Doctor of Philosophy

Effect of hypothermia on the action of sugammadex in a rat phrenic nerve-hemidiaphragm preparation

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ABSTRACT

Introduction: Anesthesiologists are often faced with the condition to use a neuromuscular blocking agent and the reversal agent in patients under hypothermia. It was shown that hypothermia affected the muscle contraction and response to neuromuscular blocking agents. However, little is known about the effect of hypothermia on the antagonism of muscle relaxation by sugammadex. Therefore, we aimed to evaluate the impact of hypothermia on the action of sugammadex.

Methods: Phrenic nerve-hemidiaphragm preparations of rats were randomly allocated into four groups; group 1, 36°C (normothermia); Group 2, 24°C (deep hypothermia); Group 3, 28°C (moderate hypothermia); and Group 4, 32°C (mild hypothermia) (according to the Swiss classification). Rocuronium was administered cumulatively until the complete blockade of first twitch (T1) of train-of-four (TOF). After 10 min, rocuronium-equimolar dose of sugammadex was administered. The recovery of T1 height and TOF ratio and recovery index were evaluated.

Results: A total of 40 phrenic nerve-hemidiaphragm preparations were included in the analysis. Dose-response curve of rocuronium showed significant difference among the four groups ($p < 0.001$). Rocuronium was potentiated in group 2 compared group 3 and group 4 (all $p < 0.001$). The recovery of T1 height demonstrated that there was delay in group 2 and group 3 compared

with group 1 (all $p < 0.001$). Additionally, the recovery of TOF ratio also showed delay in group 2 and group 3 (all $p < 0.001$). Analysis of the recovery index identified significant delay of reversal effect of sugammadex in group 2 and group 3 compared to group 1 ($p = 0.005$ and 0.028, respectively).

Conclusion: In this *in vitro* study, muscle relaxation induced by rocuronium was potentiated in deep hypothermic condition. The reversal effect by sugammadex was reduced under moderate and deep hypothermia. However, mild hypothermia had no significant effect on the action of sugammadex.

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INTRODUCTION

Despite of the effort to keep the patient in normothermic range with various warming devices, the incidence of perioperative hypothermia was reported to be 20-90%.[1)] High incidence of hypothermia is explained by the impaired thermoregulatory function by anesthetic agents and exposure to cold air in operating room and unwarmed fluid.[2, 3)] Besides, hypothermia was often used for therapeutic purpose as the benefit of hypothermia was proved after cardiac arrest, surgical repair of aortic aneurysms, and brain trauma.[4, 5)] During therapeutic hypothermia neuromuscular blocking agent has been frequently used to prevent shivering.[6)] Thus, anesthesiologists are often faced with the case to use a neuromuscular blocking agent and the reversal agent in patients under hypothermia.

For the optimal function of human body, maintenance of normothermia is essential. The change of core body temperature causes decrease of organ function. The decreased function of organs induces the alteration of pharmacologic effect of some drugs.[7)] The effects of hypothermia on muscle relaxants were tried to be clarified through various studies during decades. Some human studies commonly reported that the duration of action of steroidal neuromuscular blocking agent was prolonged and that reversal of the muscle relaxation by neostigmine was delayed under hypothermia.[8-10)] Thus, more vigilant monitoring would be required especially in case of reversing the muscle relaxation under hypothermia.

Meanwhile, sugammadex, the modified gamma cyclodextrin, has become increasingly used. Sugammadex which encapsulates rocuronium molecule in a ratio of 1:1 has proven to be more effective and safer than anticholinesterase in many studies.[11)] Previous clinical trials evaluating the efficacy of sugammadex under mild hypothermia demonstrated that the antagonism of muscle relaxation tended to be slightly delayed and the delay was explained by the pharmacokinetic changes of sugammadex.[12, 13)] However, it was conceivable that hypothermia reduced the effect of sugammadex itself. Therefore, we aimed to evaluate the effect of hypothermia on the antagonism of muscle relaxation by sugammadex using rat isolated phrenic nerve-hemidiaphragm preparations.

METHODS

This study was processed after the approval from Instituitional Animal Care and Use Committee of Asan Institute for Life Sciences, Asan Medical Center (approval number 2016-13-054). Male Sprague-Dawley rats (250-350 g) were used for this study. Rats were raised in the Laboratory Animal Facility of the Asan Institute for Life Sciences in University of Ulsan.

