Fuzzy Logic Control of Depth of Muscle Relaxation using Cisatracurium

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ABSTRACT

In this paper, the muscle relaxant agent (i.e., cisatracurium) and three clinical control methods (i.e., 13 patients undergoing intermitted bolus control, 15 patients undergoing intensive manual control and 15 patients) undergoing automatic fuzzy logic control (FLC), were used for maintaining depth of muscle relaxation (DOM) during surgery. Cisatracurium, a muscle relaxation drug with long-term effect, low metabolic loading, but long delay time, is widely used in operating rooms and ICUs. Meanwhile, the rules for the FLC were developed from the experimental experience of intensive manual control after learning from 15 patient trials. According to experts' experimental experience, our FLC inputs were chosen from T1% error and trend of T1% which differ from other previous studies on eliminating the effect of time delay from cisatracurium. In individual clinical experimental results, the mean(SD) of the mean T1% error in 13 patients for intermitted bolus control, in 15 patients for intensive manual control, and in 15 patients for automatic control was 8.76(1.46), 1.65(1.67), and 0.48(1.43), respectively. The t *test results show that automatic control is not significantly different from intensive manual control. The results show that a simple fuzzy logic controller derived from anesthetists' clinical trials can provide good accuracy without being affected by the pharmacological time delay problem.*

1: INTRODUCTION

The major function of a clinical anesthetist is the maintenance of drug-induced muscle relaxation, unconsciousness, and analgesia for specific periods of time. Hence, anesthetic drugs with a rapid onset and short duration of action are highly desirable. For muscle relaxation control, intermitted bolus control is usually used because of convenience during surgery. But according to muscle relaxation measurement, intermitted bolus control inevitably leads to fluctuations in the degree of neuromuscular block, particularly with the recently introduced short-acting agents. To reduce this effect, continuous infusions of neuromuscular blocker may be used. The advantages of continuous infusion are that the minimum quantity of drug is administered and the clinical workload could be reduced, allowing more time for direct patient care. However, the immense patient-to-patient variations make it difficult to choose the correct infusion rate to maintain the desired level of neuromuscular block. To collect for this, continuous infusion dose administrated by a closed-loop control system composed of a personal computer, a neuromuscular block monitor and a syringe pump could seek the best infusion rate in any operation situations if the monitor is reliable during surgery. Furthermore, closed-loop drug therapy offers considerable benefits in patient care by providing the ability to maintain stable neuromuscular block while allowing for variations in individual response to the drug.

Table 1. Comparison of published human clinical results obtained by different medicines using an EMG monitor.

Controller	Dose	Mean of Error (SD)	Mean of SD (SD)
MacLeod et al., 1989 [10]	Atracurium	-1.3 (1.3)	1.47 (0.69)
Denai et al., 1990 [11]	Atracurium	0.98 (4.3)	3.9 (2.3)
Mahfouf et al., 1992 [7]	Atracurium	-0.26 (1.37)	3.12 (1.68)
Mason et al., 1996 [4] (phase I) (phase II) (phase III)	Atracurium	 1.1 (1.4) -0.43 (1.2) 0.28 (0.94)	 2.4 (0.68) 1.5 (0.29) 3.4 (0.88)
Shieh et al., 1996 [12]	Atracurium	0.62 (1.08)	1.75 (0.86)
Ross et al., 1997 [6]	Atracurium	-0.52 (0.55)	2.30 (0.62)
Shieh et al., 2000 [3]	Rocuronium	-0.19 (1.47)	0.66 (0.35)
Derene et al., 1997 [8]	Vecuronium	4.1 (0.7)	Not provided
Kern et al., 1997 [9]	Pancuronium	-0.76 (4.98)	6.48 (1.92)

Early research on feedback control of drug-infusion for muscle relaxation was performed on sheep [1]. The feedback controller was based on a PID algorithm, as was the first set of human clinical trials performed by Brown et al [2]. Subsequently, various control strategies with different drugs for depth of muscle relaxation (DOM) have been proposed. Table 1 shows a comparison of published human clinical results obtained with different drugs with an EMG monitor. General speaking, these studies [3-12] can be clustered into different types of anesthetic medicines, such as atracurium, rocuronium, vecuronium, and pacuronium.

