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ORIGINAL ARTICLE

Efficiency of the TOF-Cuff™ for the evaluation of rocuronium-induced neuromuscular block and its reversal with sugammadex: a comparative study vs. acceleromyography

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Abstract

Purpose The aim of this study was to compare TOF-Cuff™ (TOF-C) and TOF-Watch™ (TOF-W) data following rocuronium-induced neuromuscular block and its reversal with sugammadex.

Methods Twenty elderly patients aged 68–82 years scheduled for surgery under general anesthesia were enrolled in this study. After induction of anesthesia, neuromuscular block resulting from administration of 0.6 mg/kg rocuronium was concurrently evaluated using TOF-C and TOF-W. The onset of neuromuscular block and duration until the first twitch response following post-tetanic count (PTC) and 2 Hz train-of-four (TOF) stimulation reappeared were evaluated. When the response to the TOF stimulus was detected with both monitors, additional doses of rocuronium were administered to maintain the neuromuscular block. After surgery, 2 mg/kg sugammadex was administered when 1–2 TOF twitches were observed with the TOF-W and the time required for facilitated recovery to a TOF ratio of > 0.9 was assessed.

Results Regression analyses revealed no statistically significant differences in the mean [SD] onset of rocuronium-induced neuromuscular block [127.8 (27.2) s, 123.5 (30.5) s], time to recovery of the first PTC twitch [23.9 (8.0) min, 25.4 (8.6) min], time to recovery of the first twitch with TOF stimulation [37.2 (8.8) min, 38.9 (11.1) min] and time to adequate reversal with sugammadex [139.2 (30.6) s, 151.8 (31.5) s] between TOF-C and TOF-W, respectively. Bland–Altman analyses also showed acceptable ranges of the biases and limits of agreement between the two methods.

Conclusions TOF-C may be clinically applicable for the evaluation of both the depth of neuromuscular block and restoration of neuromuscular function.

Keywords TOF-Cuff ™ · Neuromuscular block · Elderly

Introduction

With the tremendous popularity of laparoscopic surgery, which requires adequate muscle relaxation, objective assessment of the depth of neuromuscular block is necessary to optimize surgical conditions [1, 2] and enhance patient safety [3, 4]. Although mechanomyography used to be regarded as the gold standard for neuromuscular monitoring, it is not suitable in routine clinical practice because of poor operability and its limited availability in operating theaters because it requires a large-sized machine and is expensive [5, 6]. Hence, the TOF-Watch™ (TOF-W), which uses the principle of acceleromyography, has been introduced in clinical anesthesia and further applied as a reliable monitor in numerous clinical studies [7]. Use of the TOF-W has the advantages of practicality, versatility, precision [5], and applicability at various muscles [8, 9]. In Japan, the TOF-Cuff™ (TOF-C), which utilizes the new and simple method of stimulation of the ulnar nerve at the upper arm by active electrodes incorporated into a noninvasive blood pressure cuff, has been available for clinical use since 2017. After the ulnar nerve is stimulated at the upper arm, contractile responses of the forearm muscles are principally evoked.

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The movement of the forearm may secondarily cause contraction of the brachial muscles. Simultaneously, the median and musculocutaneous nerves may also be stimulated and the evoked neuromuscular responses of the brachial muscles are recorded as changes in the generated cuff pressure. Although the simplicity of the TOF-C method may lead to increasing popularity of this neuromuscular monitoring method in clinical settings, the reliability of the data recorded with the TOF-C still needs to be evaluated. Rodiera and colleagues were the first to report the reliability of the cuff method in comparison with mechanomyography for monitoring spontaneous recovery of the TOF ratio following rocuronium-induced neuromuscular block [10]. Thereafter, the effectiveness of the cuff method has not been published in the literature. We felt the need to compare the TOF-C and acceleromyography devices usually used in clinical anesthetic practice by assessing the time to onset of neuromuscular block, duration to deep and moderate block and facilitated recovery with sugammadex. The aim of this study was to clarify whether the differences between the parameters of neuromuscular block transition indicated by the TOF-C and TOF-W are in the acceptable range.

