Change in the effect of rocuronium after pneumatic tourniquet release in patients undergoing unilateral total knee arthroplasty

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Background: A pneumatic tourniquet is commonly used in orthopedic surgery. However, neuromuscular blocking agent can be sequestered in the isolated limb and be reabsorbed into the systemic circulation after tourniquet release, potentially delaying extubation. To investigate the change in the train-of-four (TOF) ratio after tourniquet release and correlate the TOF ratio change with the extubation time.

Methods: Forty patients undergoing unilateral total knee arthroplasty were enrolled. Before and after the pneumatic tourniquet release, 10 measurements of the TOF ratio were averaged and compared. Additionally, we investigated the correlation between the percentage change in the TOF ratio before and after tourniquet release and the extubation time.

Results: Among the 40 patient subjects, 30 showed a TOF ratio before tourniquet release and 10 showed only a TOF count. Of the 30 patients with a TOF ratio, 21 showed a TOF ratio increase after tourniquet release and 9 showed a TOF decrease; both increase and decrease were statistically significant \(P < 0.001\) and \(P = 0.008\), respectively. The extubation time showed a weak negative correlation with the percentage change in the TOF ratio after tourniquet release \(P = 0.004\).

Conclusions: In orthopedic surgery using a pneumatic tourniquet, neuromuscular function monitoring may be required to monitor the change in the effect of neuromuscular blocking agent before and after tourniquet release, which may help to improve anesthesia safety. (Anesth Pain Med 2015; 10: 36-41)

Key Words: Neuromuscular blocking agents, Total knee arthroplasty, Tourniquets, Train-of-four monitoring.

INTRODUCTION

Pneumatic tourniquets are widely used in orthopedic surgery to improve surgical field visibility and decrease intraoperative blood loss. Despite their advantages, pneumatic tourniquets can lead to the release of ischemic metabolites and cause transient hemodynamic changes after deflation [1]. Drugs administered prior to pneumatic tourniquet inflation can be affected by tourniquet pressure release due to a transient change in pharmacokinetics and pharmacodynamics [2,3]. Neuromuscular blocking agent (NMBA), which is systematically distributed after administration, can be sequestered in the isolated limb when a tourniquet is inflated and be reabsorbed into the systemic circulation after tourniquet release [3]. In addition, NMBA administered after pneumatic tourniquet inflation may not be delivered to isolated limbs and its pharmacokinetics may also be affected after tourniquet release. Changes in the NMBA effect may affect the reversibility of paralysis, altering the recovery period of general anesthesia [3].

Most patients undergoing total knee arthroplasty are elderly and have altered drug metabolism, changes in receptor sensitivity, and impairment of the normal homeostasis [4]. Decreased drug elimination and total body water in elderly patients can also prolong the effect of NMBA [5,6]. Use of pneumatic tourniquets can alter the effect of NMBA, causing changes in the recovery from neuromuscular block in elderly patients who are undergoing orthopedic surgery under general anesthesia. In our present study, we evaluated neuromuscular function with the train-of-four (TOF) ratio change before and after tourniquet release and determined the relationship between the TOF ratio change and the extubation time in patients undergoing total knee arthroplasty.

The aim of the present study was to determine whether the
TOF ratio change after tourniquet release affects delayed extubation in elderly patients.

### MATERIALS AND METHODS

After obtaining Institutional Review Board approval (approval number 2013-0009), 40 patients admitted for elective unilateral total knee arthroplasty were enrolled. Patients with known neuromuscular disorder, hepatic or renal disease, severe cardiopulmonary dysfunction, past history of drugs that might alter rocuronium metabolism, and/or a body mass index (BMI: kg/m$^2$) < 18 or > 35 were excluded. Patients’ demographics are shown in Table 1.

