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Comparison between objective methods (TOF watch Sx) versus subjective method (Peripheral nerve stimulator) to monitor non-depolarising neuromuscular blockade

Anaesthesiology

KEYWORDS:

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ABSTRACT

Introduction: Acceleromyograph (AMG) is the gold standard for neuromuscular monitoring but at present, peripheral nerve stimulator (PNS) is mostly used in routine clinical settings. Our aim is to compare the accuracy of visual assessment (subjective) of the TOF responses using a PNS with that of AMG using TOF watch Sx, which is a reproducible method (objective) of measurement.

Patients and methods: Sixty patients scheduled to undergo elective surgery under general endotracheal anaesthesia with neuromuscular blocking drugs were enrolled in this cross over study. TOF-Watch SX *(Organon, Swords, Dublin Co., Ireland)* or a PNS (innervator272, fisher&paykelhealthcare, Auckland, Newzeland) applied to each hand randomly. After induction of anaesthesia, vecuronium 0.1 mg/kg was injected while TOF stimulations were applied every 12 s at the wrist site until maximal blockade. Tracheal intubation was performed after registration of zero on TOF watch or complete abolition of twitch response on PNS whichever comes late. Intubating condition and time to intubaton was observed by an independent anaesthesiologist. Degree of agreement was analysed with Bland and Altman plot.

Results: The time to register zero on PNS is earlier compared to those patients monitored by AMG [PNS, 92.8(27.42); TOF watch SX, 142.6(27.4); p=0.001). The mean difference of the measurements between AMG and PNS methods is 49.8 seconds (95% limits of agreement 88.2, 11.4 sec).

Conclusions: We found that there is a considerable lack of agreement between the AMG and PNS, with discrepancies of up to 77 second.

Introduction

Neuromuscular blocking agents (NMBA) are being used in clinical anesthesia for more than six decades from now [1]. Neuromuscular blockade facilitates tracheal intubation and provides the muscle relaxation essential to certain operations. Dr. Mencke et al. demonstrated, in a study published in 2003[2], that the use of a neuromuscular blocking drug (NMBD), compared with placebo, not only improved the conditions for tracheal intubation, but also resulted in fewer vocal cord injuries and less postoperative hoarseness. The same group [3] in their second article demonstrated that neuromuscular monitoring improved endotracheal intubating conditions but opined that tracheal intubation at maximum intensity of neuromuscular block was not associated with a decrease in vocal cord injuries. However Clinical neuromuscular monitoring is frequently but not always used [4] and a monitor to assess neuromuscular function is not considered mandatory but "should be immediately available" according to guidelines of practice of anesthesia in Quebec and in Canada[5,6].

A study by Fawceu WJ et al [7] on residual curarisation after administration of atracurium or vecuronium by bolus doses or infusions revealed that a peripheral nerve stimulator (PNS) was not used in 45% of the cases. As stated by VibyMogensen [4] "Many anesthesiologists do not agree with the extensive use of nerve stimulators and argue that they manage quite well without these devices. Martin et al[8] demonstrates that simple neuromuscular monitoring*(visual evaluation of the thumb movements)* is required to achieve adequate muscle relaxation during surgical procedure but they failed to show benefit of neuromuscular monitoring over clinical tests, head lifts tests[9]in diagnosing residual curarisation while using intermediate duration NMBA like vecuronium and atracurium for muscle relaxation.

Assessment of neuromuscular blockade rested solely on clinical observations in the past but is now often assisted by data obtained from use of peripheral nerve stimulators (PNS). Although many publications express neuromuscular blockade in terms of precise measurement of the height of twitches, the popularity and potential of using a PNS in the clinical setting lies in the fact that useful information can be obtained by observing patient's response to stimuli with the use of inexpensive equipment.

Most often the clinician evaluates the intensity of neuromuscular block by simply visualizing the force of isometric muscle contraction at thumb elicited by a constant current peripheral nerve stimulator(PNS).The major disadvantage of this method is that measurements are quite subjective, which tends to create substantial inter observer variability.