Patients and methods

The study protocol was approved by the Hospital Ethics Committee on Human Rights in Research (Nihon University Itabashi Hospital, Clinical Research Judging Committee). After registration with the University Hospital Medical Information Network (ID: UMIN000031154), 20 patients consented to participate in this study. The subjects were American Society of Anesthesiologists (ASA) physical status I–III patients (I: $n=10$, II: $n=8$, III: $n=2$), 65 years of age or older, who were scheduled to undergo elective artificial knee joint replacement surgery under general anesthesia. None of the patients were allergic to neuromuscular blocking agents nor were they taking any drugs known to interact with these agents.

On arrival at the operating room, all patients were monitored by electrocardiogram, noninvasive blood pressure, and pulse oximetry. An intravenous catheter was inserted into a forearm vein or a dorsal vein. The unilateral femoral nerve block with 15 mL of 0.25% levobupivacaine was performed under ultrasonic guidance. General anesthesia was induced with 0.1–0.3 μg/kg/min remifentanil, 1–2 μg/kg fentanyl, and 1–2 mg/kg propofol administered intravenously, while patients received 100% oxygen through an anesthesia facemask. After insertion of a supraglottic airway without a neuromuscular blocking agent, anesthesia was maintained with 4–6% end-tidal desflurane and a continuous infusion of 0.1–0.3 μg/kg/min remifentanil, as required. A TOF-W (Organon Ltd, Dublin, Ireland) was set on the right forearm. The electrodes were placed on the ulnar nerve proximal to the wrist and the acceleration transducer was attached to the thumb with a hand adaptor. Next, the pressure cuff of the TOF-C (RGB Medical Devices, Madrid, Spain) was rolled around the left upper arm with the stimulating electrodes positioned over the ulnar nerve proximal to the elbow. After calibration of the response using the preset mode with 50 mA stimulation, the ulnar nerve was stimulated with square-wave stimuli of 0.2 ms duration, which were delivered in a TOF mode at 2 Hz every 15 s. After checking stable TOF responses for a few minutes, all the patients received rocuronium 0.6 mg/kg intravenously. The following variables were measured in all patients: onset time (s) from the time of administration of rocuronium to maximum depression of T1, time (min) from the administration of rocuronium to spontaneous recovery of the post-tetanic count (PTC) and TOF count, and the time (s) required for facilitated recovery from the end of injection of sugammadex to a TOF ratio of >0.9.

Statistics

Among the test variables, reversal time after the administration of sugammadex is judged to be most linked to patient safety. Our previous study [11] revealed that the average [SD] time for reversal of rocuronium-induced moderate neuromuscular block with sugammadex recorded using the TOF-W was 173.4 [54.8] s. We considered a 30% change in the reversal time observed between the two monitors to be clinically relevant. To detect this difference with $a=0.05$ and a power of 0.80, it was necessary to include 19 patients in this study. Considering potential dropouts, we enrolled 20 patients in this study. Their data are presented as mean [SD]. Linear correlations between the measured parameters were studied using the method of least squares analysis. Agreement between the two methods was assessed using the statistical method of Bland and Altman [12] and bias and limits of agreement for each variable were calculated.

Results

Data from all the patients were analyzed. Median values of the patients' baseline age, height, and weight were 76.0 [3.8] years, 151.2 [7.9] cm, and 56.3 [8.1] kg, respectively, and the number of males and females was 3 and 17, respectively. As shown in Fig. 1, regression analyses revealed no statistically significant differences in the onset of rocuronium-induced neuromuscular block [127.8 (27.2) s vs. 123.5 (30.5) s], time to recovery of the first twitch of the PTC [23.9 (8.0) min vs. 25.4 (8.6) min], time to recovery of the first twitch of the TOF count [37.2 (8.8) min vs. 38.9 (11.1) min], and the time for adequate reversal with sugammadex [139.2