Twenty rats were anesthetized with intraperitoneal injection of 50 mg kg^{-1} tiletamine/zolazepam (Zoletil50®, Virbac, Carros, France). After the assurance of appropriate anesthetic depth by the noxious stimulation of toe with a forcep, incision was created on the middle of the chest. The diaphragm and accompanying phrenic nerves were excised en bloc. Each phrenic nerve and hemidiaphragm was prepared and mounted in an organ bath filled with Kreb's solution (118 mmol l^{-1} NaCl, 30 mmol l^{-1} $NaHCO_3$, 11.4 mmol l^{-1} glucose, 5.0 mmol l^{-1} KCl, 2.5 mmol l^{-1} $CaCl_2$, 1.0 mmol l^{-1} KH_2PO_4 and 1.0 mmol l^{-1} $MgCl_2$). The bath solution was aerated with 95% oxygen and 5% carbon dioxide gas mixture and the alpha stat was used for the management of acidity. Temperature was maintained constant by circulation of thermostatically controlled water throughout the whole experimental period. Preparations were randomly assigned into 4 groups: group 1, 36°C (normothermia); group 2, 24°C (deep hypothermia); group 3, 28°C (moderate hypothermia); and group 4, 32°C (mild hypothermia) according to the Swiss classification.[14)]

The peripheral portion of phrenic nerve was connected to bipolar platinum electrodes and the central tendinous portion of the hemidiaphragm was connected to a force displacement transducer (Grass FT03, Grass Instrument Co., Quincy, Massachusetts, USA) to measure the isometric contraction of the hemidiaphragm at a resting tension of 2 g. Using a nerve stimulator (S88, Grass) and stimulation isolation unit (SIU5, Grass), train-of-four (TOF) stimulation (frequency 2 Hz, duration 0.2 ms) consisting of four supramaximal square-wave pulses was applied to the phrenic nerve via the bipolar platinum electrodes every 20 s throughout the study. Muscle contraction responses were recorded and then digitized with a PowerLab acquisition system (AD Instruments, Austin, Texas, USA) and stored on a computer using data charting

software (LabChart, ADInstruments).

After initiation of TOF stimulation, at least 30 min was allowed for stabilization of contraction responses with phrenic nerve stimulation. Then, rocuronium (Esmeron®, NV Organon, BH Oss, The Netherlands) 300 mcg as an initial loading dose was applied in the organ bath. If there was no change in first twitch (T1) height more than 3 times or 10 min elapsed, a booster dose of 150 mcg was added cumulatively until the first twitch response disappeared completely. After another 10 min, an equimolar dose of sugammadex (Bridion®, MSD, Oss, The Netherlands) corresponding to the total dose of administered rocuronium was added into the organ bath to evaluate the recovery of muscle contractions at different temperature. Equimolar sugammadex was calculated by the following formula:

Equimolar dose of sugammadex (mcg) = Dose of administered rocuronium (mcg) * 3.57

$$3.57 = \frac{\text{Molar mass of sugammadex [2178 (g/mol)]}}{\text{Molar mass of rocuronium [609.678 (g/mol)]}}$$

In all groups, we observed the antagonism of muscle relaxation for 30 min after sugammadex administration and we measured the following variables: T1 and TOF ratio at every 5 min until 30 min; time to recovery of T1 from 25 to 75% of the baseline value (recovery index).

Statistical analysis

All data are presented as the mean ± standard deviation or median (interquartile range [IQR]). To determine the sample size, we performed a pilot study and measured the recovery index in two groups (n = 3 for each). The recovery index of 32°C group was 611.3 ± 89.9 s and the recovery index of 36°C group was 302.3 ± 121.7 s. The calculated sample size with $\alpha = 0.05$ and power = 0.9 was eight in each group. Considering the dropouts, we decided on 10 samples/group.

Baseline characteristics including body weight, whole mass of phrenic nerve-hemidiaphragm preparation, mass, length and width of hemidiaphragm were compared using one-way analysis of variance (ANOVA). Dose-response curve of rocuronium was fitted using sine curve, one of the cyclic function. The frequencies of sine curve of each group was compared to evaluate the

effect of temperature on relaxation induced by rocuronium. Reversal by sugammadex was analyzed using slope of linear regression. The criteria for determining the degree of reversal was the recovery of T1 height and the recovery of TOF ratio. Recovery index was also compared among the groups using one-way ANOVA. All the statistical analysis was performed using R program (version 3.1.2). A p-value of less than 0.05 was considered significant.

RESULTS

Forty preparations were included in the analysis. All the groups contained 10 preparations each. There were no significant differences among the groups in baseline characteristics.

The dose-response curves of rocuronium were presented in figure1. The frequency of the dose-response curve showed significant difference among groups (overall p value < 0.001) (Table1). *Post hoc* analysis demonstrated that the frequency of group 2 was increased compared to that of group 3 and group 4 ($p = 0.010$, $p < 0.001$, respectively), while there was no significant difference between group 2 and group 1 ($p = 0.215$).

Table 1. Frequency of dose-response curve of rocuronium

Group	1 (n = 10)	2 (n = 10)	3 (n = 10)	4 (n = 10)	p
Frequency of dose-response curve	0.50566 [0.50540; 0.50596]	0.50624 *† [0.50596; 0.50669]	0.50537 [0.50514; 0.50553]	0.50496 [0.50480; 0.50514]	< 0.001

Note: Group 1, 36°C; group 2, 24°C; group 3, 28°C; and group 4, 32°C.

