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THE EFFECT OF DEXAMETHASONE ON THE ONSET TIME AND RECOVERY PROFILES OF CISATRACURIUM-INDUCED NEUROMUSCULAR BLOCK

Anaesthesiology

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ABSTRACT

The effect of dexamethasone injection on cisatracurium-induced neuromuscular block was compared according to different injection time points. **Material and Methods:** One hundred patients were randomly assigned to three groups: 8 mg of dexamethasone injected intravenously 2–3 h before anesthesia (group A), just before anesthesia induction (group B), and at the end of surgery (control group). **Results:** Eighty patients were finally enrolled. The onset time (median [interquartile range], seconds) was significantly hastened in group A compared to that in group B and control group. The onset time in group B was faster than the control group. The recovery time was significantly hastened in group A compared to that in group B and control group. The total recovery time was significantly hastened more in group A than group B and control group. **Conclusions:** A single dose of 8 mg of dexamethasone hastened the onset and total recovery times of cisatracurium-induced block by approximately 16 and 7%, respectively if administered 2–3 h prior to surgery.

KEYWORDS

Neuromuscular monitoring, Cisatracurium, Dexamethasone

Introduction:
Dexamethasone is an effective agent for the prevention and treatment of postoperative nausea and vomiting (PONV), and its preoperative administration can provide better postoperative emotional state and physical comfort, and reduce the severity of postoperative pain and requirement of analgesics [1,2]. In addition, it is known that intravenous and perineural dexamethasone injection, as an adjuvant agent of regional anesthetics, can prolong the duration of analgesia and anesthesia by a variety of mechanisms, including peripheral and central mechanisms [3,4].

Several investigators have been interested in determining whether chronic steroid medications can influence the time course of neuromuscular blockers (NMBs) during anesthesia, because some patients may take steroid medication for chronic diseases. They showed that chronic treatment with steroids shortened the duration of neuromuscular block in patients receiving atracurium or rocuronium [5,6]. However, during the perioperative period, a single-dose steroid, such as dexamethasone and prednisone, can be administered in patients for the prevention and treatment of PONV. It is not yet clear whether a single steroid injection would have an effect similar to chronic medication. A recent study reported that a single dose of 8 mg dexamethasone showed different results in the time course of rocuronium, an aminosteroid non-depolarizing NMB, according to different injection time points. Dexamethasone (8 mg) injection administered 2–3 h before surgery hastened the clinical duration, recovery index, and total recovery time of rocuronium; however, dexamethasone injection immediately before the induction of anesthesia did not influence the time course of the NMB [7]. However, to date, no studies have been conducted on the effect of dexamethasone on the onset time and recovery profiles (clinical duration, recovery index, recovery time, and total recovery time) of cisatracurium, a benzylisoquinolium non-depolarizing NMB.

In the present study, we tested our hypothesis that a single dose of dexamethasone administered 2–3 h prior to the induction of anesthesia would also hasten the onset time and recovery profiles of cisatracurium in patients receiving general anesthesia.

Materials and Methods:
This prospective, randomized, double-blind study. we enrolled 117 patients aged 20–65 years. We excluded patients who had taken a steroid medication within the last 24 h or had received chronic steroid medication or medicines, such as furosemide, magnesium, or cephalosporin, known to influence the neuromuscular function. In addition, patients with neuromuscular disease, diabetes, a history of allergy to cisatracurium and dexamethasone, a body mass index (BMI) > 25, as well as pregnant or breastfeeding women were excluded.

All patients were premedicated intramuscularly with 0.05 mg/kg of midazolam 30 min before anesthesia. Standard monitoring included an electrocardiogram, non-invasive blood pressure, end-tidal partial pressure of carbon dioxide (ETCO2), and peripheral pulse oximetry. The patients and investigators were blinded to the study medications; a non-investigating nurse randomized medications by using a random number table, and produced them as indistinguishable, numbered syringes.