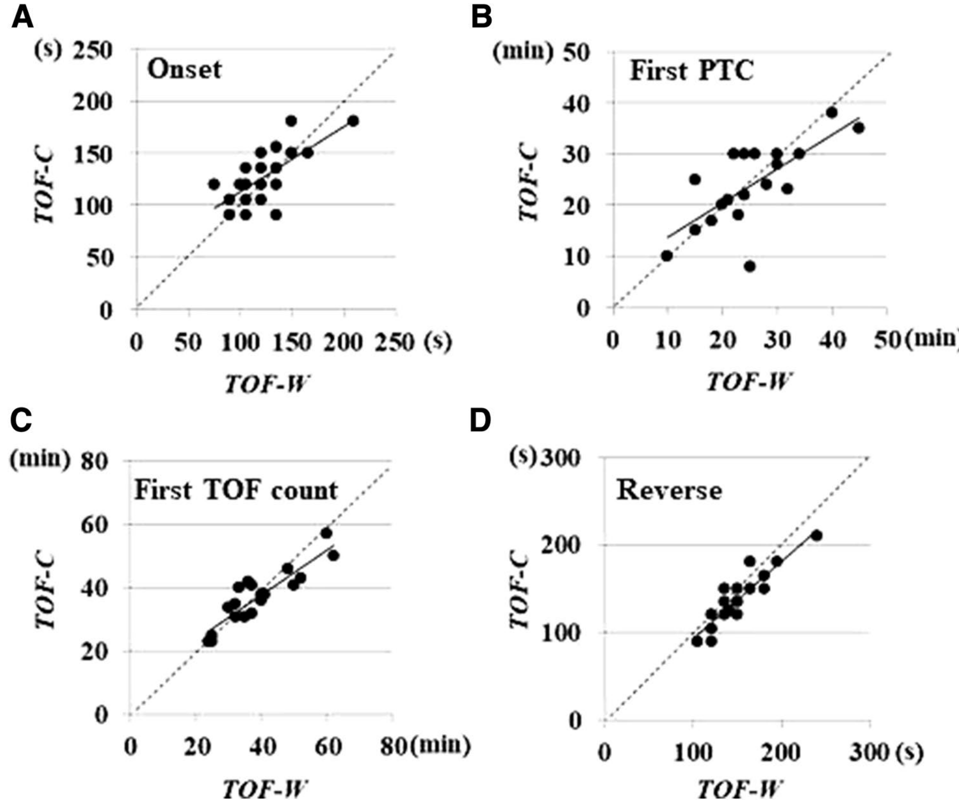

Fig. 1 **a** A linear regression of onset time of rocuronium between TOF-W and TOF-C. Onset time in TOF-C (s) = 0.62. Onset time in TOF-W + 50.9, $R^2 = 0.489$. **b** A linear regression of the time for reappearance of the first PTC in TOF-C (min) = 0.67. The time for reappearance of the first PTC in TOF-W + 6.99, $R^2 = 0.513$. **c** A linear regression of the time for reappearance of the first TOF count between TOF-W and TOF-C. The time for reappearance of the first TOF count in TOF-C (min) = 0.71. The time for reappearance of the first TOF count in TOF-W + 9.47, $R^2 = 0.800$. **d** A linear regression of the reversal time to a TOF ratio > 0.9 with sugammadex in TOF-C (s) = 0.88. The reversal time to a TOF ratio > 0.9 with sugammadex in TOF-W + 5.34, $R^2 = 0.821$. *TOF-W* TOF-Watch, *TOF-C* TOF-Cuff, *PTC* post-tetanic counts

(30.6) s vs. 151.8 (31.5) s] between the TOF-C and TOF-W, respectively. Bland–Altman analyses also showed acceptable ranges of bias (averaged difference between the TOF-W and TOF-C) and limits of agreement of the two methods (Fig. 2). The bias [95% confidence interval] and limits of agreement were − 4.3 [− 14.2 to 5.6] s and − 49.5 to 40.9 s for the onset of neuromuscular block, 1.5 [− 1.3 to 4.3] min and − 11.1 to 14.1 min for the time to the first twitch of the PTC, 1.7 [− 0.5 to 3.9] min and − 8.4 to 11.9 min for the time to the first twitch of the TOF count, and 12.6 [6.7–18.5] s and − 14.3 to 39.6 s for TOF ratios > 0.9, respectively.

Discussion

The results of our study demonstrated that the TOF-C, a cuff pressure-based myography device, is reliable for evaluating the onset and depth of rocuronium-induced neuromuscular block, as well as its reversibility with sugammadex, similar to the TOF-W that is commonly used in clinical anesthesia. Linear regression analyses and the biases and limits of agreement in Bland–Altman plots indicated that the data observed by both methods are basically similar. Accordingly, the TOF-C can be used to determine the optimal timing of tracheal intubation, the need for additional doses of neuromuscular blocking agents, and the timing of safe extubation in daily clinical practice.