Measurement of profound neuromuscular block using train of four [TOF] is amongst the most subjective measurements made in routine clinical anaesthesia. TOF-watch accelerographic PNS provides objective measurement of neuromuscular block that may improve our ability to quantitate intense blockade required for endotracheal intubation.

Monitoring onset of neuromuscular block provides useful and important information on muscle relaxation and the conditions and timing for tracheal intubation. Although clinical tests like muscle tone, head lift, eye opening, tongue protrusion, handgrip, tidal volume, peak inspiratory pressure etc. may give some clue regarding neuromuscular function during recovery phase from anaesthesia, the only method for reliably monitoring neuromuscular block for tracheal intubation is the stimulation of an appropriate nerve and observation of evoked response in the muscle supplied. The use of peripheral nerve stimulation allows the clinician to assess the intensity of neuromuscular blockade (NMB) to permit tracheal intubation and ensure immobility. Thomas M. Hemmer ling in [10] in his clinical update suggested that, there is no substitute for objective neuromuscular monitoring; for research purposes, Mechanomyography (MMG) is the gold standard; however, the most versatile method in the clinical setting is acceleromyography (AMG) since it can be applied at various muscles and has a long track record of clinical utility. Acceleromyography measures acceleration of a given end-organ, e.g., the thumb when moved by the adductor pollicis muscle (AP). Acceleromyography shows good agreement with MMG or electromyography (EMG) when the set-up has been carefully established [11, 12]. In general, the accuracy of AMG decreases when less movement, or acceleration, occurs at the end-organ, such as at the corrugator supercilii (CS) or the orbicularis occuli muscle

(OO). For optimal result, the hand should be placed in a cast, as with mechanomyographic recordings and accuracy depends on the mass of the acceleromyographic probe. In a developing country like India, AMG is available only in handful of teaching hospitals. At present, peripheral nerve stimulator is the only monitoring method commercially available in most of the hospitals to measure neuromuscular block (NMB) subjectively in routine clinical settings. Subjective monitoring is mostly used at the hand to evaluate the response of the AP. objective methods depends on observer experience[13, 14] (especially with AMG), at best, each method serves to count the number of train of four (TOF) responses. Our aim is to compare the accuracy visual assessment (subjective) of the TOF responses using a PNS with that of AMG using TOF watch Sx, which is a reproducible method (objective) of measurement**Review of Literature**

Muscle relaxants have been used in clinical anesthesia ever since Griffith and Johnson reported that "curare may prove to be a drug which will occasionally be of great value" [1] the intervening period has taught us the usefulness of muscle relaxants, and that the response to these agents varies widely between individuals [15, 16]. The response may be further altered by certain disease states, electrolyte imbalances and/or drug interactions [17, 18, 19, 20, 21]. There are several periods during the course of general anesthesia when the use of Neuromuscular blockade (NMB) is important and neuromuscular monitoring is necessary. Although clinical experience and some studies have shown that endotracheal intubation without the use of neuromuscular blocking drugs (NMBDs) is possible [22,23,24,] profound anesthesia is usually required and intubating conditions are less optimal as compared with complete NMB [25]. Mencke et al[2] found in a double-blind controlled study that the use of atracurium during a propofol-fentanyl induction scheme improved the quality of intubating conditions and decreased postoperative hoarseness and vocal cord damage. The insertion of an endotracheal tube using NMBDs enhances its ease and safety, and reduces postoperative patient discomfort. Even laryngeal mask airway (LMA) insertion may be facilitated by using a sub maximal dose of a NMBD [26]. Furthermore, intermittent positive pressure ventilation (IPPV) with an LMA and a sub-paralyzing dose of NMBD may facilitate mechanical ventilation and avoid air leakage with the danger of subsequent ventilation problems (decrease in tidal volumes, air obstruction due to vocal cord adduction) [27]

However, one study has shown that when using the LMA with IPPV, NMB does not alter the incidence or severity of pharyngolaryngeal discomfort [28] possibly because pharyngeal mucosal pressures are not influenced by NMB [29]. To minimize patient morbidity and optimize use of operating room time, monitoring of neuromuscular blockade is essential during the peri operative period. Clinical assessment of neuromuscular function and use of nerve stimulators are the most common monitoring methods. An understanding of the techniques used to monitor neuromuscular function, coupled with knowledge of the relevant physiology and pharmacology, will enable anesthesiologists to pursue our goal of optimal patient care.