One general problem with biomedical control algorithms obtained by simulations is that there are enormous patient-to-patient variations in dynamic model parameters. This is compounded by large time-varying parameters for an individual patient during the course of an operation, making it difficult to design a fixed-parameter PID controller that will be suitable in all cases. Another problem is that the effect of time delay in a DOM study is more serious than in other control fields because of pharmacological reasons. In delay time control studies, many control theories [13-20] using model-based methods have been proposed. But

most of these methods have disadvantages such as being time-consuming, needing a precise model, or being too complicated to implement in real practice. Thus, these kinds of control algorithms are not recommended for clinical application. Moreover, accidental disturbances or noise generated from external interferences (e.g. surgical stimulations or medication interactions) may cause system unstable through learning wrong control rules. These mistakes can endanger a patient's life.

Table 2. Brief summary of cisatracurium studies

Authors	CL (mL/min/kg)	Vss (mL/kg)	$X_{E(50)}$ (ng/mL)	$t_{1/2\,\beta}$ (min)	k_{E0} (min^{-1})	δ	Onset Time (min)
D.F. Kisor, et. al., 1999 [22]	4.7	145		25			
A.M.D. Wolf, et.al., 1996 [24]	5.7	161	98	23.5	0.179	4	
S. Sorooshian, et.al., 1996 [25]	319 (ml/min)	elderly=13.28 young=9.6	90 98		0.06 0.071	3.7 4.1	3 4
J.Y. Lepage, et.al., 1996 [26]	Have 3 groups			27 ~ 48		4.8 ~ 5.8	
D.F. Kisor, et. al., 1996 [27]	4	168					
T.V. Tran, et. al., 1998 [28]	3.7 ± 0.8	118~89	153 ± 33	23.9 ± 3.3	0.054 ± 0.013	6.9 ± 1.3	
N.B. Eastwood,et. al., 1995 [29]	approximate 4.84			30.0 ~ 34.2			

Cisatracurium besylate (51W89; Nimbex™), a non-depolarizing neuromuscular blocking agent, is one of the 10 isomers of atracurium and is approximately three times more effective than atracurium [21]. Studies [22-29] about cisatracurium PK/PD model identification have provided results that are summarized in Table 2. With an ED_{95} of 0.05 mg kg^{-1}, cisatracurium has a neuromuscular blocking profile similar to that of atracurium except for a slower onset and less propensity to release histamine than atracurium [22-28]. The results of Sorooshian et al. [25] indicated that the onset of blocking was delayed in the elderly; with mean values being 3.0 min and 4.0 min in the young and the elderly, respectively. Lepage et al. pointed out that with 0.1 mg/kg injected over 20-30 sec, median onset time was 4.8 min, and spontaneous recovery durations (min to 5%, 25%, and 95% of T1 value) were 27, 33, and 48 min, respectively [26]. Kisor et al [22,24,27] has estimated the data for mean plasma-concentration against time for cisatracurium pharmacokinetics in adult patients with normal organ function. Then, this paper is the first trial in automatically control neuromuscular block by cisatracurium. We not only provide an approach for modern DOM control via cisatracurium, but also compare with other two control approaches, intermitted bolus control and intensive manual control.

