

Effects of methylprednisolone on the duration of rocuronium-induced neuromuscular block

A randomized double-blind trial

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Abstract

Background: We aim to investigate whether intraoperative use of methylprednisolone could affect the duration of rocuronium-induced neuromuscular blockade.

Methods: A double blind, randomized, placebo-controlled trial was conducted. A total of 136 patients underwent gynecologic laparoscopic surgery were randomly divided into 3 groups: pregroup, receiving intravenous injection of methylprednisolone (40 mg) 30 minutes before induction of anesthesia; postgroup, receiving intravenous injection of methylprednisolone (40 mg) immediately after induction of anesthesia and intubation; and control group, receiving intravenous injection of normal saline. Patients were intravenously administrated with rocuronium 0.6 mg/kg, and changes in adductor pollicis evoked twitch responses were measured by ulnar nerve stimulator.

Results: We found that all patients achieved maximum blockade effects, and there was no difference in onset time among the 2 groups. For time required to achieve train-of-four ratio (TOFR) 90%, pregroup (64.50 ± 10.52 minutes) and postgroup (65.29 ± 11.64 minutes) were significantly shorter than that of the control group (71.04 ± 10.55 minutes, $P = .027$), whereas clinical duration and total duration were significantly shorter in the 2 groups received methylprednisolone than the control group. However, there was no significant difference between the 2 treatment groups either in clinical duration and total duration of muscle relaxants, or time required to achieve TOFR 90%. No significant difference was found in recovery index among the 3 groups.

Conclusion: Our findings suggest that a single intravenous injection of methylprednisolone, no matter preoperatively or intraoperatively, could shorten the duration of rocuronium-induced neuromuscular blockade.

Abbreviations: PONV = postoperative nausea and vomiting, TOF = train-of-four, TOFR = TOF ratio.

Keywords: intraoperative, methylprednisolone, rocuronium-induced neuromuscular blockade

1. Introduction

Corticosteroid could affect the effect of muscle relaxant. Some *in vitro* studies found that betamethasone attenuated the effects of nondepolarizing muscle relaxants, and this action was similar to other various nondepolarizing muscle relaxants.^[1] Soltesz et al^[2] had shown that for patients with long-term use of prednisolone, rocuronium had a prolonged onset time of muscle relaxation while the duration of action was shortened. Case reports suggested that patients with long-term oral prednisone had complete resistance to a maximal dose of rocuronium.^[3]

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However, currently, information about the effects of single relevant perioperative corticosteroids on muscle relaxation is relatively limited. One clinical study observed that dexamethasone only shorten the duration of rocuronium-induced neuromuscular blockade if dexamethasone was administered 2 to 3 hours before surgery; however, intraoperative use of dexamethasone had no similar effects.^[4]

In our clinic, we always use methylprednisolone intraoperatively for mild to moderate allergy or asthma because of its more rapid onset time than dexamethasone. On the other hand, methylprednisolone is a common perioperative corticosteroid that can be used to prevent postoperative nausea and vomiting (PONV),^[5,6] relieve postoperative pain,^[7-9] improve lung function,^[10-12] attenuate laryngeal edema after extubation and airway obstruction,^[13,14] suppress perioperative inflammatory response,^[15-20] reduce perioperative mortality, shorten extubation time and length of stay, and increase comfortable feeling in patients.^[21]

The purpose we design this study is not only to know whether single use of methylprednisolone affect muscle relaxant, but also the affection between methylprednisolone which was administered after anesthesia intubation and muscle relaxant during the surgery.

2. Materials and methods

The present investigation was a randomized and double-blinded study, approved by the ethics committee of Obstetrics and

Gynecology Hospital, Fudan University (Shanghai, China). The study was successfully registered in Chinese Clinical Trials Registry (registration number: ChiCTR-IOR-15005906). After written informed consent was obtained, 136 patients underwent general anesthesia for laparoscopic gynecological surgery in Obstetrics and Gynecology Hospital, Fudan University, from March to September 2015, were enrolled. Inclusion criteria included aged between 18 and 60 years old, American Society of Anesthesiologists physical status diagnosed as I or II, and estimated operation time >1 hour. Exclusion criteria included neuromuscular diseases, laboratory abnormalities in electrolytes, liver and kidney dysfunction, allergy to muscle relaxants, medication history of glucocorticoids, anticholinergics, magnesium and aminoglycoside antibiotics within the past 1 week,^[22–25] and pregnancy. Patients were randomly divided into 3 groups using computer-based random number table: pregroup, receiving methylprednisolone 40 mg half an hour before induction of anesthesia; postgroup, receiving methylprednisolone 40 mg after induction of anesthesia and intubation; and control group, receiving normal saline.