The patients were allocated to one of the three groups . In group A, the patients received 8 mg dexamethasone in 0.9% normal saline (total volume, 2 ml) intravenously, 2–3 h before anesthesia in a ward, followed by 2 ml of 0.9% normal saline just before the induction of anesthesia and at the end of surgery. In group B, the patients received 2 ml of 0.9% normal saline intravenously, 2–3 h before anesthesia, followed by 8 mg of dexamethasone in 0.9% normal saline (total volume 2 ml) intravenously just before the induction of anesthesia and 2 ml of 0.9% normal saline intravenously at the end of surgery. In the control group, the patients received 2 ml of 0.9% normal saline intravenously 2–3 h before anesthesia and just before induction of anesthesia. Subsequently, 8 mg dexamethasone in 0.9% normal saline (total volume 2 ml) was administered intravenously at the end of surgery or after obtaining a TOF ratio of 0.9, if the surgery was completed within 1 h. The settings of mechanical ventilation with 50% oxygen-air mixture were also adjusted to maintain the ETCO2 between 35–45 mmHg.

The necessary sample size was calculated by taking the level of statistical significance as $\alpha = 0.05$ and $\beta = 0.2$ using an expected effect size of 0.3, which is larger than the medium effect size (0.25) suggested by Cohen, owing to lack of evidence for calculating the effect size [10]. We required 37 patients in each group, and we enrolled 39 patients given the assumption of a 5% dropout rate.

Statistical analysis:
We excluded data of patients from whom we could not get any results of the onset time, clinical duration, recovery index, recovery time, or total recovery time. SPSS was used for statistical analysis.

Results:
Eighty patients were ultimately enrolled in this study. Thirty-seven patients (9 patients in group A, 11 patients in group B, and 17 patients in control group) were excluded from the data analysis .

Table 1: The Effect of Dexamethasone on the Onset Time and Recovery Profiles of Cisatracurium-induced Neuromuscular Block

	Group A (n = 30)	Group B (n = 28)	Control group (n = 22)

Onset time (s)	520.0 [500.0–560.0]*,†	562.5 [514.0–589.0]*	586.5 [575.0–642.5]
Clinical duration (min)	18.7 [16.7–20.0]	19.7 [18.7–21.5]	19.3 [18.5–21.6]
Recovery index (min)	16.3 [13.9–18.4]	18.7 [15.3–19.4]	17.9 [16.5–20.3]
Recovery time (min)	28.5 (27.3–29.6)‡,§	32.3 (31.0–33.6)	30.9 (29.9–31.8)
Total recovery time (min)	47.1 (45.5–48.6)‡,§	52.8 (51.6–54.0)	50.5 (48.7–52.3)
ICNMB (n [%])	19 (63.3)	19 (67.9)	20 (90.9)

The onset time in group B was also faster than control group . The differences in onset time [mean (95% CI) min] were -41.9 (−91.9 to 8.1), −95.4 (−148.8 to 42.0), and −53.5 (−107.7 to 0.9) seconds, between group A and B, group A and control group, and group B and control group, respectively.

The recovery time [mean (95% CI) min] was significantly hastened in group A compared to that in group B [28.5 (27.3–29.6) vs. 32.3 (31.0–33.6) min, $P < 0.001$] and control group [28.5 (27.3–29.6) vs. 30.9 (29.9–31.8) min, $P = 0.015$] . However, we found no significant difference between group B and the control group ($P = 0.241$). The differences in recovery time [mean (95% CI) min] were −3.8 (−5.7 to −1.9), −2.4 (−4.5 to −0.4), and 1.4 (−0.7 to 3.5) min, between group A and B, group A and control group, and group B and control group, respectively.

The incidence of incomplete neuromuscular block was not significantly different among the groups, with 63.3, 67.9, and 90.9% incidence in A (n = 30), B (n = 28), and control (n = 22) groups, respectively ($P = 0.07$). However, if the missing data was included, it was significant different among the groups with 71.8, 74.4, and 94.9% incidence in groups A (n = 39), B (n =39), and control (n =39), respectively ($P = 0.019$).