None of our patients received premedication. General anesthesia was induced by propofol at 2 mg/kg, followed by tracheal intubation after intravenous administration of rocuronium at 0.6 mg/kg and the TOF ratio reached zero. Anesthesia was maintained by the administration of 6-8 vol% desflurane and a fresh gas flow of 1 L/min of a 50% oxygen and nitrous oxide mixture. The depth of anesthesia was monitored using the bispectral index (BIS; BIS A-1050; Aspect Medical Systems, Newton, MA, USA) and was maintained at 40–60 BIS during surgery. All patients were ventilated with a tidal volume of 8–10 ml/kg and respiratory rate of 10–12 breaths/min during surgery to maintain an end-tidal carbon dioxide concentration of 30–35 mmHg. Body temperature (BT) was monitored with an esophageal temperature probe (Esophageal Stethoscope; DeRoyal Inc., Powell, TN, USA) and maintained at 35.5°C–36.5°C by a forced air-warming system (Bair Hugger™ Model 505; 3M, St. Paul, MN, USA). Neuromuscular transmission (NMT) was monitored by the acceleromyographic response of the adductor pollicis muscle using surface electrodes (TOF-Watch® SX; Organon Ireland Ltd., Dublin, Ireland).

Before the initial NMBA administration during anesthesia induction, a calibration of the TOF was performed and the TOF ratio was repeatedly monitored every 15 seconds until extubation. A pneumatic tourniquet applied to the ipsilateral thigh was inflated to 350 mmHg during the surgical procedure and deflated after skin layer closure was completed. The TOF ratio was recorded 10 times before and after tourniquet release. When the TOF ratio could not be calculated, a TOF count was alternatively recorded. When spontaneous respiratory movement was observed within 30 minutes before tourniquet release, the patient’s breathing was assisted by synchronized intermittent mandatory ventilation and no additional rocuronium was administered. After TOF measurement was completed, volatile anesthetics were immediately discontinued and patients were ventilated with a fresh gas flow of 8 L/min of 100% oxygen. When spontaneous respiratory movement appeared and the TOF count was ≥ 4, a single dose of neostigmine (50 μg/kg) and glycopyrrolate (8 μg/kg mixture) was administered.

Extubation was performed when the patient showed all of the following conditions: adequate spontaneous breathing, intentional response to verbal command, and a TOF ratio > 0.9. Extubation time was defined as the time from volatile anesthetic discontinuation to the completion of extubation. Simultaneously with the TOF ratio, the mean blood pressure and BT were recorded every minute and averaged values were used.

Based on the findings of a previous study, a sample size of 20 patients was calculated to detect a 50% change in the TOF ratio after tourniquet release with a type I error of 0.05 and power of 0.8. In our present pilot study, we assumed that the TOF ratio would be observed in nearly 50% of patients and observed a TOF change in 40 patients without sample size calculation. Statistical analysis was performed using SPSS 13.0 (SPSS Inc., Chicago, IL, USA). The Shapiro-Wilk test was used to check the normality of the data. The average values of the TOF ratio, MAP, and BT measured before and after tourniquet release were compared using a paired t-test or Wilcoxon signed-rank test. A Mann-Whitney rank sum test or

| Table 1. Demographics of the Study Patients Showing a TOF Ratio or a TOF Count Only |
|-----------------|-----------------|-----------------|
| Variables       | TOF ratio appeared (n = 30) | TOF count only appeared (n = 10) |
| Age (yr)        | 68.7 ± 3.8       | 70.5 ± 4.5       |
| Sex (M : F)     | 3 : 27           | 0 : 10           |
| Body mass index (kg/m$^2$) | 27.3 ± 3.5       | 24.7 ± 2.6       |
| Amount of initially administered NMBA (mg) | 45.5 ± 5.3       | 43.0 ± 6.7       |
| Tourniquet time (min) | 114.1 ± 26.0   | 116.9 ± 22.4     |

Data are expressed as the mean ± SD or as a number. NMBA: neuromuscular blocking agent, TOF: train-of-four.
A total of 40 patients were enrolled in the present study. The TOF ratio appeared before and after tourniquet release in 30 of these patients whereas 10 patients showed only a TOF count. In the 30 patients showing a TOF ratio after tourniquet release, the TOF ratio increased in 21 (70%) and decreased in 9 (30%) cases. There were no differences in the mean blood pressure and BT between patients showing a TOF ratio increase and those showing a TOF ratio decrease after tourniquet release. However, extubation time decreased more in patients showing a TOF ratio decrease than in patients showing a TOF increase (7.8 minutes vs. 11.2 minutes, respectively, P = 0.01; Table 2).

