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석사학위 논문

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Effect of dexamethasone on the onset time and recovery profiles of cisatracurium

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이 논문을 의학 석사학위신청 논문으로 제출함

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배경

덱사메타손은 수술 후 오심 구토의 예방과 치료, 급성 또는 만성 통증의 치료를 위해 보편적으로 사용되고 있다. 특히 국소마취제와 같이 사용하는 경우 부위마취 시간을 증가 시키는 효과를 보인다고 보고되고 있다. 그러나 최근 덱사메타손이 전신마취 동안 스테로이드성 비탈분극성 근이완제인 로큐로니움의 회복 인자들을 단축시킨다고 보고된 바 있다. 본 연구에서는, 덱사메타손의 서로 다른 정주 시간에 따른 벤질아이소큐놀리움 계열의 비탈분극성 근이완제인 시스아트라큐리움의 발현시간과 회복인자들에 대한 효과를 비교하고자 한다.

방법

기관생명윤리위원회의 허락을 받은 후 본 연구에 동의한 117명의 환자들을 무작위 배정방법에 의해 3군으로 배정하였다. A군은 마취유도 2-3 시간 전, B군은 마취유도 직전, 그리고 C군은 수술 종료 시에 덱사메타손 8mg을 정주하였다. 모든 환자는 50% 산소-공기 혼합가스 하에서 프로포폴과 레미펜타닐로 마취 유도 및 유지를 하였다. 근 이완의 발현시간, 첫 연축(T1)이 기준 T1의 25%까지 회복

시간, 회복지수, 최대 연축 감소 후 사연속자극의 비가 0.9까지의 시간을 기록하였다.

결과

시스아트라큐리움의 발현시간은 A군에서 C군보다 의의 있는 단축을 보였지만(p = 0.000), B군과는 의의 있는 차이를 보이지 않았다(p = 0.119). 첫 연축(T1)이 기준 T1의 25%까지 회복시간과 회복지수는 3 군간 의의 있는 차이를 보이지 않았다. 회복시간, 최대 연축 감소 후 사연속자극의 비가 0.9까지의 시간은 A군에서 B군과 C군보다 의의 있는 단축을 보였다 (p = 0.000 vs. P = 0.015 그리고 p = 0.000 vs. P = 0.08).

결론

마취유도 2-3시간 전 덱사메타손 1회 정주 한다면, 벤질아이소큐놀리움 계열의 비탈분극성 근이완제인 시스아트라큐리움의 근이완의 발현과 회복시간을 평균 약 15%와 9% 단축시킨다. 그러나, 마취유도 직전 덱사메타손의 투여는 근이완의 효과에 의의 있는 영향을 미치지 않는다.

Ⅰ. Introduction

Dexamethasone is one of the famous effective agents used for prevention and treatment of postoperative nausea and vomiting (PONV), and preoperative dexamethasone 8mg enhances the recovery quality in addition to its effect on PONV [1, 2]. Dexamethasone also usually has been used as an adjuvant agent during regional anesthesia as well as peripheral nerve blocks for prevent or treatment of acute or chronic pain [3, 4]. They reported that intravenous or perineural injection of dexamethasone prolonged the duration of analgesia regardless of admission routes.

Chronic medication of glucocorticoid, such as prednisolone and betamethasone, influence the time course of neuromuscular block: the duration of neuromuscular block was hastened following the administration of atracurium or rocuronium [5, 6]. In experimental study [7, 8], dexamethasone and methylprednisolone also showed the similar results. However, it was not clear whether a single injection of steroid might lead to a similar effect. There were, recently, reports that a single dose of dexamethasone 8mg showed the different results according to injection times. They reported that single injection of dexamethasone, 2 to 3 hr prior to surgery, might hasten the recovery profiles (clinical duration, recovery index, as well as total recovery time) of rocuronium, but single injetion of dexamethasone immediately before induction of anesthesia did not influence the time course of the neuromuscular block [9]. The interactions between corticosteroids and NMBAs are not limited to one class of benzylisoquinolones or aminosteroids. However, there is lack of clinical reports on the dexamethasone effect of onset time and recovery profiles of cisatracurium, benzylisoquinolium series of non-depolarizing NMBAs. So, we hypothesized that the onset time and recovery profiles of cisatracurium would also shorten if dexamethasone was administered 2 to 3

