regimen with small dose of succinylcholine is more appropriate in common sense.

Recently sugammadex, a novel muscle relaxant antagonist, has drawn extensive attention. Lee et al [15] reported that large dose of sugammadex could quickly reverse the neuromuscular block effect of rocuronium, which seemed to be outstanding in management with CICV scenario. But the reverse of muscle relaxation does not promise the instant recovery of breathing [16], just as the breathing suppression caused by propofol and remifentanil lasted for a certain period of time in the absence of muscle relaxants in group C of this study. Therefore, more evidences are needed to prove the role of sugammadex in management of CICV. On the other hand, sugammadex may not soon be widely used in clinics due to the economic reasons [17], and small dose of succinylcholine may be applied to cope with CICV for a considerably long time.

There are some limitations for this study. Firstly, all the study objects were females. Just as mentioned above, the basic metabolic rate of males is higher than that of females, and males may be more susceptible to hypoxia. On the other hand, higher basic metabolic rate may lead to faster drug metabolism and faster recovery of spontaneous breathing. Which of the above two factors may take the major role is undetermined; therefore, the effects of two regimens in this study on male patients leave for investigations. Secondly, the body weight of patients included in this study was normal, and whether the same findings can be yielded in obese patients is unknown. For patients with obesity, doses of induction drugs can not be calculated based on actual body weight, while whether ideal body weight or fat-free body weight [18, 19] should be adopted is unclear. Especially, the data on changes of intubation conditions and apnea time of obese patients are unavailable. However, it is certain that patients with morbid obesity have shorter duration in hypoxia tolerance, and it is imperative to enroll such patients for further investigations. Thirdly, the dose of succinylcholine (0.6 mg/kg) used in this study was based on the findings of El-Orbany et al [2], which was the minimum effective dose. However, the opioids adopted by El-Orbany et al [2] was fentanyl, while remifentanil can help to improve the intubation conditions, the minimum effective dose of succinylcholine may be decreased with combination use of remifentanil 1 μg/kg. Therefore, 0.6 mg/kg may not be the optimal dose in this induction regimen, and the proper dose of succinylcholine may be determined through dose-effect relationship investigations in future.

In conclusion, compared with single use of remifentanil 1.5 μg/kg, the combination use of remifentanil 1 μg/kg and succinylcholine 0.6 mg/kg may offer better intubation conditions and may not prolong apnea time under anesthesia induction with propofol 2 mg/kg, which may be beneficial in case of CICV.

Disclosure of conflict of interest

None.

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