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Original Article

Effects of priming with mivacurium on histamine release and muscle relaxation

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Abstract: *Objective:* The aim of this study was to investigate the effects of priming with mivacurium (MIV) on histamine release and muscle relaxation. *Methods:* Forty patients undergoing elective surgery were selected and randomly divided into groups A, B, C, and D (n = 10 each). Five minutes after induction of anesthesia using propofol (PRO) and sufentanil (SUF), group A received saline, and groups B, C, and D received priming doses of MIV of 0.014 mg/kg, 0.021 mg/kg, and 0.028 mg/kg, respectively. The priming interval was 2 min for each group. *Results:* After priming, groups B, C, and D received a residual dose of MIV, and 2 ml of venous blood was then sampled at different time points (before MIV injection, T0; 2 min after MIV injection, T1; and 5 min after MIV injection, T2) to measure the plasma histamine concentration. The mean arterial blood pressure (MAP) and heart rate (HR) of each patient were also recorded at the corresponding time points, together with muscular relaxation monitoring. Compared with group A, the onset times of MIV in groups B, C, and D were significantly shorter, the plasma histamine concentrations and HRs at T1 were lower, but MAP was higher. Compared with group B, the plasma histamine concentration at T1 in group D was lower ($P < 0.05$). *Conclusions:* Priming with MIV can effectively reduce MIV-induced histamine release and the incidence of side effects, and it can shorten the onset time of muscle relaxation. Increasing the priming dose can further reduce histamine release.

Keywords: Priming principle, mivacurium, histamine, muscle relaxant effects

Introduction

Mivacurium (MIV) belongs to a group of benzyl isoquinoline nondepolarizing muscle relaxants and is used in short surgeries. Compared with traditional intermediate-acting muscle relaxants, such as cisatracurium, rocuronium (ROC), and others, MIV has a shorter *in vivo* effect duration, and its significant advantage of a short duration of action can reduce the effects of residual muscle relaxants on anesthesia and tracheal extubation [1]. The onset of muscle relaxation caused by MIV administration is slow [2]; although increasing the dose can speed up the onset rate, the dose for intubation can still induce histamine release in a dose-dependent manner [3]. Increasing human endogenous histamine can result in changes in the circulatory and respiratory systems, thus affecting the clinical safety and use of MIV. Histamine is an important active amine in humans, and the normal plasma concentration under physiological conditions is 0.3-1.0 ng/mL [4]. When allergic reactions occur, mast cells and basophils release histamine, which then acts on the histamine receptors in tissues and organs, thus directly causing such adverse reactions as vasodilation, increases in vascular permeability, heart rate acceleration, smooth muscle contraction, mucus secretion, etc. When the histamine concentration exceeds 10 ng/mL, it may induce bronchospasm or cardiac arrest [5]. Muscle relaxants are one of the most important factors during anesthesia that can trigger allergic reactions, which induce the release of histamine via the mechanisms of immune response and nonimmune response. The priming technique has multiple applications in clinical anesthesia and can effectively reduce the onset time of nondepolarizing muscle relaxants [6], but its effects on MIV-induced histamine release and muscle relaxation have not been previously reported. This study was designed to evaluate the effects of priming with MIV on histamine release and muscle relaxation.

Table 1. Comparison of general information among the four groups

	Group A	Group B	Group C	Group D	F value	*P* value
n	10	10	10	10		
Gender(M/F)	5/5	4/6	6/4	5/5		
Age (years)	39.9 ± 14.2	47.0 ± 12.1	47.0 ± 11.5	41.2 ± 13.5	0.8529	0.4743
BMI (kg/m^2)	23.9 ± 2.7	23.9 ± 2.6	23.5 ± 2.0	24.8 ± 2.3	0.9438	0.4297

Values are mean ± SD or number of patients. Differences were not significant among groups.