*, $p = 0.010$ (vs group3); †, $p < 0.001$ (vs group 4)

The recovery of T1 height showed significant difference among groups ($p < 0.001$) (Figure 2) (Table 2). *Post hoc* analysis revealed considerable delay in group 2 and group 3 compared with group 1 (all $p < 0.001$). However, there was no difference between group 1 and group 4 ($p = 0.178$).

The recovery of TOF ratio had similar pattern with that of T1 height (Figure 3) (Table 2). The recovery of TOF ratio significantly differed among groups ($p < 0.001$). *Post hoc* analysis demonstrated that the recovery of TOF ratio of group 2 and group 3 was significantly delayed compared with that of group 1 (all $p < 0.001$). However, no difference was observed between the recovery of TOF ratio of group 1 and group 4 ($p = 0.075$).

Table 2. Recovery after sugammadex administration

Group	1 (n=10)	2 (n=10)	3 (n=10)	4 (n=10)	p
Slope of the curve, T1 height	0.069 [0.052;0.099]	0.024 * [0.018;0.029]	0.018 * [0.015;0.024]	0.034 [0.034;0.039]	<0.001
Slope of the curve, TOF ratio	0.062 [0.052;0.114]	0.021 * [0.014;0.024]	0.012 * [0.008;0.019]	0.032 [0.027;0.037]	<0.001

Note: Group 1, 36°C; group 2, 24°C; group 3, 28°C; and group 4, 32°C.

*, $p < 0.001$ (vs group 1)

The recovery index was also evaluated and presented as median [IQR] (Table 3). Since not all preparations have reached more than 75% of initial T1 height, analysis was conducted with the data from which the recovery index was obtained. There was significant difference among the groups ($p = 0.001$). The recovery index of group 2 and group 3 were significantly prolonged compared with that of group 1 ($p = 0.005$ and 0.028, respectively). However, there was no difference between the recovery index of group 1 and group 4 ($p = 0.067$).

Table 3. Recovery index of each group

Group	1 (n=8)	2 (n=4)	3 (n=3)	4 (n=9)	p
Recovery index (s)	237.0 [185.5;391.0]	698.5 * [657.5;855.0]	813.5 † [700.0;927.0]	535.0 [515.0;639.0]	0.001

Note: Group 1, 36°C; group 2, 24°C; group 3, 28°C; and group 4, 32°C.

*, $p = 0.005$ (vs group 1); †, $p = 0.028$ (vs group 1)