hr prior to induction of anesthesia compared with the administration during induction of anesthesia. The aim of the present study was to compare the dexamethasone effect on the onset time and recovery profiles of cisatracurium in patients premedicated dexamethasone for prophylaxis of PONV according to the different injection time points.

Ⅱ. Material and Methods

This prospective, randomized, double blind study was approved by our Institutional Review Board. We enrolled one hundred and seventeen patients who were 20 to 65 years old adults, American Society of Anesthesiologists (ASA) physical status Ⅰ or Ⅱ, and were scheduled to undergo elective surgery under general anesthesia. We excluded the patients who took a steroid medication within the last 24 hours, receiving the chronic steroid medication and medicines known to influence neuromuscular function such as furosemide, magnesium or cephalosporin. We also excluded the patients with neuromuscular disease, diabetics, allergic history to cisatracurium and dexamethasone, a body mass index (BMI) > 25, pregnant or breastfeeding women, and missing data in record. After obtaining the informed consent from all patients or guardians, one hundred and seventeen patients were enrolled. The study protocol adhered to published guidelines on pharmacodynamics studies of NMBA [10].

All patients were pre-medicated with midazolam 0.05 mg/kg, intramuscularly, 30 minute before anesthesia. Standard monitoring included an ECG, non-invasive blood pressure, end-tidal partial pressure of carbon dioxide, and peripheral pulse oximetry. Patients and investigators were blinded to the study medications, which were produced and randomized (using a random number table) by the non-investigable nurse as indistinguishable, numbered syringes.

Patients were allocated to one of 3 groups. In the group A, patients received dexamethasone 8mg in 0.9% normal saline (total volume 2 ml) intravenously 2-3 hours before anesthesia, followed by 2 ml of 0.9% normal saline at just before induction of anesthesia and end of surgery. In the group B, patients received 2 ml of 0.9% normal saline intravenously 2-3 hours before anesthesia, followed by dexamethasone 8mg in 0.9% normal

saline (total volume 2 ml) intravenously just before induction of anesthesia, and then 2 ml of 0.9% normal saline intravenously at the end of surgery. In the group C, patients received 2 ml of 0.9% normal saline intravenously 2-3 hours before anesthesia and just before induction of anesthesia, followed by dexamethasone 8mg in 0.9% normal saline (total volume 2 ml) intravenously end of surgery (table 1).

General anesthesia was induced with the targeted effect-site concentration of propofol 4 μg/mL and remifentanil 3 ng/ml, followed the intubation without aid of neuromuscular blocking agents 3 minutes later. For the maintenance of anesthesia, an effect-site concentration of propofol and remifentanil were adjusted to maintaining blood pressure within normal ranges, and 40 to 60 of bispectral index score. Mechanical ventilation with a 50% oxygen-air mixture was also adjusted to maintain $ETCO_2$ within normal ranges.

Neuromuscular function was assessed by acceleromyography of the adductor pollicis muscle with train-of-four (TOF) using the neuromuscular transmission module and was displayed on an anesthetic monitoring system (Anesthetic Monitoring System S/5TM, Datex-Ohmeda Inc., Helsinki, Finland). The arm was kept in the same position during the entire study procedure. The stimulus current needed to achieve the maximal response of the adductor pollicis muscle was automatically detected in each patient. The search began with a 10 mA stimulus and the response was measured. The current was increased in steps of 5 mA until the increase in response to the increase in the current was no longer. This maximal current was then automatically increased by 15%, resulting in a supramaximal current. If the supramaximal current was not found or the response was too weak, the current was set at 70 mA. After the supramaximal current of 0.2 ms duration square waves and a 1 second cycle time was obtained, TOF stimuli was started to observe the potentiation of the first twitch (T1) of TOF (%

T1 potentiation) and TOF ratios at 2 Hz, every 15 s, 0.1 ms duration as a baseline value. And then, all patients received cisatracurium 0.05 mg/kg.