Patients and methods

We conducted a prospective, consecutive, cross over study at Sri Venkateswara Institute of Medical science University over a period of between august2009-august2010

After ethics committee approval, all patients who agreed to participate in the study gave written informed consent. Exclusion criteria were history of neuromuscular disease , patients on treatment with drugs thought to interfere with neuromuscular transmission, patients with predicted difficult tracheal intubation, patients with a medical or physical condition that is expected to interfere with the proper conduct of simultaneous neuromuscular monitoring on both arms, patients suspected to have arthritis or another disease that will cause the thumb not to move freely, patients with hepatic /or renal impairment and, patients suspected to have an allergy to narcotics, muscle relaxants or other medication used during general anesthesia. Pregnant and breast feeding mothers were also excluded from the study.

Sixty consecutive patients aged 18–60 yr, American society of anesthesiology(ASA) physical status grading I – II, undergoing elective surgical procedures under general endotracheal anesthesia in the supine position and requiring neuromuscular blocking agents were included in the study.

Patients were pre medicated with alprazolam 0.5 mg orally, on the night before surgery and 0.5 mg on the morning of surgery. After arrival in the operating room, an intravenous (IV) catheter was inserted to allow the administration of fluids (Lactated ringer's solution at the rate of 8–10 ml/kg/hr and medications, followed by intravenous midazolam (0.04mg/kg.), twenty minutes before induction of anaesthesia. All patients were monitored with continuous two lead (lead II and V5) electrocardiogram, non-invasive arterial blood pressure, end tidal carbon dioxide and pulse oximetry. For each patient, a rest period of at least 20 minute was be provided between the time of IV cannulation and the start of the study. Anaesthesia was induced with intravenous fentanyl 1.5 mcg/ kg and thiopentone 5-7 mg/ kg. In all sixty patients endotracheal intubation was facilitated by using intravenous vecuronium (0.1 mg/Kg) over 20 seconds. Anaesthesia was maintained with 66% nitrous oxide in oxygen and sevoflurane with repeated doses of fentanyl 1 mcg/ kg as necessary. Blood pressure was monitored using automated oscillotonometeric method with the cuff placed on the lower limb in order to minimize interference with arm blood flow and neuromuscular recordings.

Two pairs of ECG type pre gelled electrodes were placed over the ulnar nerve of both wrists. The negative electrode was placed distally. Each pair of electrodes was connected alternately to a TOF-Watch SX (*Organon, Swords, Dublin Co., Ireland*) stimulator and a PNS (innervator272, fisher&paykelhealthcare, Auckland, Newzeland) The acceleration transducer of TOF watch Sx was taped to the volar aspect of the thumb at the interphallangeal joint and contraction of the ipsilateral thumb (adductor pollicis muscle) was measured using AMG and a peripheral nerve stimulator on contra lateral thumb. We ensured that the electrode position was identical at both wrists and both arms were comfortably positioned on arm boards. The arm and hand were immobilized with tape, leaving only the thumb free. No special arm board was used, and no preload was applied to the thumb. To level out the effect of dominance of one hand, the two monitors (TOF-Watch Sx and PNS) were randomly allocated to the left or right hands according to a computer-generated scheme.

Monitoring neuromuscular block consisted of measurement of the elicited thumb twitch after repeated supra maximal stimulation of the ulnar nerve at the wrist via skin surface electrodes according to the train-of-four (TOF) mode every 12 s. Measurements started after induction of anesthesia. Before any neuromuscular blocking drug was administered, the supra maximal current was obtained. Stimulation was applied at 1 Hz in an ascending sequence of electric stimulations starting from 10 mA, while the current was progressively increased to 60 mA. The point at which the response reached a plateau was considered to be the supra maximal current (SMS). It was measured at both stimulation sites. Both instruments were calibrated at the wrist site by using this current using auto calibration function (CAL 1 function). Once calibration was completed in both monitors, the ulnar nerves were stimulated by two TOF stimulations (four stimulations at 2 Hz pulse, width 200 ms, square wave for 2 s were performed at both sites). The thumb movement on PNS side was visually assessed. Vecuronium 0.1 mg/kg was injected while TOF stimulations were applied every 12 s at the wrist site until maximal blockade (Onset time, or time to register zero TOF ratio i.eT4/T1=0). Tracheal intubation was performed after documenting a zero on the display of TOF watch monitor or complete absence of twitch on PNS, whichever comes late. Ventilation was controlled to maintain an end-tidal CO_2 partial pressure between 35 and 40 mm Hg. T1, first twitch of the TOF