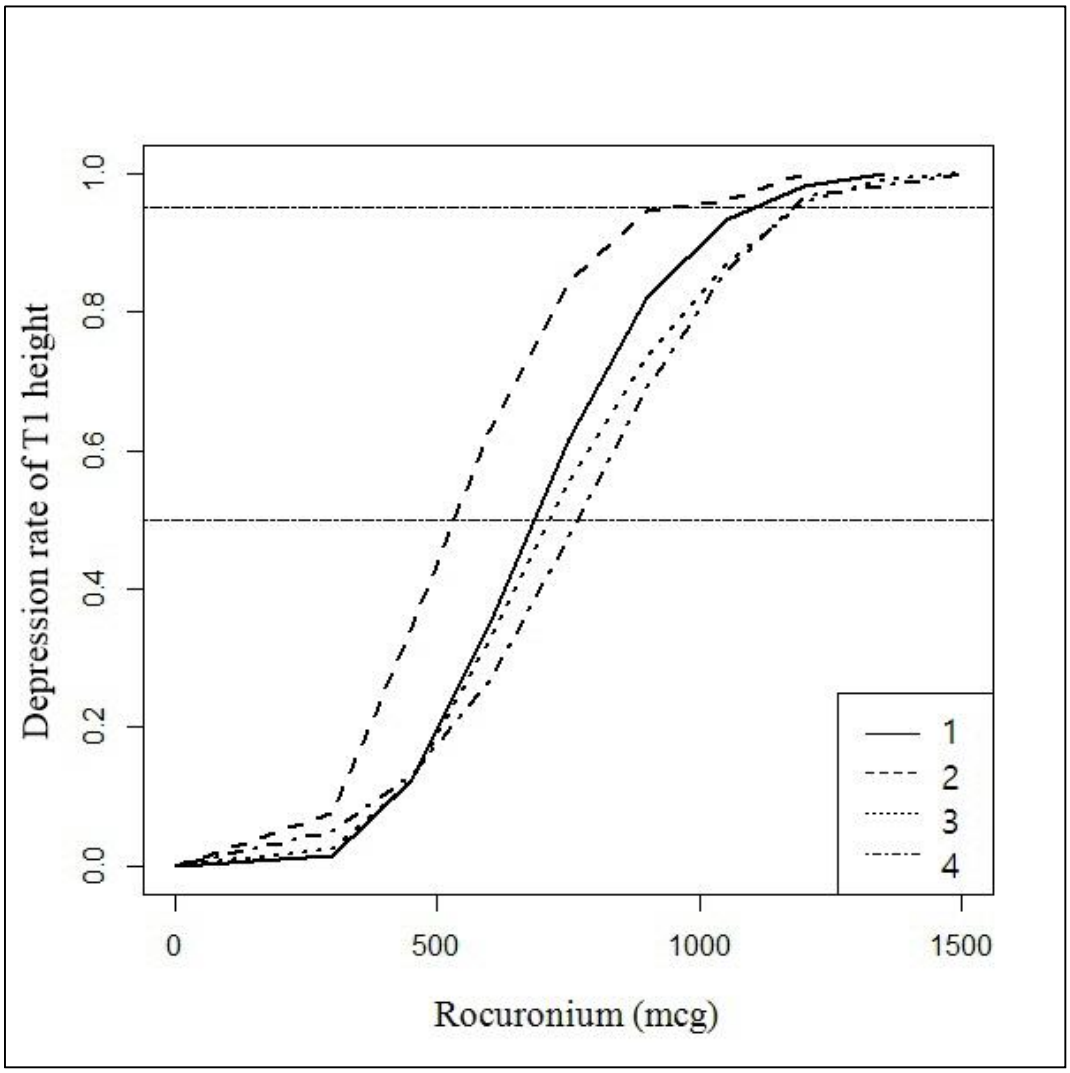

Figure 1. (A) Dose-response curves of rocuronium. (B) Frequency of the dose-response curve. Group 1, 36°C; group 2, 24°C; group 3, 28°C; and group 4, 32°C. There was significant difference in response to rocuronium among groups ($p < 0.001$).

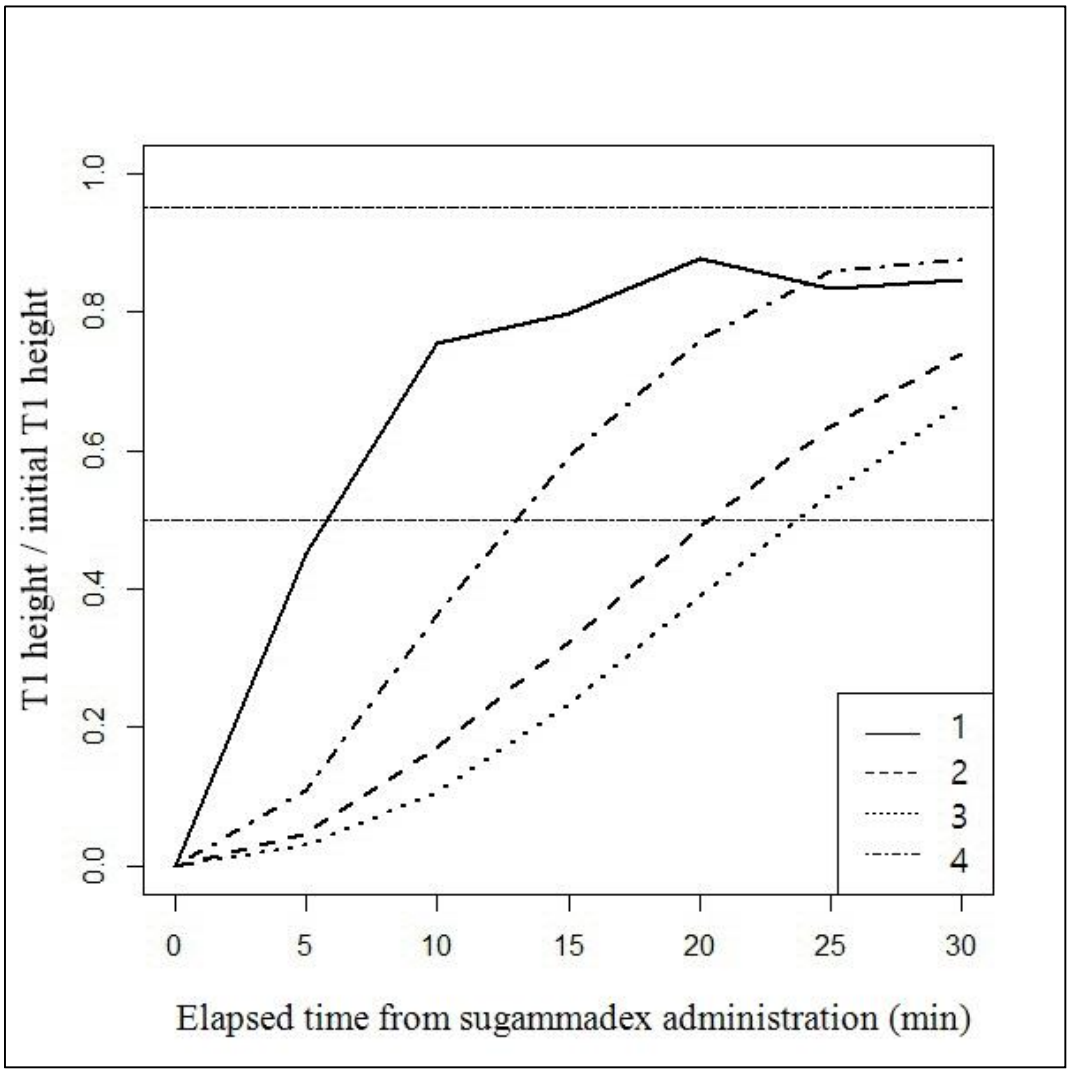

Figure 2. (A) Recovery curve of T1 twitch height by sugammadex. (B) Slope of the recovery curve of T1 twitch height. Group 1, 36°C; group 2, 24°C; group 3, 28°C; and group 4, 32°C. Recovery of T1 twitch height showed significant difference among groups ($p < 0.001$).