Patients were fasted routinely, with no additional premedication provided. After entered into the operation room, patients were laid in a supine position; afterwards, routine monitoring was conducted, including noninvasive blood pressure, electrocardiogram, finger pulse oxygen saturation, and bispectral index (Aspect Medical Systems, Norwood, MA). Upper extremity venous was opened by 18G trocar, and Ringer lactate was infused at a rate of 8 mL/kg/hour. Patients were administered according to their numbers of administration. For all patients, anesthesia was induced by intravenous infusion of propofol 2.5 mg/kg, sufentanil 0.5 µg/kg, and rocuronium 0.6 mg/kg (SFDAH20093186; Xianju Medicine Ltd., Zhejiang, China, batch No.120807), followed by tracheal intubation. After successful intubation, mechanical ventilation was performed in a volume controlled ventilation mode; tidal volume was set at 6 to 8 mL/kg, and respiratory rate was at 10 to 12/minute. Breath parameters were adjusted based on end-tidal carbon dioxide partial pressure (PetCO₂) to keep PetCO₂ at 35 to 45 mmHg. Anesthesia was maintained with propofol at a rate of 6 to 12 mg/kg/hour and remifentanyl at a rate of 0.2 to 0.25 µg/kg/minute to keep a bispectral index value in the range of 40 to 60. Oesophageal temperature was maintained at 36 to 37°C, otherwise heated intravenous fluids and warm blankets will be provided if necessary. During the surgery, if patients showed body movement or surgeons required extra muscle relaxants, rocuronium 10 to 20 mg will be added; however, those patients were then withdrew from the present study. Before the end of the surgery, ramosetron 0.3 mg was administered intravenously to prevent PONV and tramadol 100 mg was provided for analgesia. In addition, phenylephrine 100 µg will be provided if the mean arterial pressure was below 90 mmHg or decreased larger than 30% from baseline; atropine 0.5 mg was used if heart rate was below 50 beats/minute.

All 136 patients were randomly divided into 3 groups by an anesthesiologist. A nurse anesthetist prepared medications. Two syringes were numbered as no 1 and 2. In the pregroup, no 1 syringe was filled with methylprednisolone 40 mg that was diluted by normal saline to 5 mL, and no 2 syringe was filled with normal saline at a volume of 5 mL. For the postgroup, no 1 syringe was filled with normal saline at a volume of 5 mL, and no 2 syringe was filled with methylprednisolone 40 mg that was diluted by normal saline to 5 mL. For the control group, both no 1 and 2 syringes were filled with normal saline at a volume of 5 mL.

Half an hour before general anesthesia and immediately after the end of anesthesia induction and intubation, each patient was injected intravenously with no 1 and 2 syringes for 10 seconds. All researchers who monitored anesthesia and muscle relaxant were blinded to the patient groups.

Neuromuscular transmission was monitored by mechanomyography using quantitative neuromuscular transmission monitor (HXD-1, CO28; Heilongjiang Huaxiang Technology, Ltd, Harbin, China) on the arm opposite to the blood pressure cuff. After cleaning the skin with 75% alcohol, 2 electrodes were placed on the ulnar nerve in the wrist near the end. After asked to slightly clench the muscle tension sensor with a set preload of 250 g, medical tapes were fixed up. Train-of-four (TOF) stimulation was provided to ulnar nerve in a frequency of 0.1 Hz, square wave pulses of 0.25 ms, and string spacing of 12 seconds to closely monitor muscle twitch response within the adductor pollicis muscle. When patients were falling asleep, we started the research. After it became steady (<5% variations of the 1st twitch [T1] and the TOF ratio [TOFR] >2 minutes), electrical stimulation was switched on with a muscle twitch height calibrated to 100%. Rocuronium 0.6 mg/kg was administered intravenously within 5 seconds.

During the surgery, the following parameters that representing rocuronium's effects on muscle relaxation were closely monitored: onset time (time required for T1 drop to zero immediately after administration of rocuronium), clinical duration (time between administration of rocuronium and recovery to 25% twitch height of T1); total duration (time between administration of rocuronium and recovery to 95% twitch height of T1); and recovery index (T1 restored from 25% to 75%) and time required for restoring TOFR 90% (time between administration of rocuronium and T4/T1=90%).