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expressed as percentage of control response, and the TOF ratio (T4:T1) were used for evaluating the neuromuscular block. The resident anaesthesiologist caring for the patient applied TOF stimulus to both wrist simultaneously. Where as an independent observer made a visual TOF response assessment and a TOF-Watch measurement of TOF responses simultaneously at the same time as visual assessment. The same independent observer, performed endotracheal intubation condition using Cormack Lehane grading [105]

The variable measured was: onset time (time to register zero TOF ratio i.eT4/T1=0 in seconds) from the time of bolus injection of vecuronium to depression of twitch height (TH) to 100% of control values.

The duration of laryngoscopy was restricted to 15 sec at each attempt. Muscle relaxant was repeated on 25 % recovery of T_1 of TOF (clinical duration).

Statistical analysis

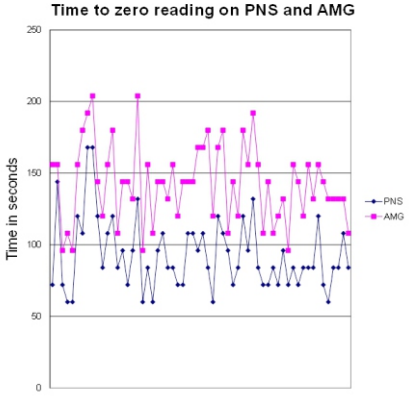
Patient data and all pharmacodynamic variables were summarized as means and standard deviations (SD). The extents of agreement between the two monitoring methods were tested by the method of Bland and Altman [106].Bias was defined as the mean difference between neuromuscular twitch responses measured by AMG and PNS and was calculated as: (AMG – PMG) /*n*, where *n* was the number of measurements. The upper and lower limits of agreement between the two methods was defined as the mean difference (bias) ± 1.96 SD. Pharmacodynamic data derived using AMG and PNS were compared between the two groups using unpaired t tests. Statistical significance was defined as $P < 0.05$. Statistical analysis was performed using Med Calc®version 11.3.3.0 (Med Calc software **bvba**).

Results

The mean (SD) [range] age of the patients are 48.5(11.5) [18–70] yr, weight 52.3 (9.7)[40-80]Kg. The majority of the study subjects are in the age group of 35-44 years (33.3%). As much as 88.3% subjects are in the age group of 35-64 years age group (Table 1).

There are 29 males and 31 females. Majority of the study subjects belongs to ASA grade I (91.7%) while 8.3% subjects belong to ASA grade II (Table 1).

Figure 1: Comparison of time to read T4/T1=0 between AMG and PNS.



AMG, acceleromyograph; PNS, peripheral nerve stimulator

Table 2: The SMS and time to assess zero (T4/T1=0) response on AMG and PNS

Variable	AMG	PNS	P value
SMS(mA)	32.33(10.7)	32.90(10.7)	0.77
Time to read zero in seconds(T4/T1=0)	142.6(27.42)	92.8(24.78)	<0.001

SMS, Supra maximal stimulus in (mill ampere), AMG, acceaccelero myograph; PNS, peripheral nerve stimulator

There is no significant difference in the supra maximal stimulating currents of the two monitors [PNS, 32.90(10.76) vs.AMG 32.33(10.75),p=0.77](Table 2,Figure 1). After vecuronium administration, T1% and TOF ratios of both monitors started to decrease simultaneously. All the patient had excellent intubating condition as per Cormach grading [106]. The time to register zero on PNS [92.8(27.42sec)] is much earlier in all the patients compared to those patients monitored by AMG (TOF watch SX) [142.6(27.4)] and this difference is statistically significant (p=0.001) (Table 2).