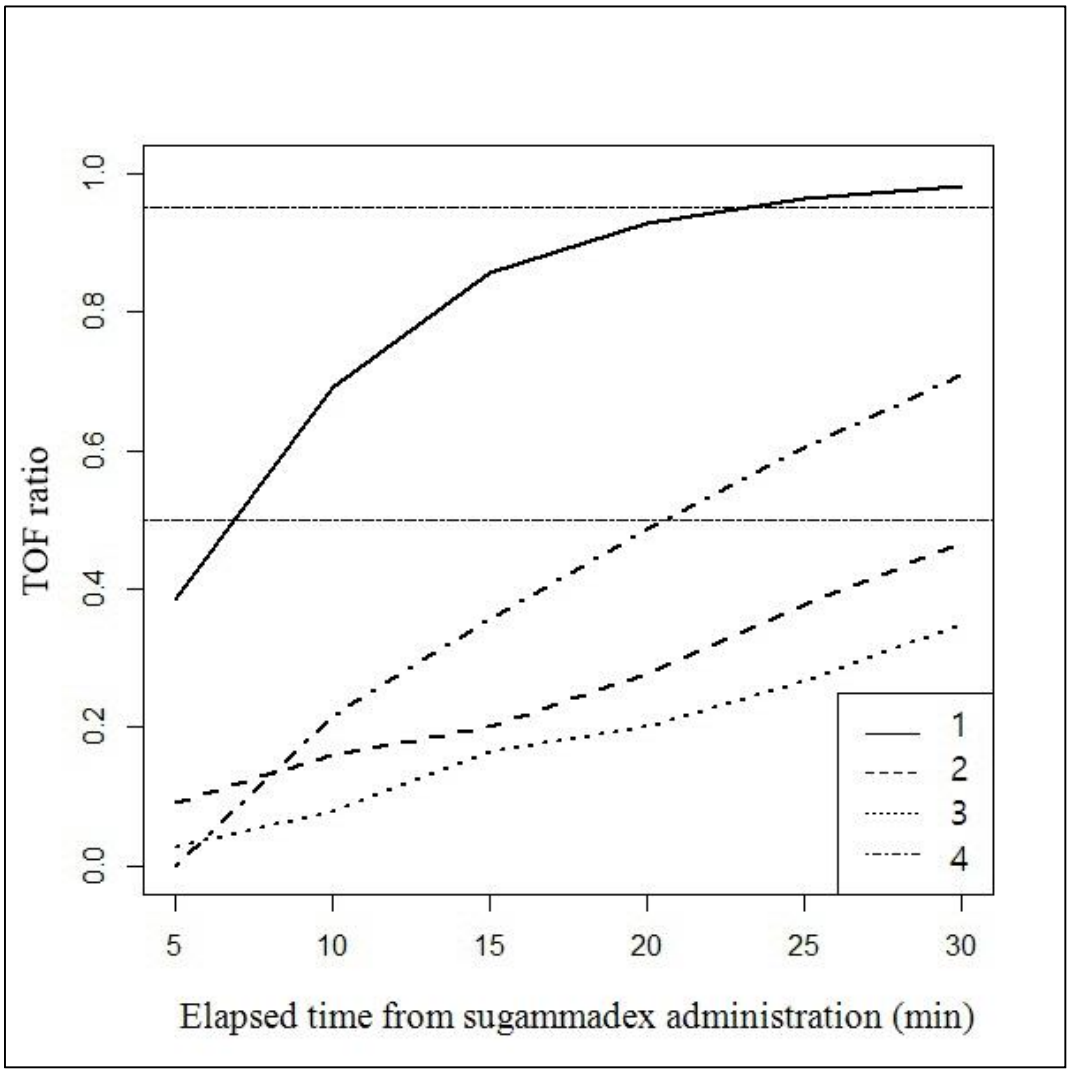

Figure 3. (A) Recovery curve of TOF ratio. (B) Slope of the recovery curve of TOF ratio. Group 1, 36°C; group 2, 24°C; group 3, 28°C; and group 4, 32°C. Recovery of TOF ratio showed significant difference among groups ($p < 0.001$).

DISCUSSION

In this study, we evaluated the association of the effect of rocuronium and the antagonism by sugammadex with hypothermia using an *in vitro* experiment. Rocuronium was potentiated under deep hypothermia. The effects of sugammadex was reduced in moderate and deep hypothermia based on the recovery of T1 height and TOF ratio. However, mild hypothermia did not affect the action of sugammadex.