Materials and methods

General information

This study was approved by the ethics committee of the Affiliated Gongli Hospital to the Second Military Medical University, and signed informed consent was obtained from all patients or their families. The clinical trial was conducted in full accordance with the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. Forty patients undergoing elective surgery were selected. These patients were aged 18-60 years, and had body mass indexes (BMIs) of 18-25 kg/m^2 and American Society of Anesthesiologists (ASA) grades I-II. No patients had a history of asthma; heart, lung, liver, or kidney dysfunctions; acid-base imbalances; water-electrolyte metabolic disorders; neuromuscular disease; hypertension; or diabetes. No patients were taking drugs preoperatively that would affect neuromuscular function, histamine receptor agonists, or antagonists.

Anesthesia and grouping

All patients were fasted routinely and were not administrated any medications before the surgery. After entering the operating room, the bilateral elbow vein of each patient was opened, and all drugs were intravenously injected via the left elbow vein. The blood pressure (BP), heart rate (HR), peripheral oxygen saturation (SpO_2), and bispectral index (BIS) of each patient were routinely monitored. The 40 patients were randomly divided into groups A, B, C, and D, with 10 patients in each group. Patients were intravenously injected with midazolam 0.05 mg/kg, sufentanil 0.3 μg/kg, and propofol 1.5 mg/kg in sequence for anesthesia induction. After the eyelash reflex disappeared, one scaling neuromuscular monitor was used to perform the train of four (TOF) and calibrate the TOF watch. Five minutes after anesthesia induction, group A received saline; groups B, C, and D received MIV (GSK Co., Ltd., batch No: 4507) 0.014 mg/kg (20% ED95), 0.021 mg/kg (30% ED95), and 0.028 mg/kg (40% ED95), respectively. Two minutes after priming, the rest doses were administered (group A: 0.21 mg/kg, group B: 0.196 mg/kg, group C: 0.189 mg/kg, and group D 0.182 mg/kg), and the administration times did not exceed 5 s. Tracheal intubation was performed after the venous blood samples were obtained for mechanical ventilation, and the partial pressure of exhaled CO_2 ($PETCO_2$) was maintained at 30-40 mmHg. Each patient was continuously administered intravenously infused propofol 25-35 mg/h and remifentanil 0.15-0.20 μg/kg/min, and BIS was maintained within 40-60. Meanwhile, routine thermal insulation measures were performed, and the skin temperature of the hand with the neuromuscular monitor was ≥ 32°C.

Determination of histamine concentration and hemodynamic monitoring

A 2-ml sample of venous blood was drawn from the right elbow vein before MIV injection (T0), 2 min after MIV injection (T1), 5 min after MIV injection (T2), and after anticoagulation with heparin (heparin was used as an anticoagulant instead of ethylene diamine tetraacetic acid [EDTA], which is recommended by the official instructions with the histamine enzyme-linked immunosorbent assay [ELISA] kit). The blood sample was centrifuged at 4°C and 3000 revolutions/min for 5 min; plasma was then separated and stored at -20°C. The human histamine ELISA kit (Demeditec, Germany, Batch No: DEE1000) was used to determine the plasma histamine concentration. The mean arterial blood pressure (MAP) and HR at T0, T1, and T2 were recorded; skin reactions were also observed.

Table 2. Comparison of muscle relaxant effects among the four groups (n = 10)

	Group A	Group B	Group C	Group D	F value	*P* value
Onset time (s)	183 ± 48	141 ± 18*	132 ± 30**	117 ± 21***	8.145	0.0003
T5 (min)	12.5 ± 4.1	15.2 ± 5.6	12.8 ± 2.8	13.6 ± 4.1	0.7807	0.5125
T25 (min)	16.6 ± 4.3	20.2 ± 7.0	15.9 ± 3.1	17.3 ± 4.6	1.49	0.2336
Total recovery time (min)	27.0 ± 6.8	33.5 ± 8.8	27.1 ± 4.5	27.7 ± 5.9	2.181	0.1072
Recovery index	4.7 ± 3.3	7.1 ± 2.1	6.0 ± 1.9	5.2 ± 0.9	2.234	0.101