2: THREE CLINICAL CONTROL METHODS

2.1: INTERMITTED BOLUS CONTROL

The intermittent bolus dose is a conventional method that is widely used in clinical anesthesia for applications such as pain control, muscle relaxation control, and consciousness control. Generally, the intermittent bolus treatment is manually executed by an anesthetist if the patient's situation becomes unstable during surgery. This open-loop control method relies completely on manual observation. In order to objectively estimate the performance of this method, we designed a closed-loop control system consisting of a syringe pump, a measurement of muscle relaxation, and a PC. The control scheme is shown in Fig. 1. However, the data from the Datex Relaxograph was only recorded in the PC but not used for feedback control. The program of intermittent bolus agent was executed by the PC to automatically control the syringe pump injecting cisatracurium into the patient every half hour and to record the infusion rate. The dosage was based on the user guide for cisatracurium. The suggested dosage in the user guide indicates the initial bolus dose is 0.1 mg/kg or 0.15 mg/kg, the incremental dose is 0.03 mg/kg every half hour, and the three suggested infusion rates are 1, 2, and 3 ug/kg/min. For example, with a patient's weight of 60 kg, the bolus dose should be 6~9 mg. The concentration of cisatracurium was diluted with normal saline to 1 mg/ml and installed in a 20 ml injection tube set on a syringe pump. From the syringe pump default setting, the maximum infusion rate as the bolus rate is 400 ml/hr if the tube is 20 ml. To summarize, a 60 kg patient needs 54~81 seconds for the initial bolus injection and 16 seconds every half hour for an incremental dose with 1 mg/ml concentration, 20 ml tube, and 400 ml/hr infusion rate through the Graseby 3500. The PC functions are to execute the injection process automatically and to record the level of muscle relaxation. In addition, the medical staff directly monitored the whole process to avoid any danger during surgery.

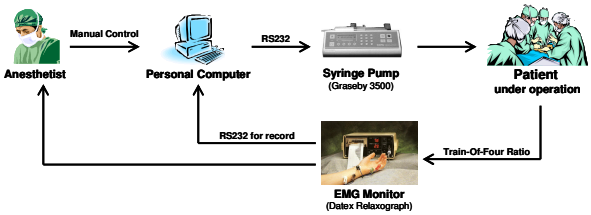

Fig. 1 Scheme of the clinical control methods. The basic components of this control system are a syringe pump, a monitor for neuromuscular blockage, and a PC.

2.2: INTENSIVE MANUAL CONTROL

The intensive manual control is composed of the anesthetist with a syringe pump, a device to measure muscle relaxation, as well as a PC that is used to send the control command, record the infusion rate, and record the level of muscle relaxation. The control scheme is shown in Fig. 1. The initial bolus strategy was also based on the user guide for cisatracurium. At the beginning of this study, the PC was operated by an anesthetist with a engineer. The anesthetist was responsible for maintaining the patient's level of muscle relaxation using the PC. The engineer was responsible for writing the adaptive program to assist the anesthetist's control: for example, the program can offer some indexes such as error, change in error, the curves of T1% and infusion rate, 3 points trend, 6 points trend, maximum infusion rate, maximum overshoot, etc. In

addition, the engineer observed the on-line anesthetist's control behavior, and analyzed the collected data in order to extract some control rules. After much coordination, the PC interface for manual control was fixed and used to control 15 patients. Finally, we found that the anesthetist's control has some significant aspects such as selecting the error and trend to be used as control inputs, and changing the control interval with different trends.

2.3: FUZZY LOGIC CONTROL (FLC)

Fuzzy theory, a means of emulating human behavior, was applied in this study to automatically maintain the level of muscle relaxation during surgery. The FLC structure was composed of four compartments, which are fuzzification, fuzzy inference, heuristic rules, and defuzzification. Generally speaking, an FLC includes some components, such as membership function, scaling factor, fuzzy set level, and inference engine type, etc. First, {Error (E)} and {Trend (T)} were selected to be our system inputs, and the output was {Dose Change (DC)}. The definitions of E and T are shown as follows,