The contraction of the muscle per se has been known to be altered with the change of temperature. The effects of temperature on contractility of skeletal muscle were covered in several studies. Many *in vitro* studies commonly reported that contractility of skeletal muscle was described to increase under hypothermic condition.[15, 16] The mechanism was presumed to be related to the adenosine triphosphate (ATP) receptor, increased sensitivity of the endplate membrane to agonist, and maximal transmitter release in deep hypothermia.[16-18]

As the temperature changes, the response to rocuronium were reported to be changed as well. Several animal studies demonstrated that neuromuscular blocking agents had prolonged effects under 30°C and that the change of pharmacokinetic factors might account for the result.[19, 20] Under hypothermia, the distribution, metabolism and excretion of some steroidal neuromuscular blocking agents including vecuronium and rocuronium are altered. The plasma clearance of these drugs is mainly caused by hepatic uptake, which is temperature-dependent. At low temperature, the hepatic uptake is reduced with decreased cardiac output and elimination rate is reduced and the concentration of the drug at the neuromuscular junction is higher than in normothermic condition.[9, 21, 22] The changed pharmacokinetics of rocuronium prolonged the effect under hypothermia.

Some *in vitro* studies and human studies also proved potentiation of steroidal muscle relaxants at hypothermia.[23-26] According to a previous study, the release of acetylcholine which was already made was maximal at 20°C-25°C and less at lower or higher temperature.[16] However, the mobilization of neurotransmitter including reuptake of acetylcholine was suppressed under

hypothermia.[16, 27, 28] Consequently, the depletion of neurotransmitter might be accelerated at 20°C-25°C. In other words, the concentration of acetylcholine at neuromuscular junction might initially increase, but once the preformed acetylcholine vesicle is exhausted, the lower concentration of acetylcholine is present at 20°C-25°C. Therefore, the sensitivity of neuromuscular junction to rocuronium was increased in deep hypothermia. The result that rocuronium was more potent in deep hypothermia in this study might be explained by the change of neurotransmitter concentration.

Besides, altered acidity accompanied with hypothermia might contribute to enhanced effect of rocuronium in deep hypothermia. There are two ways to manage the acidity during hypothermia; alpha stat and pH stat. Although pH stat has several benefits and is used in clinical situation, alpha stat is more physiological.[29] In this study using alpha stat principle, the total CO_2 concentration remained constant, but the acidity might be changed. The increased acidity of background solution under hypothermia might influence the potency of rocuronium. An *in vitro* study reporting the association of acidity with neuromuscular blocking agent identified that rocuronium was potentiated with higher acidity.[30] The authors suggested that the changes in tertiary ammonium ionization affected the sensitivity of nicotinic receptors.[30] Our result that the effect of rocuronium was enhanced at 24°C might be also associated with higher acidity in hypothermia.

There have been a few reports on the efficacy and safety of using sugammadex in hypothermia. Lee et al.[13] showed that deep rocuronium-induced neuromuscular block was safely reversed with sugammadex during mild hypothermia. Tamas Vegh et al.[12] also demonstrated that sugammadex was effective for complete recovery even in mild hypothermia after thoracic surgery. In these two studies, additional 40 s was required at low temperature, although the delay was not considered clinically or statistically significant.[12, 13] The result that there was no significant reduction of reversal effect of sugammadex under mild hypothermia was consistent with those of previous two studies. However, we identified that the antagonism of muscle relaxation by sugammadex in moderate and deep hypothermia group was significantly delayed. The effect of sugammadex, unlike that of rocuronium, was known to be independent on the

acid-base status.[31] Thus, our findings could be interpreted as the effect of temperature on sugammadex action excluding the effect of acidity, even though alpha stat was used.

A previous *in vitro* study which investigated the effect of temperature on neostigmine, the reversal effect from muscle relaxation induced by steroidal neuromuscular blocking agents at 27°C was slightly enhanced compared with normothermic condition.[24] However, we found that sugammadex was most effective in normothermic condition and the reversal effect tend to be weaker under hypothermia. The disparity between these two *in vitro* studies might be originated from the different mechanisms of action at neuromuscular junction. Because neostigmine, an anticholinesterase, has reversal effect by increasing acetylcholine at the neuromuscular junction, the interaction with cholinesterase and activity of cholinesterase are associated with the effect of neostigmine.[10] On the other hand, since sugammadex reverses the muscle relaxation by direct binding to rocuronium in 1:1 ratio, the interaction with rocuronium is important. The reduced effect of sugammadex under hypothermia might be related to a change of binding affinity between sugammadex and rocuronium in hypothermia.

Limitations of this study include that our results could not be extrapolated to clinical situation, since this study was carried out *in vitro*. However, this *in vitro* study identified that hypothermia influenced on the action of sugammadex, even without the pharmacokinetic effect. Second, the experiments were designed to focus on the phenomenon and did not investigate the biochemical mechanism at molecular level. However, this study identified that the efficacy of sugammadex was reduced under moderate and deep hypothermia. Based on this study, further studies to clarify the mechanism of reduced effect of sugammadex under hypothermia would be required.