Other information such as patient's age, height, weight, and length of surgery was also recorded.

According to our preliminary results involving 20 patients, for the control group, 70 minutes was required to restore TOFR to 90% (standard deviation [SD] as 7 minutes). Therefore, it was presumed that for the methylprednisolone group, in order to obtain a clinical significance, time required for TOFR 90% should be shortened for at least 5 minutes. Hence, in the level of $\alpha=0.05$ and $\beta=0.1$, at least 36 patients were needed in each group. Considering the possibility of excluding patients, we then chose a total of 136 patients in our present study.

All data were analyzed by SPSS17.0 (SPSS, Inc., Chicago, IL). Continuous measurement data were expressed as means (SD). If data were normally distributed, comparison among the groups was performed by one-way analysis of variance (ANOVA). When the differences of average levels among 3 groups were statistically significant, multiple comparisons with Student's–Newman–Keuls method will be carried out. $P<.05$ was considered statistically significant.

3. Results

Twenty-nine cases among 136 patients were excluded for various reasons, thus there were 107 patients completed the study (Fig. 1). No statistical difference was found in age, height, weight, body mass index, American Society of Anesthesiologists classification, and length of surgery among all the patients (Table 1).

All patients achieved a maximum effect of muscle relaxation, and successfully completed intubation. Among the 3 groups, the onset time of muscle relaxants and recovery index had no

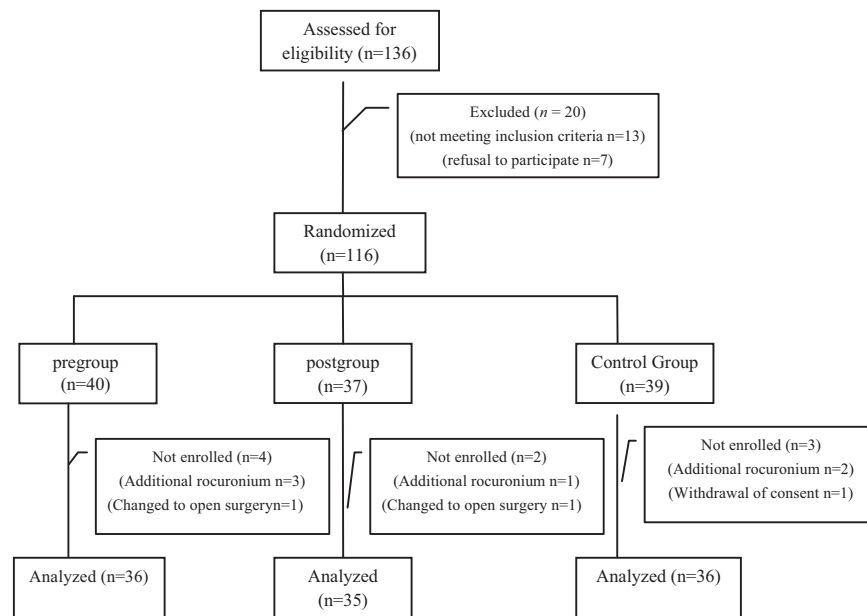


Figure 1. Flow diagram of patient enrolment.

significant difference. Compared to control group, pre-, and postgroups had significantly shorter clinical duration, total duration, and time required for TOFR 90% ($P < .05$); however, these parameters were not significantly different between pregroup and postgroup (Table 2).

4. Discussion

In the present study, we found that administration of methylprednisolone 40mg, no matter half-hour before surgery or immediately after intubation, could shorten both clinical duration, total duration, and time required for TOFR 90% of rocuronium-induced blockade; however, the onset time and recovery index were not significantly different to that of the control group. It should be emphasized that the results of clinical duration and time required for restoring TOFR 90% were more important, for clinical duration told us whether we need additional muscle relaxant and time required for restoring TOFR 90% was used to evaluate muscle relaxation and extubation safety.