$$E = T1\% - \text{Set Point} \quad (1)$$

$$T = \text{Tendency of three T1\% points} \quad (2)$$

where T1% is the index of muscle strength from the Datex Relaxograph after passing through the 3-order median filter. The trend was calculated by the curve fitting method, and three T1% values was the least requirement for curve fitting computation. From the viewpoint of control, using "Error and Trend" as the inputs is better than using "Error and Error change" for a time delay system. Then, each linguistic level of fuzzy sets for both inputs {E, T} have seven levels which are { Negative Big (NB), Negative Median (NM),Negative Small (NS), Zero (ZE), Positive Small (PS), Positive Median (PM), Positive Big (PB)}. Their membership functions for Error, Trend, and Dose Change are 25% overlap for each quantized level, and the ranges for inputs are shown in Table 3. The fuzzy set for output {DC} has seven levels which are {Increase Big (IB), Increase Median (IM), Increase Small (IS), Zero (ZE), and Decrease Small (DS), Decrease Median (DM), Decrease Big (DB)}.

Table 3. Ranges of Error (E) and Trend (T)

Level	Range of Error (E)	Range of Trend (T)
PB	$3.5 < E$	$0.2 < T$
PM	$1.5 < E \leqq 3.5$	$0.1 < T \leqq 0.2$
PS	$0.5 < E \leqq 1.5$	$0.01 < T \leqq 0.1$
ZE	$(-0.5) \leqq E \leqq 0.5$	$(-0.01) \leqq T \leqq 0.01$
NS	$(-1.5) \leqq E < (-0.5)$	$(-0.1) \leqq T < (-0.01)$
NM	$(-3.5) \leqq E < (-1.5)$	$(-0.2) \leqq T < (-0.1)$
NB	$E < (-3.5)$	$T < (-0.2)$

Furthermore, the triangular fuzzy membership function is one of the popular methods for specifying fuzzy sets and is used in this study. In addition, linguistic rules, contained in one of the fuzzy components, are always obtained from an expert's experience or from a self-learning process. But since no study of DOM control with cisatracurium has been published yet, the control rules for FLC were extracted from the results of clinical intensive manual control study. Table 4 shows our fuzzy rules. These nine rules were obtained and based on anesthetist's control experience in the studies of Intensive Manual Control.

The approach of fuzzy inference was applied as proposed by Mamdani and the center of area was found by a fuzzy defuzzification method. The defuzzification results of this study are shown in Table 5.

Table 4. Fuzzy Rules

T \ E	NB	NM	NS	ZE	PS	PM	PB
NB	DB			DM			IS
NM							
NS							
ZE	DM			ZE			IM
PS							
PM							
PB	DS			IM			IB

After fuzzy inference, defuzzification, and considering the hardware limitations (the resolution of infusion rate of syringe pump), a look-up table was obtained by applying a 0.1 scaling factor (Unit of Dose Change is ml/hr) to Table 5.

Table 5. Defuzzification result for fuzzy logic control. In addition, a look-up table for clinical control was obtained by adding a scaling factor of 0.1 to this table.

T \ E	NB	NM	NS	ZE	PS	PM	PB
NB	-4.8	-4.8	-2.5	-2.5	-2.5	2.0	2.0
NM	-4.8	-4.8	-2.5	-2.5	-2.5	2.0	2.0
NS	-3.6	-3.6	0	0	0	3.6	3.6
ZE	-3.6	-3.6	0	0	0	3.6	3.6
PS	-3.6	-3.6	0	0	0	3.6	3.6
PM	-2.0	-2.0	2.5	2.5	2.5	4.8	4.8
PB	-2.0	-2.0	2.5	2.5	2.5	4.8	4.8

Furthermore, Wada et al. [31] pointed out that the maximum infusion rate and the control interval should be selected carefully because they can reduce the amplitude of unexpected transient peaks in plasma concentrations. Hence, according to the results of clinical intensive manual control and simulations, the control interval could be changed following the degree of trend. Table 6 can be used for tuning the control intervals with different trends.

Table 6. Control interval for our FLC in clinical. Control interval will be changed with different levels of trend T.