CONCLUSIONS

In this *in vitro* study, muscle relaxation by rocuronium was potentiated in deep hypothermia. The antagonistic effect by sugammadex was reduced under moderate and deep hypothermia. However, mild hypothermia had no significant effect on the action of sugammadex.

REFERENCES

1. John M, Ford J, Harper M. Peri-operative warming devices: performance and clinical application. Anaesthesia 2014;69(6):623-38.
2. Yi J, Xiang Z, Deng X, Fan T, Fu R, Geng W, et al. Incidence of inadvertent intraoperative hypothermia and its risk factors in patients undergoing general anesthesia in Beijing: a prospective regional survey. PLoS One 2015;10(9):e0136136.
3. Bilgin H. Inadverdent perioperative hypothermia. Turk J Anaesthesiol Reanim 2017;45(3):124-6.
4. Marion DW, Penrod LE, Kelsey SF, Obrist WD, Kochanek PM, Palmer AM, et al. Treatment of traumatic brain injury with moderate hypothermia. New England Journal of Medicine 1997;336(8):540-6.
5. Hypothermia after cardiac arrest study group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346(8):549-56.
6. Chamorro C, Borrallo JM, Romera MA, Silva JA, Balandin B. Anesthesia and analgesia protocol during therapeutic hypothermia after cardiac arrest: a systematic review. Anesth Analg 2010;110(5):1328-35.
7. Sessler DI. Perioperative thermoregulation and heat balance. Lancet 2016;387(10038):2655-64.
8. Park WY, Macnamara TE. Temperature change and neuromuscular blockade by d-tubocurarine or pancuronium in man. Anesthesiology 1979;50(2):161-3.
9. Beaufort AM, Wierda JM, Belopavlovic M, Nederveen PJ, Kleef UW, Agoston S. The influence of hypothermia (surface cooling) on the time-course of action and on the pharmacokinetics of rocuronium in humans. Eur J Anaesthesiol Suppl 1995;11:95-106.
10. Heier T, Clough D, Wright PM, Sharma ML, Sessler DI, Caldwell JE. The influence of mild hypothermia on the pharmacokinetics and time course of action of neostigmine in anesthetized volunteers. Anesthesiology 2002;97(1):90-5.
11. Abrishami A, Ho J, Wong J, Yin L, Chung F. Cochrane corner: sugammadex, a selective reversal medication for preventing postoperative residual neuromuscular

blockade. Anesth Analg 2010;110(4):1239.

12. Végh T, Juhász M, László I, Vaskó A, Tassonyi E, Fülesdi B. Clinical observations on reversal of rocuronium-induced residual neuromuscular blockade by sugammadex after thoracic surgery. J Rom Anest Terap Int 2014; 21: 7-11
13. Lee HJ, Kim KS, Jeong JS, Kim KN, Lee BC. The influence of mild hypothermia on reversal of rocuronium-induced deep neuromuscular block with sugammadex. BMC Anesthesiol 2015;15:7.
14. Durrer B, Brugger H, Syme D. The medical on-site treatment of hypothermia: ICAR-MEDCOM recommendation. High Alt Med Biol 2003;4(1):99-103.
15. Zink J, Bose D. Cold potentiation of neuromuscular transmission in the avian biventer cervicis muscle. European journal of pharmacology 1974;28(1):149-56.
16. Hubbard JI, Jones SF, Landau EM. The effect of temperature change upon transmitter release, facilitation and post-tetanic potentiation. J Physiol 1971;216(3):591-609.
17. Harris JB, Leach GD. The effect of temperature on end-plate depolarization of the rat diaphragm produced by suxamethonium and acetylcholine. J Pharm Pharmacol 1968;20(3):194-8.
18. Ziganshin AU, Khairullin AE, Zobov VV, Ziganshina LE, Gabdrakhmanov AI, Ziganshin BA, et al. Effects of ATP and adenosine on contraction amplitude of rat soleus muscle at different temperatures. Muscle Nerve 2017;55(3):417-23.
19. Miller RD, Roderick LL. Pancuronium-induced neuromuscular blockade, and its antagonism by neostigmine, at 29, 37, and 41 . Anesthesiology 1977;46(5):333-5.
20. Ham J, Miller RD, Benet LZ, Matteo RS, Roderick LL. Pharmacokinetics and pharmacodynamics of d-tubocurarine during hypothermia in the cat. Anesthesiology 1978;49(5):324-9.
21. Mol WE, Fokkema GN, Weert B, Meijer DK. Mechanisms for the hepatic uptake of organic cations. Studies with the muscle relaxant vecuronium in isolated rat hepatocytes. J Pharmacol Exp Ther 1988;244(1):268-75.
22. Mol WE, Rombout F, Paanakker JE, Oosting R, Scaf AH, Meijer DK. Pharmacokinetics of steroidal muscle relaxants in isolated perfused rat liver. Biochem Pharmacol 1992;44(7):1453-9.