Individual values and the median TOF ratio before and after tourniquet release are shown in Fig. 1. There was a statistically significant increase (Fig. 1A) and decrease (Fig. 1B) in the TOF ratio after tourniquet release [0.37 to 0.39 (P < 0.001) and 0.38 to 0.32 (P = 0.008), respectively]. The mean percentage change in the TOF ratio was 15.1% in patients showing a TOF ratio increase and −10.0% in patients showing a TOF ratio decrease. The median TOF ratio increased from 0.37 to 0.40 after tourniquet release. In patients showing a TOF count only, the TOF count changed from 2 [1-3] to 2 [1-4] after tourniquet release (P = 0.038). The extubation time showed a negative correlation with the percentage change in the TOF ratio after tourniquet release (correlation coefficient = −0.54, P = 0.004; Fig. 2).

Table 2. Comparison of Variables Between the Study Patients Showing a TOF Ratio Increase or Decrease after Tourniquet Release

| Variables                        | TOF increase (n = 21) | TOF decrease (n = 9) |
|---------------------------------|-----------------------|----------------------|
| Body temperature (°C)           |                       |                      |
| Before tourniquet release       | 36.7 ± 0.6            | 36.5 ± 0.5           |
| After tourniquet release        | 36.7 ± 0.5            | 36.4 ± 0.5           |
| Mean blood pressure (mmHg)      |                       |                      |
| Before tourniquet release       | 85.8 ± 10.9           | 87.8 ± 9.9           |
| After tourniquet release        | 80.2 ± 12.1           | 82.7 ± 5.1           |
| Extubation time (min)*          | 7.8 ± 2.7             | 11.2 ± 3.6           |

Data are expressed as the mean ± SD. TOF: train-of-four. *P < 0.05.

**Fig. 1.** Change in the Train-of-four Ratio Before and After Tourniquet Release. (A) Individual values and a box plot of the train-of-four ratio change in patients with a train-of-four ratio increase after tourniquet release. The median value of the train-of-four ratio changed from 0.37 to 0.39 after tourniquet release (P < 0.001). (B) Individual values and a box plot of the train-of-four ratio change in patients with a train-of-four ratio decrease after tourniquet release. The median value of the train-of-four ratio changed from 0.38 to 0.32 after tourniquet release (P = 0.008).
DISCUSSION

A pneumatic tourniquet is advantageous for many surgical aspects, but it can alter the hemodynamic change after pressure release, as well as during inflation [7,8]. In lower limb surgery, approximately 15% of the circulating blood volume can be changed by tourniquet application, causing transient and significant changes in hemodynamic parameters [9]. When tourniquet pressure is released, some factors, including reperfusion blood flow to the isolated limb, reflex vasodilation, and systemic reabsorption of ischemic metabolites in the ischemic limb, have been shown to play major roles in the transient hemodynamic change [7,10,11]. Moreover, the pharmacokinetics and pharmacodynamics of drugs administered before tourniquet inflation can also be affected by tourniquet appliance. Previous studies revealed that the plasma concentrations of midazolam, fentanyl, and sufentanil increased after tourniquet release [2,12]. And the increased plasma concentration could be explained by reabsorption in the isolated limb of the sequestered drug, which was administered prior to tourniquet inflation. In our current analysis, the TOF ratio increased after pneumatic tourniquet release and was correlated with the extubation time.

NMBA can facilitate tracheal intubation and improve the surgical environment during general anesthesia, but the residual effects of NMBA can prolong muscle weakness, impair the airway reflex, and subsequently delay recovery from anesthesia [13]. Thus, intraoperative NMT monitoring can be required to improve the quality of recovery following general anesthesia, particularly in orthopedic surgery, where pneumatic tourniquets are frequently used and may affect the plasma concentration of anesthetic drugs. Because the recovery from neuromuscular blockade has been related to the plasma concentration and the drug-receptor affinity [14,15], pneumatic tourniquet release may alter the plasma concentration of NMBA by changing the volume of distribution or by releasing the sequestered drugs in the isolated limb.