We measured and recorded the onset and recovery characteristics defined as follows; (1) The time in seconds between the start of injection of cisatracurium and maximal T1 depression (onset time); (2) The time in minutes between the start of injection of cisatracurium and 25% twitch height of T1 (clinical duration); (3) The time in minutes between 25% and 75% twitch height recovery of T1 (recovery index); (4) The time in minutes between the 25% twitch height recovery of T1 and a recovery of neuromuscular block to a TOF ratio of 0.9 (recovery time); and (5) The time between the start of cisatracurium injection to a recovery of neuromuscular block to a TOF ratio of 0.9 (total recovery time). Gender, ASA physical status, age, height, weight and BMI were also measured or calculated.

We calculated the necessary sample size using the level of statistical significance as $\alpha = 0.05$ and $\beta = 0.2$ based on an effect size 0.3, a 30% reduction of total recovery time with cisatracurium 0.05 mg/kg with dexamethasone 8mg pre-treatment 2-3 hours before anesthesia could be considered clinically significant. Thirty seven patients were needed in each group and we finally enrolled the thirty nine patients upon consideration of dropout rate 5%.

SPSS (Windows ver. 21.0, SPSS Inc., Chicago, IL) was used for statistical analysis. All measured values were denoted as mean ± standard deviation (SD) or number of patients were analyzed using the one-way ANOVA except gender and ASA physical status using the χ^2test. If a significant intergroup difference was found, the Scheffe's method for Post-Hoc test was used. Significance was defined as $P < 0.05$.

Ⅲ. Result

Eighty patients finally enrolled because thirty seven patients were excluded due to missing data, and no significant differences in gender, ASA physical status, age, height, weight, and BMI were found among all the groups (Figure 1, Table 2).

The onset time was significantly hastened in group A compared with group C ($p = 0.000$, table 3), but it was not significantly compared with group B ($p = 0.119$, table 3). Even though there was not significant differences between group B and group C, group B was showed the more decreased trend of onset time (561.4 ± 71.0 vs. 614.9 ± 99.3 second, table 3). No significant differences in clinical duration and recovery index were observed among the 3 groups (table 3). Recovery time and total recovery time were significantly hastened in group A compared with group B and group C ($p = 0.000$ vs. $P = 0.015$, $p = 0.000$ vs. $P = 0.08$, respectively, table 3). However, there was no significant difference between group B and group C.

Ⅳ. Discussion

We have shown that intravenous injection of dexamethasone 8mg 2 to 3 hours prior to surgery hastened the onset time, recovery time, and total recovery time of cisatracurium. However, the administration of dexamethasone immediately before induction of anesthesia did not affect the onset time and the recovery profiles of cisatracurium.

Chronic medication of glucocorticoid, such as prednisolone and betamethasone, influence the time course of neuromuscular block: the duration of neuromuscular block was hastened [5, 6, 11, 12]. The interactions between corticosteroids and NMBAs are not limited to one class of benzylisoquinolones or aminosteroids. Parr et al. [12] reported that the betamethasone had significantly less depression of muscle contraction (twitch) force at all concentrations of vecuronium in animal study, which is characterized by resistance to neuromuscular block. The duration of an atracurium-induced neuromuscular block also was shorter in patients with long-term medication with prednisolone, while onset time showed the prolonging trend with insignificant difference [11]. Soltesz et al. [5] reported that the onset time of rocuronium was prolonged, while the clinical duration and the total recovery time was hastened in patients with chronic prednisolone medication (more than 4 weeks) due to chronic inflammatory bowel disease. Parr et al. [6] also reported that the premedication of betamethasone for several months was hastened the neuromuscular blocking effect of vecuronium. In experimental study [7, 8], dexamethasone and methylprednisolone also showed the similar results.