T	PB	PM	PS	ZE	NS	NM	NB
Interval (sec)	30	60	90	120	180	90	60

3: PATIENTS AND METHODS

3.1: PATIENTS FOR CLINICAL TRIAL

This study was approved by the Ethics Committee of the National Taiwan University Hospital. A total of 43 ASA I or II patients, aged 18-70 and weighting 51-100 kgs, undergoing surgery anticipated to last at least 60 min were registered as subjects and gave written informed approval. They were divided into three groups for comparing three different control methods: intermittent bolus control (13 patients), intensive manual control (15 patients), and automatic control (15 patients). Except for the different approaches in dose-delivery of muscle relaxant during the period of maintenance, every patient received a standardized anesthetic management. Patients with hepatic, renal or neuromuscular disease or those taking medications known or suspected to interfere with neuromuscular transmission were excluded. On arrival in the operating room, blood pressure was measured either noninvasively with a cuff attached to the arm or invasively with an arterial line injected into the artery not involved in neuromuscular monitoring. Pulse oximetry and electrocardiography (ECG) were monitored continuously.

3.2: ANESTHESIA PROCEDURE

An attending anesthesiologist and the engineer who designed the proposed system were present for monitoring the patient and handling any dysfunction of the infusion system. After the standard anesthesia monitors were set up, sodium thiopental (0.5 mg/kg) and fentanyl (0.2 μg/kg) was given for the calibration process. Sodium thiopental (5 mg/kg), fentanyl (2 μg/kg) and succinylcholine (1.5 mg/kg) were injected for endotracheal intubation. Cisatracurium (male: 0.09 mg/kg, female and children: 0.06 mg/kg) was injected intravenously for the initial blockage. Isoflurane was given for the maintenance of anesthesia. Neuromuscular blockage was monitored and controlled according the following protocol throughout the operation.

3.3: NEUROMUSCULAR MONITORING, COMPUTER, DATA INPUT AND DATA OUTPUT

Stimulating electrodes for the Datex Relaxograph were placed over the ulnar nerve of the non-infusion hand, while the sensing electrodes were placed over the hypothenar area. The ulnar nerve was stimulated supramaximally with repeated train-of-four (TOF) via surface electrodes at intervals of 0.5 sec (2 Hz). The TOF stimulus was repeated every 10 sec to produce the expected degree of neuromuscular block more than every 20 sec. The system consisted of a PC interfaced with a Datex Relaxograph to monitor neuromuscular block and a medical infusion pump (Graseby 3500, SIMS Graseby Ltd, Watford, Herfordshire, UK) to administer cisatracurium.

The PC programs for automatic control were established by "Borland C++ Builder", and communication between the two devices was via serial links. The default setting for control aim in EMG (i.e. T1% value) was 10%, and 2 mg · ml^{-1} concentration of cisatracurium was diluted to 1 mg · ml^{-1} to proceed the volume flow rate (ml · hr^{-1}) control of infusion pump. In addition, the patient's weight was entered to calculate the loading dose of muscle relaxants.

3.4: STATISTIC ANALYSIS FOR CLINICAL TRIALS

According to a previous study [3], an operational definition of the "stable period", the start of this period can be defined in two ways, depending on whether or not there is an overshoot above the target after starting automatic control. Besides, the stable period ends when the muscle relaxants stops and surgery is completed. Also, the beginning of the "controller of operation" is defined by the time when the maintenance starts after finishing endotracheal intubation. The controller of operation ends at the same as the stable period.

4: CLINICAL CONTROL RESULTS

Our clinical control results have three compartments: intermittent bolus control, intensive manual control, and automatic fuzzy logic control. The patient number for these studies are 13, 15 and 15, respectively. In control error computation, means of mean error for these groups are 8.76(1.46), 1.65(1.67) and 0.48(1.43), respectively. And their means of mean standard deviation are 2.39(2.02), 3.28(1.57) and 2.60(1.43), respectively. Their overall control results were summarized in Tables 7. For observing and estimating entire control process, one of the actual control processes by intermittent bolus control is shown in Fig. 2, by intensive manual control in Fig. 3 and by automatic fuzzy logic control in Fig. 4. Finally, the three control results are briefly summarized in Table 8.