23. Yoneda I, Okamoto T, Aoki T, Fukushima K. The effect of temperature on the action of several neuromuscular blocking agents in vitro. Masui 1991;40(5):743-8.

24. Aziz L, Ono K, Ohta Y, Morita K, Hirakawa M. Effect of hypothermia on the in vitro potencies of neuromuscular blocking agents and on their antagonism by neostigmine. Br J Anaesth 1994;73(5):662-6.

25. Aziz L, Ohta Y, Yamada T, Morita K, Hirakawa M. The effect of isoflurane and temperature on the actions of muscle relaxants in rat in vitro. Anesth Analg 1995;80(6):1181-6.

26. Smeulers NJ, Wierda JM, van den Broek L, Gallandat Huet RC, Hennis PJ. Effects of hypothermic cardiopulmonary bypass on the pharmacodynamics and pharmacokinetics of rocuronium. J Cardiothorac Vasc Anesth 1995;9(6):700-5.

27. Carpenter DO. Temperature effects on pacemaker generation, membrane potential, and critical firing threshold in Aplysia neurons. J Gen Physiol 1967;50(6):1469-84.

28. Ward D, Crowley WJ, Johns TR. Effects of temperature at the neuromuscular junction. Am J Physiol 1972;222(1):216-9.

29. Baraka A. Alpha-stat vs. pH-stat strategy during hypothermic cardiopulmonary bypass. Middle East J Anaesthesiol 2004;17(4):705-12.

30. Aziz L, Ono K, Ohta Y, Morita K, Hirakawa M. The effect of CO2-induced acid-base changes on the potencies of muscle relaxants and antagonism of neuromuscular block by neostigmine in rat in vitro. Anesth Analg 1994;78(2):322-7.

31. Bom A, Mason R, McIndewar I. Org 25969 causes rapid reversal of rocuronium-induced neuromuscular block, independent of acid-base status. Anesthesiology 2002;96:A1009.

<Korean Abastract>

백서의 반횡격막-신경 표본에서 저체온증이 슈가마덱스의 작용에 미치는 영향

연구배경 및 목적: 마취과의사들은 종종 저체온증의 환자들에게 신경근 차단제와 길항제를 사용하는 상황을 맞닥뜨리게 된다. 이전의 여러 연구들은 저체온증이 근육의 수축과 신경근 차단제에 대한 반응을 변화시킨다는 것을 보고하였다. 그러나 저체온이 슈가마덱스에 의한 신경근 차단의 길항에 어떠한 영향을 끼치는지에 대해서는 알려진 바가 거의 없다. 그래서 본 연구에서는 저체온 상황에서 슈가마덱스의 작용이 어떻게 변화하는지 알아보고자 하였다.

연구재료 및 방법: 백서의 반횡격막-신경을 무작위로 4 군으로 나누어 배정하였다. 각 군은 스위스 분류 체계에 의하여 분류하였으며, 1 군은 정상 체온인 36℃, 2 군은 중증 저체온인 24℃, 3 군은 중등도 저체온인 28℃, 4 군은 경증 저체온인 32℃에서 실험이 진행되었다. 각 백서에서 얻어진 반횡격막-신경 표본은 정해진 온도의 수조에 담그고, 사연속자극(train-of-four, TOF)을 주어 첫 번째 반응의 높이(T1)가 완전히 나타나지 않을 때까지 점증적으로 로큐로니움을 투여하였다. 완전 차단이 이루어진 시점으로부터 10 분 후에 로큐로니움과 등몰의 슈가마덱스를 투여하고 30 분 동안 T1 의 회복과 첫번째에 대한 네번째 반응의 높이를 백분율로 표시한 TOF 비의 회복, 회복지수를 평가하였다.

결과: 최종적으로 40 개의 반횡격막-신경 표본이 분석해 포함되었다. 로큐로니움에 대한 용량-반응 곡선은 네 군 간 비교에서 유의한 차이를 보였다 ($p < 0.001$). 특히 2 군의 경우 3 군, 4 군에 비해서 로큐로니움의 효과가 증강된 것을 확인할 수 있었다 (모든 $p < 0.001$). T1 의 회복을 비교해보았을 때, 2 군과 3 군은 1 군에 비하여 회복이 지연되었다 (모든 $p < 0.001$). TOF 비의 회복 역시 2 군과 3 군에서 1 군에 비하여 지연되었다 (모든 $p < 0.001$). 회복지수도 1 군에 비해 2 군과 3 군에서 유의하게 연장되어 있었다 (각각 $p = 0.005, 0.028$).

결론: 이번 생체 외 실험에서, 로큐로니움에 의한 신경근 차단 효과는 중증 저체온에서 증강됨을 확인할 수 있었다. 슈가마덱스에 의한 신경근 차단의 역전 효과는 중등도와 중증 저체온 환경에서 감소되었다. 그러나 경증 저체온은 슈가마덱스의 작용에는 유의한 영향을 끼치지 못하였다.