Single-dose injection of dexamethasone is frequently administered during anesthesia for prevention and treatment of PONV and due to its anti-inflammatory and analgesic properties [1, 2, 13-15]. However, it was not clear whether a single injection of steroid might lead to a similar

effect. There were, recently, reports that a single dose of dexamethasone 8mg showed the different results according to injection times [9]. They reported that single injection of dexamethasone, 2 to 3 hr prior to surgery, hastened the recovery profiles (clinical duration, recovery index, as well as total recovery time) of rocuronium, but single injection of dexamethasone immediately before induction of anesthesia did not influence the time course of the neuromuscular block. In our study, we found that recovery time and total recovery time were significantly hastened following a cisatracurium-induced neuromuscular block in patients with dexamethasone 8mg 2 to 3 hr before anesthesia. And we also found that clinical duration and recovery index were insignificantly decreasing trend , compared with dexamethasone 8mg just before induction of anesthesia. It means that the time difference between groups is one of potential factors about the effects of glucocorticoids on the duration of the neuromuscular block. Soltesz et al. [9] also suggested that its effect would have been even more pronounced if the time interval from steroid injection to administration of NMBA had been longer. We also agree that single injection of dexamethasone just before induction has no effect on the duration of neuromuscular block because which time did not allow enough time to produce an effect, compared with single injection of dexamethasone 2 to 3 hr before anesthesia.

A shorter duration of neuromuscular block reduces the risk of postoperative re-curarization but it has a change to increases the possibility of an insufficient neuromuscular block. Especially, patients underwent neurosurgery require the higher dose of dexamethasone to reduce intracranial pressure and neuromuscular block might be even more attenuated. Therefore, neuromuscular monitoring is mandatory in patients who undergo surgery required deep neuromuscular block.

Interestingly, our study showed the difference finding on the onset time

compared with the result of Soltesz et al. [9], which was no significant difference. Mean (ranges) ED_{95} of rocuronium is 0.305 (0.257-0.521) mg/kg and ED_{95} of cisatracurium is 0.04 (0.032-0.05) mg/kg. Soltesz et al. used rocuronium 0.3 mg/kg, which is close to the medium value of ED_{95}, but our study used cisatracurium 0.05 mg/kg, which is close to the upper limit value of ED_{95}. Therefore, there is inequivalent dose between rocuronium used in soltesz's study and cisatracurium used in our study, by which the reason of different result may be explained.

Glucocorticoids have a direct facilitatory effect at the impulse generating end of the motor nerve axon, act presynaptically stimulating synthesis, and release of acetylcholine [7, 16-18]. Dalkara and Onur [7] revealed that glucocorticoids have a direct facilitatory action on neuromuscular transmission by a presynaptic action. However, the underlying pharmacologic mechanisms for the attenuation of the neuromuscular block remain still unclear [8, 19-21]. Soltész et al. [9] suggested that dexamethasone probably does not produce a direct antagonistic effect at the motor end plate because patients receiving dexamethasone about 15 min prior to the administration of rocuronium did not show the attenuation of the neuromuscular block. Methylprednisolone and hydrocortisone themselves potentially inhibited the muscle-type acetylcholine receptor and produced noncompetitive antagonism of the muscle-type nicotinic acetylcholine receptor at clinical concentrations. Combined application of vecuronium and methylprednisolone showed additive effects on both receptor forms [8]. Leeuwin et al. [21] reported that dexamethasone antagonized the blocking effect of d-tubocurarine with significantly increased the LD_{50} of d-tubocurarine, and the suggested mechanism was its direct presynaptic effects at the neuromuscular junction. Dal Belo et al. [19] investigated the action of prednisolone at the neuromuscular junction in mouse isolated phrenic nerve-diaphragm and

rat external popliteal/sciatic nerve-tibialis anterior muscle preparations. They showed that steroid prevented the neuromuscular blockade by d-tubocurarine and steroid had the presynaptic facilitatory effect. Nocente et al. [22] investigated the interaction between betamethasone and vecuronium, a nondepolarizing muscle relaxant by mechanomyographic evaluation and suggested that corticosteroids may interact with non-depolarizing muscle relaxants both in prejunctional and postjunctional acetylcholine receptors.