Table 7. Control Results of Intermitted Bolus Control, Intensive Manual Control, and Automatic Control

	Patient No	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	Mean
Intermitted Bolus Control	Duration of Steady-state (sec)	10000	8000	12000	14000	5000	16000	5000	3000	6000	5400	6300	6000	6400	X	X	7391
	Mean of T1%	4.49	0	0.68	0.20	3.27	1.59	0.08	2.32	0.40	2.39	0.09	0.04	0.61	X	X	1.24 (1.46)
	SD of T1%	7.09	0	2.06	0.98	4.62	2.55	0.77	4.17	1.75	3.26	0.72	0.37	2.68	X	X	2.39 (2.02)
Intensive Manual Control	Duration of Steady-state (sec)	7000	6100	9000	3400	7800	7250	6500	3800	7800	6300	5000	3800	5250	5050	10150	6280
	Mean of T1%	9.12	7.31	8.18	8.08	9.38	9.93	11.50	8.52	8.61	8.46	8.80	8.89	5.68	4.32	8.44	8.35 (1.67)
	SD of T1%	1.66	4.62	6.44	3.84	1.85	2.79	5.00	4.66	1.16	3.17	3.64	1.56	1.75	2.36	4.65	3.28 (1.57)
Automatic Control	Duration of Steady-state (sec)	4200	6000	4000	6500	5000	4700	8100	6200	3920	8000	5500	2700	2750	11000	4150	5515
	Mean of T1%	9.79	8.65	9.00	10.37	8.35	8.09	9.38	10.03	13.73	10.52	9.23	7.52	10.22	9.71	8.23	9.52 (1.43)
	SD of T1%	4.33	1.19	6.76	2.08	2.62	3.44	3.05	1.83	3.21	2.45	1.19	0.96	1.74	1.84	2.24	2.60 (1.43)

In statistical analysis, first using analysis of variance between each group, the P-value of ANOVA in these three methods is 2.61×10^{-17} ($P < 0.001$) calculated by Microsoft® Excel. This means that these three groups have significant difference within each method. Second, using analysis of Student's *t* test to calculate the difference between intermittent bolus and intensive manual control, the result shows that their P-value is 4.09×10^{-12} ($P<0.05$) and has significant difference. Between intermittent bolus and automatic control, the *t* test result shows that their P-value is 2.97×10^{-14} ($P<0.05$) and has significant difference. Between intensive manual control and automatic control, the P-value is 0.051 ($P > 0.05$) and there is no significant difference.

Table 8. Summarized control results. The table shows the patient numbers and means of the mean error(SD).

Control method	Patients	Mean of the mean error (SD)
Intermittent bolus	13	8.76 (1.46)
Intensive manual control	15	1.65 (1.67)
Automatic fuzzy control	15	0.48 (1.43)