The interaction between glucocorticoids and neuromuscular blockade drugs has attracted great attention in recent years. On the one hand, nondepolarizing neuromuscular blockade drugs exert shorter duration of action on patients with long-term use of prednisone.^[26] On the other hand, Carlson et al^[27] had observed

elevated cortisol levels in sepsis patients with abnormal neuromuscular system; in other words, glucocorticoids can affect the transmission of nerve muscle activity, thereby reducing the duration of action in nondepolarizing muscle relaxants. However, the mechanism of interaction between glucocorticoids and neuromuscular blockade drugs is still unknown, which may be related to the synthesis, release, and store of acetylcholine at the presynaptic neuromuscular junction, as promoted by glucocorticoids.^[28,29] This hypothesis was reinforced by the glucocorticoid-mediated increase the frequency and quantal content of end-plate potentials and miniature end-plate potentials in the mouse isolated diaphragm.^[30-32]

Although clinical doses of methylprednisolone range from 20 to 250 mg,^[13,14,21,33,34] in some studies, it can be up to 10 mg/kg.^[16] However, low-dose methylprednisolone had no difference to that of high-dose methylprednisolone, while it can significantly reduce the side effects of glucocorticoids.^[35,36] In our clinical practice, 40 mg methylprednisolone was more preferentially used especially for treating patients who were mild to moderate allergic. Therefore, in the present study, a single dose of intravenous methylprednisolone 40 mg was chosen. In this study, a recommended dose of rocuronium for intubation, 0.6 mg/kg, was selected, thus all patients can achieve a maximum blockade effects of muscle relaxation in order to successfully complete

Table 1

Patients' characteristics among 3 groups.

	Pregroup (n=36)	Postgroup (n=35)	Control group (n=36)	P
Age, y	39.3 (11.4)	38.0 (9.9)	39.4 (11.3)	.90
Height, cm	161.1 (3.7)	160.9 (4.1)	160.5 (5.4)	.86
Weight, kg	58.1 (4.7)	56.7 (6.2)	57.9 (7.5)	.66
BMI, kg/m ²	22.4 (1.5)	21.9 (2.0)	22.5 (2.9)	.55
Operation time, (,min	93.3 (21.2)	93.6 (29.7)	91.7 (30.9)	.73

Values are mean (SD). BMI = body mass index, SD = standard deviation.

Table 2

The effect of methylprednisolone administration on the time course of rocuronium-induced neuromuscular blockade.

	Pregroup (n=36)	Postgroup (n=35)	Control group (n=36)	P
Onset time, s	105.5 (31.9)	98.7 (30.0)	99.6 (35.9)	.49
Clinical duration, min	37.8 (5.3)	36.6 (4.9)	40.8 (6.0)	.00
Total duration, min	52.3 (6.7)	52.7 (5.6)	55.9 (5.0)	.02
Recovery index, (min)	9.5 (1.7)	9.8 (2.1)	10.2 (2.2)	.27
TOFR 90%, min	64.5 (10.5)	65.3 (11.6)	71.0 (10.6)	.03

Values are mean (SD). SD = standard deviation, TOFR = train-of-four ratio.

intubation. The reason we choose the patients with laparoscopic gynecological surgery under general anesthesia was that this surgery has a low requirement for muscle relaxation; therefore, the experimental observations can be easily achieved.

It should be emphasized that we do not expect to reverse the muscle relaxant effects of methylprednisolone on rocuronium. We aimed to explore the impact of methylprednisolone, as a widely used perioperative drugs, on muscle relaxants. The results showed that administration of methylprednisolone before or during surgery may shorten the duration of action of rocuronium on muscle relaxation. Currently, neuromuscular monitoring is not a conventional item in a considerable number of hospitals. Thus, it should be aware that during surgery, if methylprednisolone is being used due to antiinflammatory or prevention of PONV, its impact on muscle relaxation should be taken into account.

There are several limitations in our study design. First, all subjects in our study were female, thus, whether similar results can be obtained in male patients cannot be warranted. Currently, there is no study implying the participation of gender factors in the drug actions of methylprednisolone or nondepolarizing neuromuscular blockade drugs. Second, the present study used a single dose of methylprednisolone 40 mg, although this dose is being frequently used in clinical practice, perioperative surgery might need higher doses, even up to 10 mg/kg.^[16] In addition, it is not clear that whether a dose-dependent effect of methylprednisolone on the duration of rocuronium exists, thus further study is needed to investigate whether higher doses of methylprednisolone could shorten the duration of action of muscle relaxants. Third, the subjects we chose are the patients undergoing laparoscopic gynecological surgery. However, Wang et al had suggested that for laparotomy, rocuronium had an extended duration of action in laparoscopic surgery.^[37] Therefore, further study is needed to investigate whether our results are applicable to laparotomy.

In summary, our present study showed that a single intravenous injection of methylprednisolone 40 mg, no matter in the preoperative or intraoperative surgery, could shorten the duration of action of rocuronium.

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