The present study has a limitation. The dose (0.05 mg/kg) of cisatracurium, which is not the clinical intubation dose, was used in our study, because the GCRP guidelines recommend the use of low doses for assessment of onset and time course of the neuromuscular block [10]. Therefore, it is necessary the additional study using intubation dose of NMBAs for the results in clinical condition.

Ⅴ. Conclusion

A single dose of dexamethasone 8mg hastened the onset time and the total recovery time of cisatracurium-induced neuromuscular block by about 15% and 9%, respectively, if administered 2 to 3 hours prior to surgery. Therefore, we have to pay attention to the possibility of an insufficient neuromuscular block in patients who require the high dose of steroid preoperatively and undergo surgery required deep neuromuscular block.

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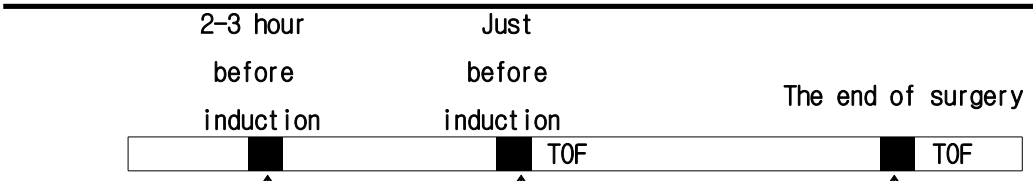
Table 1. Schematic Protocol of This Study



	2-3 hour before induction	Just before induction	The end of surgery
Group A	Dexamethasone	Normal saline	Normal saline
Group B	Normal saline	Dexamethasone	Normal saline
Group C	Normal saline	Normal saline	Dexamethasone

The group A received dexamethasone 8mg in 0.9% normal saline (total volume 2 ml) intravenously 2-3 hours before anesthesia. The group B received dexamethasone 8mg in 0.9% normal saline (total volume 2 ml) intravenously just before induction of anesthesia. The group C received dexamethasone 8mg in 0.9% normal saline (total volume 2 ml) intravenously end of surgery. TOF; Train-of-Four.

Figure 1. CONSORT Flow Chart. The group A received DEXA 8mg in 0.9% normal saline (total volume 2 ml) intravenously 2-3 hours before anesthesia. The group B received DEXA 8mg in 0.9% normal saline (total volume 2 ml) intravenously just before induction of anesthesia. The group C received DEXA 8mg in 0.9% normal saline (total volume 2 ml) intravenously end of surgery.