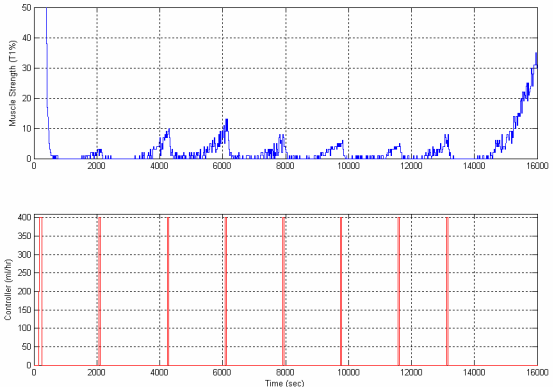

Fig. 2 Clinical result of Intermittent Bolus Control

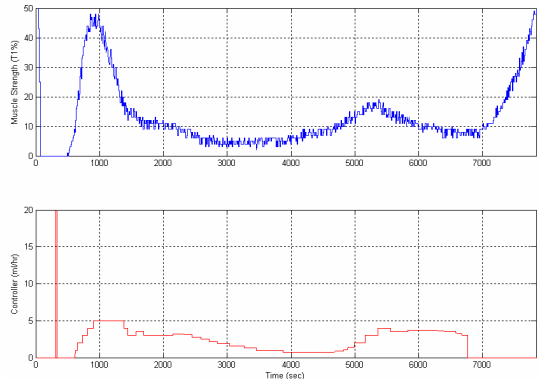

Fig. 3 Clinical result of the Intensive Manual Control

5: DISCUSSION AND CONCLUSION

Since using cisatracurium to control depth of muscle relaxation has not yet been presented, this study is the first automatic control trial to use the FLC based on experts' experience to maintain the muscle relaxation for reducing clinical experimental hazard. Compared with previous researchers' results, the mean of the mean T1% and error in automatic control is 9.52 and 0.48, respectively. Except Derene's [8], the other results of mean of mean T1% error are between 0.19 to 1.3 after taking absolute calculation. The best results were presented by Shieh et al [3] who used rocuronium with hierarchical rule-based FLC. That study pointed out that the onset time (delay time) of rocuronium is shorter than vecuronium. However, these previous DOM studies did not mention how to overcome the delay time problem. The effect of delay time should not be ignored during control because it will lead to overshooting and error generation. How to eliminate the overshoot is important for error calculation. Moreover, if system had been affected by delay time, the overshoot could not be avoided except by using a model-based controller. On the other hand, in the clinical trials, when muscle relaxation was coming to a set point by metabolism and anesthesia was given at the same time, the overshoot would occur. However, cisatracurium is a kind of neuromuscular blocker agent with longer onset time, which makes it more difficult to control the reduction.

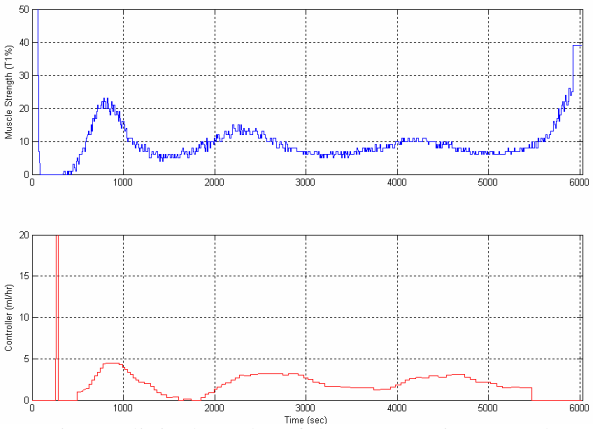

Fig. 4 Clinical results of the Automatic Control

From the viewpoint of pharmacology, the control strategies in different studies can not be compared they use different drugs. In these DOM studies using atracurium [4, 6, 7, 10-12] its pharmacologic characteristic is more similar to cisatracurium, for which the Mahfouf [7] control result based on model-based method is best. The model-based control method can obtain better results than other methods because the controller was designed by many control theories. It is common phenomena occurs in actual conditions that if system increases its accuracy, its robustness would degrade simultaneously. We consider that model-based approach may not suitable for clinical trials because the patient-to-patient variation is so great that the model would be overly complex. Therefore, robustness is more important than other control abilities in clinical trials, and using FLC to control would be better.

Generally speaking, the purpose of designing an automatic control system is to reduce or replace direct human intervention. By continuously sensing the instrument and automatic control feedback, the patient could be kept intensively anesthetized during surgery. In addition, our clinical results show that using automatic fuzzy logic control with the inputs of Error

and Trend, can effectively overcome the system delay problem, effectively maintain the muscle relaxation level of the patient, and reduce anesthetist workload during surgery. Moreover, the rules for our fuzzy logic control could be extracted off-line from our clinical data by data mining. These extracted rules would completely and precisely express the experts' knowledge, and its control results might be better than the presented controller.

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