In our present study, the observed TOF ratio change after tourniquet release might suggest how tourniquets affect the action of NMBA, but the presence of both a TOF ratio increase and decrease cannot clearly explain the tourniquet effect. Moreover, the clinical significance of this remains uncertain. Because 10 of our 40 patients showed a TOF count only, the effect of a pneumatic tourniquet on the NMBA effect was difficult to predict. When a tourniquet is released, the sequestered amount of NMBA and ischemic metabolites can be reabsorbed into the systemic circulation, causing transient metabolic acidosis and potentiation of the effect of NMBA [16]. On the other hand, tourniquet release can allow blood flow to the ischemic limb, increasing the volume of distribution and possibly decreasing the plasma concentration of NMBA. In our current results, the increased volume of distribution after tourniquet release would be more likely to attenuate the NMBA effect than the release of sequestered rocuronium. Although a previous study showed a transient increase in the plasma concentration of vecuronium and a decreased TOF ratio after tourniquet release [3], our evaluation of rocuronium showed a different result, which may be related to the pharmacokinetic properties of this drug [17]. Moreover, an exsanguination procedure prior to tourniquet inflation and a long inflation time may decrease the effect of the sequestered amount of drug. BT also potentiates the effect of NMBA [18]. Accordingly, we provided a forced air-warming system externally and the BT did not change after tourniquet release, minimally affecting the TOF ratio. Due to the many factors affecting the NMBA effect, perioperative NMT monitoring is strongly recommended.

The extubation time in our study was found to be inversely correlated with the percentage change in the TOF ratio after tourniquet application, suggesting that an increased NMBA effect may delay extubation. Compared with patients with a TOF ratio increase, patients with a TOF ratio decrease showed a longer extubation time. Because it is difficult to predict the TOF ratio after tourniquet release, there is a need to closely

![Correlation Between the Extubation Time and the Percentage Change in the Train-of-Four Ratio Before and After Tourniquet Release. There was a weak negative correlation between the percentage change in the train-of-four ratio and the extubation time (coefficient = −0.54, P = 0.004).](image-url)
monitor the TOF ratio in procedures that use a tourniquet. Although there would be many possible causes for the differences between the two groups, extubation time may be prolonged by several factors, including individual variations in drug-receptor affinity, potentiated effects of NMBA with volatile anesthetics, or sequestered rocuronium. The effect of a pneumatic tourniquet on factors affecting the NMBA effect could be investigated in a future study.

There were several limitations to our present study. First, because of the relatively small sample size, the correlation between the TOF ratio change and extubation is still not definitive. Moreover, for comparison of the NMBA effect or the extubation time, it would be preferable to measure the TOF ratio at the time of the administration of the reversal agent or to measure the duration to reach a TOF ratio > 0.9. Therefore, further analysis in a study with a well-controlled design and more detailed clinical outcomes in a large population is required to validate our results. Second, we did not investigate the time from the administration of rocuronium to tourniquet inflation and from tourniquet release to the end of surgery. Consideration of the duration before tourniquet inflation and after tourniquet deflation may be required to determine the effect of the tourniquet on pharmacokinetics and clinical outcomes in the recovery from anesthesia. In our present study, data were collected in patients undergoing a specific surgical procedure in which the process was similar and thought to be relatively homogenous.

Third, rocuronium may not be suitable for investigating the change after tourniquet release because of its lower potency and short duration of action. To investigate the clinical effect of NMBA, a more potent drug with increased affinity for receptors in the neuromuscular junction is preferable [19]. In addition, volatile anesthetics such as desflurane can potentiate the NMBA effect, hindering assessment of the effect of NMBA on delayed extubation [20-22]. Therefore, further studies incorporating a higher dose of rocuronium or total intravenous anesthesia would be preferable. In addition, the effect of a pneumatic tourniquet on the other class of NMBA, such as benzylisoquinoline, which has a different drug metabolism, could also be of interest to explore in the future.

In conclusion, the pneumatic tourniquet may change the TOF ratio after tourniquet pressure release and cause an unpredictable recovery mode. Because it is difficult to predict whether the TOF ratio would increase or decrease after tourniquet release, monitoring of this ratio before and after tourniquet release may be required.

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