Values are mean ± SD. Compared with group A, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Table 3. Comparison of plasma histamine concentrations in the four groups at different time points

	n	Histamine (ng/ml)			F value	*P* value
		T_0	T_1	T_2		
Group A	10	0.40 ± 0.11	2.98 ± 0.70[a]	0.98 ± 0.11	106.892	< 0.001
Group B	10	0.44 ± 0.01	1.71 ± 0.21[a,b]	0.89 ± 0.13	203.584	< 0.001
Group C	10	0.45 ± 0.13	1.61 ± 0.22[a,b]	0.72 ± 0.21	101.033	< 0.001
Group D	10	0.48 ± 0.10	1.09 ± 0.57[a,b,c]	0.69 ± 0.23	7.429	0.003
F value		1.117	28.384	6.074		
P value		0.355	< 0.001	0.002		

Values are mean ± SD or number of patients. Values are mean ± SD or number of patients. compared with T0, [a]P < 0.05; compared with group A, [b]P < 0.05; compared with group B, [c]P < 0.05. Group A: T1-T0: t = 11.514, P < 0.001. Group B: T1-T0: t = 19.103, P < 0.001. Group C: T1-T0: t = 14.355, P < 0.001. Group D: T1-T0: t = 3.333, P = 0.003. T1: B-A: t = 5.495, P < 0.001. C-A: T = 5.904, P < 0.001. D-A: T = 6.621, P < 0.001. D-B: t=3.228, P = 0.004.

Neuromuscular monitoring

Each patient was connected to a TOF-Watch SX neuromuscular monitor (OrganonTeknika, Netherlands) prior to anesthesia induction; the sensor was fixed to the palm side of each patient's thumb, and the associated electrode was placed on the skin surface of the ipsilateral wrist ulnar nerve. Neuromuscular monitoring data were transferred to a per-sonal computer using a fiberoptic cable (TOF-Link®) and saved using TOF-Watch® SX Monitor software (Organon Ltd.). TOF (current: 50 mA, pulse width: 0.2 ms, frequency: 2 Hz, and inter-string interval: 15 s) was then performed, and the following were recorded: onset time of the muscle relaxant injections (from the end of all MIV injections to recovery of the first twitch from the TOF response to 0), recovery of the first twitch from the TOF res-ponse to 5% and 25% (T5, T25) relative to baseline, and recovery index (time between 25% and 75% recovery of first twitch). Total recovery time (the time between administration of mivacurium and a TOF ratio of 0.95) was also recorded.

Statistical analysis

SPSS 13.0 software was used for the statistical analysis; the measurement data were expressed as mean ± standard deviation. Comparisons between groups were performed using one-way analysis of variance (ANOVA), pairwise comparisons were performed using Tukey's test, and comparisons within groups were performed using ANOVA of repeat measurements, with $P < 0.05$ considered to be statistically significant.

Results

General information

The gender composition, age, and BMI among different groups had no statistical significance ($P > 0.05$, **Table 1**).

Comparison of muscle relaxant effects

Compared with group A, the onset times in groups B, C, and D decreased significantly ($P < 0.05$), but there were no statistical differences among groups B, C, and D ($P > 0.05$). There were no significant differences in T5, T25, total recovery time, or recovery index ($P > 0.05$, **Table 2**).