Discussion:

In the present study, 8 mg of dexamethasone hastened the onset time of cisatracurium when injected intravenously 2–3 h before surgery and immediately before the induction of anesthesia. It also hastened the recovery and total recovery times of cisatracurium when injected intravenously 2–3 h before surgery. However, its administration immediately before the induction of anesthesia did not show any significant effect on the recovery profiles of cisatracurium. It is known that NMBs can interact with many drugs, such as most antibacterials, procainamide, quinidine, magnesium, calcium antagonists, phenytoin, lithium, steroids, and furosemide [10]. In particular, the studies on interaction between NMBs and steroids were usually focused in patients receiving chronic steroid medication [5,6,10]. These reports documented that chronic steroid medication could interact with NMBs, resulting in resistance to NMB action. The onset time showed the controversial effect according to NMBs, while the recovery profiles such as clinical duration and total recovery time were hastened. However, it is not clear whether a single steroid injection would have a similar effect. We frequently encounter patients requiring a perioperative single-dose injection of dexamethasone because of its antiemetic, anti-inflammatory, and analgesic properties, rather than patients receiving chronic steroid medication [1,2,8,9,10]. For the prevention of PONV, dexamethasone is commonly injected prior to surgery at the induction of anesthesia, owing to its delayed onset [9,10]. Recently, Soltesz et al. [7] examined whether dexamethasone required more time to influence the time course of NMB by analyzing its interaction with rocuronium. They documented that a single-dose injection of 8 mg dexamethasone 2–3 h before surgery hastened the clinical duration, recovery index, and total recovery time, while injection administered 15 min prior to rocuronium administration did not attenuate the effect of rocuronium. The present study using cisatracurium also showed that the recovery profiles, except for clinical duration and recovery index, were hastened in patients who received 8 mg dexamethasone 2–3 h before anesthesia; however, dexamethasone injection just before induction did not significantly influence the effect of cisatracurium. These findings can be supported by the results of Robinson's study [10], in which betamethasone induced resistance to nondepolarizing NMB by increasing the ED50 for atracurium by 27% and vecuronium by 45%. Furthermore, the onset time was hastened by a single-dose injection of 8 mg dexamethasone 2–3 h before surgery in the present study; however, in the study of Soltesz et al. [7] dexamethasone did not influence the onset time according to different injection time points. This discrepancy can be explained by the incidence of incomplete neuromuscular block. Soltesz et al. [7] reported that 0.3 mg/kg rocuronium (ED95) led to complete neuromuscular block in nearly all patients; however, the present study showed high incidence of incomplete neuromuscular block.

There are some limitations associated with the present study. First, we used ED95 of cisatracurium (0.05 mg/kg), which is lower than the clinical intubation dose, because the guideline recommends using low doses to assess the onset and recovery profiles of NMB [8,10]. This dose was not sufficient to induce complete neuromuscular block above 95% T1 depression. The incidence of incomplete neuromuscular block was 63.3, 67.9, and 90.9% in groups A, B, and control, respectively, and if the missing data were included, it was increased to 71.8, 74.4, and 94.9% in groups A, B, and control, respectively, owing to below 75% T1 depression. Second, we performed endotracheal intubation without NMB, which is not recommended for routine clinical situationsThird, we did not show intubation-induced hemodynamic changes because we did not record them despite the observation for maintaining blood pressure within 20% changes of initial rest systolic blood pressure. Therefore, we calculated the necessary sample size with an expected effect size of 0.3, which is larger than that of medium standardized effect size (0.25) suggested by Cohen. However, in this study, the differences in onset time between group A and B and group A and control group were 41.9 and 95.4 s, respectively. The differences in total recovery time between group A and B and group A and control group were 5.7 and 3.4 min, respectively. The differences of onset time between the groups are sufficient to be considered as clinical meaningful significance, whereas the differences of recovery and total recovery times between the groups are not. Finally, the power of the present study may be decreased because of the 33.4% dropout rate due to below 75% T1 depression. Despite these limitations, this study showed that the onset time was significantly hastened with meaningful statistical difference by the administration of dexamethasone 2–3 h before surgery.

Conclusion:

a single 8 mg of dexamethasone accelerated the onset and total recovery times of cisatracurium-induced neuromuscular block by approximately 15 and 9%, respectively, if administered 2–3 h before surgery. Therefore, clinicians should be aware that insufficient neuromuscular block is possible in patients who require a high-dose steroid preoperatively and in patients who undergo surgery that requires deep neuromuscular block. In addition, to obtain results that reflect the clinical conditions, an additional study with enough effective size and power in which clinical intubation doses of NMBs are used is necessary.

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