Table 3: Distributions of time difference (in second) between AMG and PNS

Time difference (AMG-PNS) in seconds	No. of subjects	Percentage
0-30	10	17
31-60	32	53
61-90	17	28
91-120	1	2
Total	**60**	**100**

AMG, acceacceleromyograph; PNS, peripheral nerve stimulator

Table 3 shows the distributions of time difference (in second) between AMG and PNS. Seventy percent of the subjects registered zero on AMG display with in a delay of 60 second after reading zero on PNS. Only one subject took more than 90 seconds (96 seconds) to register a zero on AMG after PNS showed zero on its display(Table 3,Figure 2). The data in figure 3 provides a moderate degree of correlation (r2=0.52, p<0.001). The probability is very small and we can safely conclude that time to achieve adequate neuromuscular depth for endotracheal intubation as measured by AMG and PNS are related. However, this correlation does not mean that the two methods agree.

Table 4: Vecuronium time course of action variables (seconds).

Variable	AMG	PNS	Bias	Limit of agreement	
				Lower	Upper
Onset time	142.6(27.42)	92.8(24.78)	49.8(19.6)	11.4	88.2

Values are mean (SD), AMG, acceleromyograph; PNS, peripheral nerve stimulator; bias, difference between the two monitors; limits of agreement=bias ±(1.96 SD); onset time, time from start of vecuronium administration until registration of zero on TOF watch or PNS (T4/T1=0).

So we plotted a Bland and Altman analysis (figure 4, table 4), to see the degree of agreement between two modality of monitoring to achieve adequate neuromuscular block during endotracheal intubation. The 95% limits of agreement (88.2, 11.4) contain 95% (59/60) of the difference scores. The mean difference (bias) of the measurements between AMG and PNS methods is 49.8 seconds. The SD of the difference is 19.61 and the width of the 95% limits of agreements is 76.8. The 95% confidence interval for the bias is 44.73 to 54.86seconds.The 95% confidence interval for the lower limit of agreement is 2.64 to 20.06 seconds. For the upper limit of agreement the 95% confidence interval is 79.53 to 96.95seconds. These intervals are wide, reflecting the small sample size and the great variation of the differences. They show, however, that even on the most optimistic interpretation there can be considerable discrepancies between the two monitors and that the degree of agreement is not acceptable. The Bland Altman plot (figure 4) further reveals that the line of equality lies outside the 95% confidence interval of the mean difference indicating significant systematic difference. Thus, the difference in reading between AMG and PNS may be as close as 11 seconds to as big as 88 seconds, which would be unacceptable for clinical purposes.

Discussion

In routine clinical practice, neuromuscular monitoring is frequently

used to detect residual curarisation effects. When neuromuscular function is monitored, it is usually thought that the stimulation site must be over a peripheral nerve to elicit the most accurate response [107]. Adductor pollicis neuromuscular monitoring with stimulation of the ulnar nerve is widely used in anesthesia. It is the "gold standard" used to monitor the level of block and to compare neuromuscular blocking drugs and the response of other muscles to these drugs[108,109]. Monitoring of the corrugator supercilii muscle (CS) may be used to determine the earliest time for tracheal intubation as it reflects laryngeal relaxation better than monitoring at the adductor pollicis muscle (AP). Acceleromyography, although well established for the AP, might be problematic at this muscle because of the limited capability of the conventional acceleromyographic probe to detect acceleration created by this small muscle (CS). Recently, it has been shown that use of AMG at the eye muscles, such as the CS, is limited, especially in detecting the maximum degree of neuromuscular block (NMB) [86]. The accepted method of stimulating the adductor pollicis uses electrodes placed at the wrist over the ulnar nerve. The choice of electrodes includes needles, gel electrodes or spherical-ended probes or plates. The initial concern about burns caused by spherical-ended probes was later alleviated with the use of EKG type of pregelled electrodes [110, 111]. Needle electrodes may be more useful for an obese patient as needle electrodes give the best contact but there are many objections to their use. Their placement in an awake patient causes discomfort. They have been associated with infection, broken needles and intraneural placement. There are several configurations for the placement of the electrodes. The ulnar nerve-adductor pollicis muscle system has been used most frequently because of its accessibility and resemblance to the standard laboratory single nerve muscle preparation. There are at least four ways suggested by investigators to stimulate the ulnar nerve [54,55]. The output from a nerve stimulator includes an anode (often colored RED) and a cathode (often colored BLACK). These two terminals from the output are attached to the electrodes on the patient. The electrode placed near the nerve concentrates the current on the nerve and is termed the active electrode. The other electrode which is placed further away and is used to complete the circuit is called the inactive or indifferent electrode. When the ulnar and median nerves were stimulated, it was found that if the active electrode is the cathode (negative), the responses to single twitch stimuli were greater [54, 55] However, polarity did not affect twitch height if the electrodes were placed within 5 cm of each other at the wrist [54].This was presumably because the negative electrode was never so far from the nerve that it could not stimulate it. Increasing the distance of the electrode from the nerve reduces twitch height since the increase in resistance causes a decrease in current density and possible failure to produce a supra maximal stimulus. In all our cases we placed the negative electrode nearer to the nerve to be stimulated.