Plasma histamine concentrations before and after the injection

The plasma histamine concentrations in the four groups were increased at T1 ($P < 0.05$), but showed no statistical differences at T0 or T2 (*P*

Table 4. Comparison of mean arterial pressure (MAP) in the four groups at different time points

	MAP (mmHg)			F value	*P* value
	T_0	T_1	T_2		
Group A	80.1 ± 7.8	67.1 ± 8.7[a]	82.9 ± 7.9	10.719	< 0.001
Group B	80.3 ± 7.1	73.5 ± 5.3[a,b]	78.8 ± 5.3	3.592	0.041
Group C	80.4 ± 6.8	74.1 ± 5.3[a,b]	83.9 ± 4.8	7.599	0.002
Group D	80.1 ± 6.3	74.6 ± 6.4[a,b]	80.7 ± 6.1	5.877	0.004
F value	0.0054	2.855	1.382		
P value	1	0.05	0.264		

Values are mean ± SD. compared with T0, [a]P < 0.05; compared with group A, [b]P < 0.05. MAP: A: T1-T0: t = 3.518, P = 0.002. B: T1-T0: t = 2.427, P = 0.025. C: T1-T0: t = 2.311, P = 0.032. D: T1-T0: t = 2.937, P=0.023. T1: B-A: t = 1.987, P = 0.062. C-A: t = 2.173, P = 0.043. D-A: t = 2.196, P = 0.041.

> 0.05). The plasma histamine concentrations in groups B, C, and D at T1 were lower than those of group A ($P < 0.05$). The plasma histamine concentration in group D at T1 was lower than that of group B ($P < 0.05$), but there was no significant difference in plasma histamine concentration between groups B and C at T1 ($P > 0.05$, **Table 3**).

Hemodynamic changes and adverse reactions

The four groups all showed MAP reduction at T1. MAPs in groups B, C, and D at T1 were higher than that in group A ($P < 0.05$), but there were no statistically significant differences in MAPs between T0 and T2 for any group ($P > 0.05$). The four groups all exhibited HR increases at T1. Compared with group A, the HRs in groups B, C, and D at T1 decreased ($P < 0.05$), but there were no statistically significant differences in HR between T0 and T2 for any group ($P > 0.05$). After MIV injection, there were 3, 2, 0, and 1 cases of skin symptoms (flushing) in groups A, B, C, and D, respectively (**Tables 4** and **5**).

Discussion

The onset times in groups B, C, and D were 141 ± 18 s, 132 ± 30 s, and 117 ± 21 s, respectively; these times were significantly shorter than the onset times observed in group A (183 ± 48 s, $P < 0.05$). Therefore, this study confirmed that priming can significantly reduce the onset time of nondepolarizing muscle relaxants. Although group D exhibited a significantly different onset time from that of group A ($P < 0.001$), there were no significant differences among groups B, C, and D.

In terms of the maintenance and restoration of muscle relaxation, the T5, T25, total recovery time, and recovery index measurements in the three priming groups showed no significant difference from group A ($P > 0.05$). This result was consistent with the study by Jung *et al*. [7], which concluded the following in comparing the duration and recovery index of cisatracurium and priming with ROC before cisatracurium administration: priming can speed up the onset time of cisatracurium, but has no effect on the maintenance and recovery.

MIV, a nondepolarizing muscle relaxant, has been used in clinical practice. According to previous studies, the total recovery time with 0.20 mg/kg MIV (3ED95) is 17.7 ± 6.4 min [2], and MIV is suitable for short procedures such as ear, nose, and throat surgeries. Administration of antagonistic drugs is not required during the recovery period with MIV, so potential side effects of those drugs can be avoided. However, MIV is not an entirely ideal muscle relaxant, and it has the distinct disadvantage of a long onset time. Dieck *et al*. [2] used a combination of MIV, propofol, and remifentanil for anesthesia induction, and found the onset time of 0.20 mg/kg (3ED95) MIV to be 4 min.