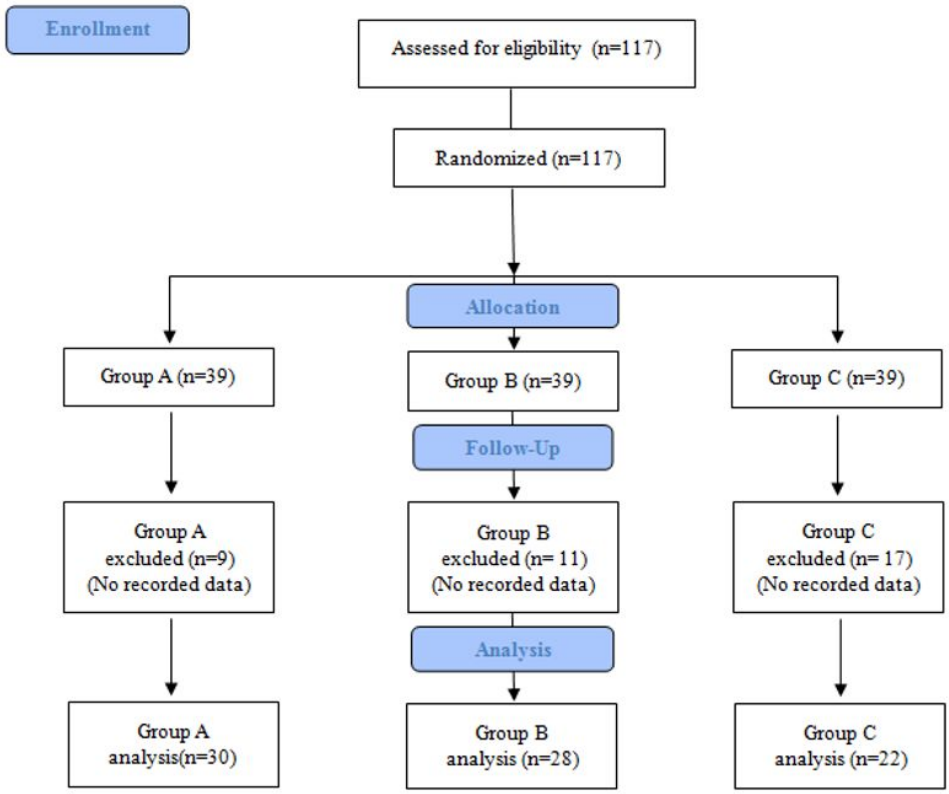


Table 2. Demographic Data

	Group A (n=30)	Group B (n=28)	Group C (n=22)
Gender (Male/Female)	20/10	22/6	14/8
ASA physical status (I/II)	22/8	21/7	17/5
Age (years)	40.97 ± 12.89	37.00 ± 12.56	37.68 ± 13.45
Height (cm)	169.30 ± 8.57	172.96 ± 6.95	169.86 ± 7.92
Weight (kg)	64.00 ± 8.73	68.25 ± 8.74	66.36 ± 9.64
BMI	22.25 ± 1.74	22.74 ± 1.87	22.89 ± 1.97

Values are expressed as mean ± standard deviation or number of patient. There are no significant differences among groups. The group A received dexamethasone 8mg in 0.9% normal saline (total volume 2 ml) intravenously 2-3 hours before anesthesia. The group B received dexamethasone 8mg in 0.9% normal saline (total volume 2 ml) intravenously just before induction of anesthesia. The group C received dexamethasone 8mg in 0.9% normal saline (total volume 2 ml) intravenously end of surgery. BMI ; body mass index.

Table 3. The Effect of Dexamethasone on The Onset Time and Recovery Profiles of Cisatracurium-Induced Neuromuscular Blockade

	Group A (n=30)	Group B (n=28)	Group C (n=22)
Onset time (second)	519.5 ± 60.0*	561.4 ± 71.0	614.9 ± 99.3
Clinical duration (minute)	18.6 ± 2.5	20.5 ± 3.9	19.6 ± 3.4
Recovery index (minute)	17.1 ± 4.7	18.1 ± 3.3	18.7 ± 4.5
Recovery time (minute)	28.4 ± 3.0*†	32.3 ± 3.3	30.9 ± 2.1
Total recovery time (minute)	47.1 ± 4.2*†	52.8 ± 3.0	50.5 ± 4.1

Values are expressed as mean ± standard deviation. There are no significant differences among groups. The group A received dexamethasone 8mg in 0.9% normal saline (total volume 2 ml) intravenously 2-3 hours before anesthesia. The group B received dexamethasone 8mg in 0.9% normal saline (total volume 2 ml) intravenously just before induction of anesthesia. The group C received dexamethasone 8mg in 0.9% normal saline (total volume 2 ml) intravenously end of surgery. BMI ; body mass index. *$P < 0.05$ vs Group C, †$P < 0.05$ vs Group B.