It is possible that monitoring neuromuscular block in the limb with the intravenous (i.v) infusion may be misleading because first, the injected neuromuscular blocker may diffuse retrogradely into the hand muscles through venous paths, as demonstrated by the isolated arm technique [112]; and second, the temperature of the infused fluid may influence the temperature of the arm, thereby modifying its local blood flow. However Merle JC et al[113] evaluated the neuromuscular block (maximum degree of depression of the elicited first twitch and the onset time of depression of twitch height to 50%, 90% and 100% of control) and skin temperature (at the thenar eminence) were monitored in both the limb with the i.v. infusion and the non cannulated upper limb ; found no significant difference in either onset time, degree of neuromuscular block or skin temperature between the two upper limbs and concluded that each upper limb, irrespective of whether an i.v. infusion is in progress, may be used for monitoring onset of neuromuscular block.

In most studies, the timing of tracheal intubation is determined by neuromuscular monitoring or occurs at a predetermined time after administration of neuromuscular blocking drugs. In clinical practice however, neuromuscular monitoring and accurate timing are rarely used, and many anesthesiologists commence laryngoscopy based on the clinical "feel" of the patient. Smith I and Saad RSG [114], using clinical judgment alone ,predicted satisfactory intubating condition after rocuronium , allowing intubation to be completed within an acceptable time period after rocuronium administration, however they opined that ,this interval could probably would have been shortened by neuromuscular monitoring. They further concluded that, clinical judgment underestimated the time required for adequate onset of vecuronium, resulting in less favourable intubating condition [Excellent, 30(10%); Good, 11(33%); Poor, 4(16%)] according to Kreig score [115]. In contrast to them, we used almost the same dose of vecuronium (0.1mg/kg) to achieve neuromuscular relaxation and found excellent intubating condition (Cormach grading) for all the patients in a reasonably shorter time by adopting neuromuscular monitoring. Although Smith I and Saad RSG [114] did not find any effects of improved intubating conditions on hemodynamic responses to endotracheal intubation, other author [116] reported an attenuated hemodynamic response to laryngoscopy and intubation by adopting an objective assessment of neuromuscular relaxation prior to endotracheal intubation.

Many authors[9,14] confirmed visual assessment of the TOF ratio tends to overestimate the ratio determined mechanographically.Brull and Silverman [117] in his Videotape analysis apparently has identified a mechanism which may account for this discrepancy: when the resting thumb is stimulated without preload, it typically does not return to its initial resting position and on average the thumb returned to a position that was on the 56% above the initial resting baseline. Thus, the overall thumb movement in response to the fourth stimulus appeared greater than the actual displacement elicited by this impulse. However, we considered AMG as gold standard for assessing adequacy of neuromuscular block and found that almost 70% of the subjects monitored by PNS overestimated the degree of block by 11—60 seconds. So we suggest that, one should wait for an additional 60 seconds before attempting endotracheal intubation after visual estimation of zero TOF ratios on PNS, if AMG like sophisticated and costly equipments is not available.

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