The known methods for accelerating the onset of nondepolarizing muscle relaxants include using large doses of medication, priming, and medical combinations. MIV is associated with dose-dependent histamine release, and a large histamine release can severely affect the circulatory and respiratory systems; therefore, increasing the amount of MIV to shorten the onset time is not desirable. Priming is commonly used in clinical practice to shorten the onset times of muscle relaxants. In general, the muscle relaxant is administered with the intubation dose twice during anesthesia induction. The first injection dose is typically 1/10 to 1/6 of the total dose; after a few minutes, the rest of the dose is administered to accelerate the onset. The priming muscle relaxant occupies about 70% of the N2 cholinergic receptors in advance without producing clinically significant muscle relaxation effects; when the priming dose reaches its peak effect, the intubation-dose muscle relaxant will rapidly occupy 90% to 92% of the receptors, so the

Table 5. Comparison of heart rate (HR) and skin symptoms (flushing) among the four groups

	HR (beats/min)			F value	*P* value	Skin flushing
	T_0	T_1	T_2			
Group A	70.8 ± 6.7	97.4 ± 7.7[a]	70.6 ± 6.1	50.422	< 0.001	3
Group B	66.4 ± 7.7	84.0 ± 8.1[a,b]	68.1 ± 8.6	14.218	< 0.001	2
Group C	65.2 ± 7.4	79.2 ± 7.3[a,b]	63.9 ± 8.1	12.432	< 0.001	0
Group D	65.5 ± 8.3	76.9 ± 8.6[a,b]	69.9 ± 7.6	4.943	0.015	1
F value	1.187	13.349	1.542			
P value	0.328	< 0.001	0.22			

Values are mean ± SD or number of patients. compared with T0, [a]P < 0.05; compared with group A, [b]P < 0.05. HR: A: T1-T0: t = 8.241, P < 0.001. B: T1-T0: t = 4.98, P < 0.001. C: T1-T0: t = 4.259, P < 0.001. D: T1-T0: t = 3.096, P = 0.006. T1: B-A: t = 3.792, P = 0.001. C-A: t = 5.424, P < 0.001. D-A: t = 5.616, P < 0.001.

onset of muscle relaxation is significantly accelerated [8].

Factors in the use of priming to reduce the onset time of muscle relaxants include the priming dose, priming interval, and type of muscle relaxant [9]. There are numerous clinical studies on the use of priming techniques for muscle relaxants, but the results vary. Yavascaoglu *et al.* [10] studied the influence of the priming technique on the onset time of ROC and intubating conditions, and found that the onset time of ROC 0.10 mg/kg (33% ED95) is significantly shorter than that of ROC 0.06 mg/kg (20% ED95), and that the use of a 3-min priming interval is more effective than that of a 2-min interval. However, Li *et al*. [11] concluded that preinjecting 30% ED95 ROC facilitates shortening of the onset time of cisatracurium and prolongs the recovery time, and that the optimal priming interval is 2 min; this conclusion regarding the priming interval differs from those of the studies described above. For a long time, the priming dose selections were also controversial. Although Yavascaoglu *et al*. [10] confirmed that increasing the priming dose of ROC can shorten the onset time, its side effects cannot be ignored, especially when using a larger priming dose, and patients often experience muscle weakness and anxiety when they awake [12]. Kopman *et al.* [13] demonstrated that increasing the priming dose may increase the risk of side effects, even at a 10% ED95 dose of the muscle relaxant; even though this dose is small, it can still produce clinically detectable muscle relaxant effects. This study set 2 min as the priming interval and set the priming doses at 20%, 30%, and 40% ED95 MIV. To avoid uncomfortable experiences by conscious patients, priming doses of the muscle relaxant were administered after the patients fell asleep.

MIV is metabolized by pseudocholinesterase (butyrylcholinesterase), and its effect is significantly prolonged in the presence of enzyme abnormalities. Butyrylcholinesterase deficiency was recently identified as a major risk factor for distressing awareness during emergence from anesthesia. Since a lack of neuromuscular monitoring significantly increases this risk, neuromuscular monitoring should be utilized even when using short-acting neuromuscular blocking agents such as mivacurium [14].