In our study, although almost all the data were within the range of the upper and lower limits of agreement in Bland–Altman analyses, there was a following tendency in each measurement. The biases suggest that the onset time of rocuronium-induced neuromuscular block indicated by the TOF-C is slower than that shown by the TOF-W. On the other hand, the TOF-C indicated an earlier time to recovery of the first twitch in the PTC and TOF count, and to adequate reversal with sugammadex. Since the TOF-C senses the coarse movements of the more centrally located larger muscles, it is estimated that the TOF-C may express the transition of neuromuscular block in the brachial muscles, which have a lower sensitivity to non-depolarizing neuromuscular agents. For instance, the biceps brachii muscle, the contraction of which seems to influence the cuff pressure the most, has a greater ratio of type II (fast muscle) fibers than the adductor pollicis muscle [13]. Fast muscle fibers have a larger number of nicotinic acetylcholine receptors in the endplate [14] and, therefore, have a lower sensitivity to non-depolarizing neuromuscular blockers as compared to slow muscle fibers [15]. Differences in the fiber composition of the muscles being measured might produce minor differences in the results. However, the most objective value of patient safety in clinical practice is a TOF ratio of > 0.9, which indicates full recovery of neuromuscular function. As shown in Fig. 2d, the bias [12.6 s] and variation in the difference in the time to recovery with sugammadex between