Compared with other commonly used nondepolarizing muscle relaxants (such as ROC, vecuronium, or cisatracurium), the intubation dose of MIV can induce a significant histamine release, thus resulting in adverse effects on patients' circulatory and respiratory systems [1]. Studies have demonstrated that pretreatment using histamine receptor antagonists (such as promethazine or ranitidine) can effectively weaken the histamine release action of MIV [15-17]. However, promethazine causes central inhibition effects; when combined with various anesthetic drugs, it may induce delayed recovery. Ranitidine may induce nausea and vomiting, and may increase the risks associated with anesthesia induction. Savarese *et al.* [3] studied the effects of MIV on the circulatory system and found that reducing the injection speed (60 s produced better results than did 10-15 s) or reducing the dose can effectively reduce the plasma histamine level. However, significantly slowing the injection speed (60 s) increases the induction time, and reducing the dose of muscle relaxants reduces the onset rate; in both cases, the risks of regurgitation and aspiration increase. Priming has been proven to effectively accelerate the onset times of nondepolarizing muscle relaxants; thus, priming is widely used in clinical anesthesia applications. However, the effects of priming on MIV-induced histamine release have not been reported.

To avoid interference from other anesthesia induction drugs and to control the duration of MIV-induced histamine release within 1-5 min [1], this study evaluated plasma histamine concentrations at 5 min after the induction drug was injected, as well as at 2 and 5 min after the muscle relaxant was injected. The plasma histamine concentration in group A at 2 min after 0.21-mg/kg MIV injection was 2.98 ng/ml. In Naguib's study [1], which utilized the same dose and medication time as this study, the mean plasma histamine concentration at 1 min after injection was 2.10 ng/ml. The results varied slightly due to different plasma histamine detection time points. Compared with group A, histamine release in the other three groups decreased significantly; increasing the priming doses resulted in commensurate decreases in histamine release. There are several possible reasons for this result. First, priming with MIV effectively extends the medication time, and slowing the injection speed can reduce MIV-induced histamine release. Second, after priming, the additional dose can be reduced, possibly resulting in a reduction in histamine release; a larger priming dose may reduce the need for an additional dose. Third, histamine release is a self-limiting process that can produce rapid tolerance after repeated medication. When the first-time intravenous injection of the muscle relaxant produces a histamine release, there will be no additional release of histamine if the second dose is not higher than the first dose [18].

Histamine acts on the histamine receptors in tissues and organs (H1, H2, H3), and the human body is very sensitive to increases in histamine concentration, especially in the circulatory system. Histamine can act on the H1 and H2 receptors, thus resulting in positive chronotropic and double inotropic effects in the heart; furthermore, it can expand the peripheral arteries and partial coronary blood vessels, and reduce the venous return [19]. When histamine acts on the H3 receptor, it can regulate the release of a variety of neurotransmitters, thus reducing the HR and myocardial contractility [20]. In addition, it can stimulate the adrenal medulla via the H2 receptor to release catecholamine, further accelerating the HR [21]. In this study, the MAP in group A at T1 decreased an average of 16%, and the HR increased an average of 24%. The MAP at T1 decreased an average of 8% in the priming groups, and the HR increased approximately 20%. The adverse effects on the circulatory system were significantly reduced in the three priming groups. This study also confirmed the dose-dependent characteristics of histamine's influence on the circulation system. There were significantly fewer cases with skin symptoms in groups C and D than in group A, and group C had no patients exhibiting skin symptoms. However, the patients in group C still exhibited circulatory effects. Therefore, the MIV-induced release of histamine causes circulatory system and skin symptoms that have no correlation with each other, and skin symptoms cannot be used to evaluate the effects on the circulatory system.

In summary, priming with MIV can both increase the onset rate of muscle relaxation and reduce the release of histamine and its adverse effects. Furthermore, increasing the priming dose can further reduce histamine release. However, when using a larger priming dose, patients may experience muscle weakness and anxiety when they wake up. In clinical practice, a priming dose of 20-30% ED95 MIV should be used with caution.

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Disclosure of conflict of interest

None.

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