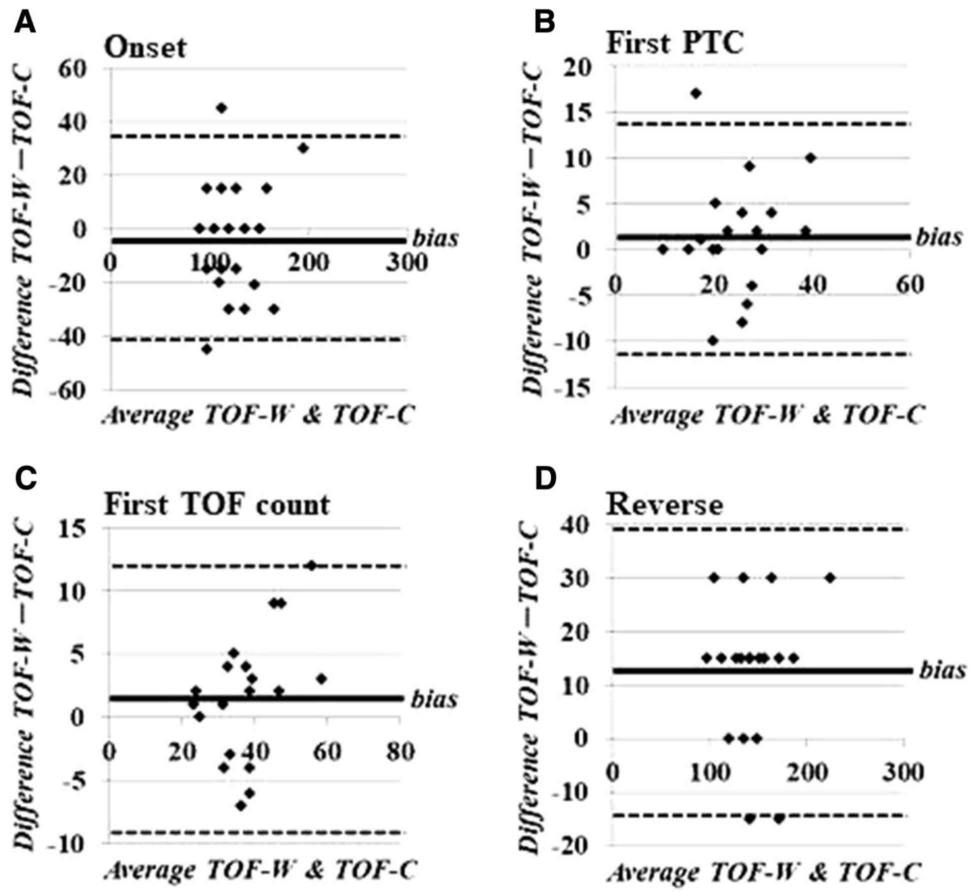

Fig. 2 Bland–Altman analyses of **a** onset time of rocuronium-induced neuromuscular block, **b** the time for reappearance of the PTC and **c** the TOF count, and **d** the reversal time to a TOF ratio > 0.9 between the TOF-W and TOF-C. Solid horizontal lines show the bias and dotted horizontal lines show limits of agreement of the two methods. *TOF-W* TOF-Watch, *TOF-C* TOF-Cuff, *PTC* post-tetanic counts

the TOF-W and TOF-C [− 15 to 30 s] were almost within the limits of agreement [− 14.3 to 39.6 s]. This suggests that the TOF-C has similar ability as the TOF-W to evaluate facilitated recovery with sugammadex.

In this study, we used the TOF-Watch™, which is proven to be suitable for clinical practice, and not the TOF-Watch SX™ as a comparative contrast. The TOF-Watch SX™ estimates raw TOF ratios based on T1 and T4 height and, therefore, often presents a TOF ratio of over 100% (e.g., 110%) during control stimulation or after sufficient recovery from neuromuscular blockade. To detect minor residual block with the TOF-Watch SX™, normalization of the TOF ratio (current TOF ratio / baseline TOF ratio) is necessary [7, 16]. However, the TOF-Watch™ does not show raw data since it uses a different algorithm, and hence displays the TOF ratio within 100% [17]. It is important to remember that the TOF-Watch™ may indicate a faster recovery from neuromuscular block than the TOF-Watch SX™. It is highly possible that the data measured by the TOF-C are similar to that measured by the TOF-W, and the data denoted by the TOF-Watch SX™ may not be equivalent and interchangeable for study purposes.

We only enrolled elderly patients in this study. Aged patients have wider variability in the duration of action of neuromuscular block [18, 19] and its reversibility with sugammadex [20] when compared with younger patients because of physiological changes in hepatic and renal blood flow and function with age. Studies using the TOF-W have shown that decreased cardiac output delays the onset and reversal time of neuromuscular block in the elderly [11, 21]. Therefore, we deliberately evaluated only the elderly in this study to determine whether the TOF-C could accurately indicate changes in rocuronium-induced neuromuscular block. Our results indicated that the TOF-C can reliably predict the depth of neuromuscular block, similar to the TOF-W. Although the findings of this study could also be applicable to pediatric and younger adult patients, further study is warranted to confirm its utility.

Some limitations should be considered in this study. First, we did not detect the maximal current used for ulnar nerve stimulation and a constant current of 50 mA was used with both monitors and in all patients. In general, a stimulus current of 50 mA is sufficient to obtain stable contractions of the adductor pollicis muscle [22], although it is undeniable that in some cases supramaximal stimulation currents may not have been applied. In particular, it has been reported that the mean supramaximal current detected by the TOF-C is about 60 mA [10]. Although aged patients may have lower skin conductance and require higher stimulus currents, we purposely selected a stimulus intensity of 50 mA to prevent unintentional multiple nerve stimulation and/or direct muscle stimulation in this study. Not only the ulnar nerve, but the brachial plexus should be stimulated by the TOF-C at the elbow. Therefore, a stimulus current of 50 mA may not have reached the maximal current for the other branches of the brachial plexus. Next, in this study, most targeted patients were female whose muscle mass and arm circumference should be smaller than male. It is, therefore, expected that variations in the nerve reactivity to electrical stimuli and cuff pressure evoked by contraction of the brachial muscles between gender differences may have been unavoidable due to the nature of the cuff method.

In conclusion, the TOF-C can effectively assess the depth of neuromuscular blockade, providing a reliable degree of muscle relaxation during the onset, maintenance, and recovery phase of rocuronium-induced neuromuscular block, even in elderly patients with a wider individual variability in the duration of action of neuromuscular blockers. The cuff method fulfills the basic requirements for a clinical neuromuscular monitor.

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Compliance with ethical standards

Conflict of interest Shunichi Takagi and Takahiro Suzuki have received speaker fees from MSD Inc., Japan.

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