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Split dose of succinylcholine for modification of seizure during multiple monitored electroconvulsive therapy

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Study Objective : *Electroconvulsive therapy is a treatment for psychiatric patients who fail medical treatment or have severe manifestation. Multiple monitored electroconvulsive therapy ensures adequate stimulation and results in rapid improvement of the symptoms. Single dose injection of short acting muscle relaxant is sometimes inadequate for the latter stimulation and results in too strong convulsion and injury. We compared succinylcholine dispensed in two divided doses with the usual single dose for modification of convulsion.*

Design : *Randomized double blind crossover trial.*

Setting : *Tertiary care public hospital.*

Patients : *Forty adult psychiatric patients who required multiple monitored electroconvulsive therapy.*

Interventions : *After anesthetized, patients in conventional single dose regimen received 1 mg/kg succinylcholine before stimulation then two consecutive electrical stimuli were given in 3 minutes apart. Split dose regimen consisted of 0.75 mg/kg succinylcholine before first stimulation and 0.25 mg/kg before second stimulation.*

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Measurements : *Isolated lower limb with tourniquet and compared the convulsion severity with another side to identify the poor modification of convulsion.*

Main Result : *The incident of poor session in single dose regimen was 43.6 % compared with 10.3 % in split dose regimen (p=0.004). The average time from the end of seizure to 20 % muscle twitch height recovery in single dose and split dose were 125 seconds and 183 seconds respectively (p=0.001).*

Conclusions : *Split dose of succinylcholine is suitable for modification of seizure during multiple monitored electroconvulsive therapy.*

Keywords : *Succinylcholine, Split Dose, Multiple, Electroconvulsive.*

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เทวารักษ์ วีระวัฒกานนท์, อรนุช เกี่ยวข้อง, สมรัตน์ จารุลักษณานันท์, สหดล ปุญญถาวร, ดนัย อุดมพรวิวัฒน์. การแบ่งให้ซัคซินิลโคลีนเพื่อลดความรุนแรงของการชักจากการรักษาด้วยการช็อคไฟฟ้าแบบหลายครั้งติดต่อกัน. จุฬาลงกรณ์เวชสาร 2548 มิ.ย; 49(6): 313 - 24

วัตถุประสงค์ : *การรักษาด้วยการช็อคไฟฟ้าเป็นทางเลือกหนึ่งในการรักษาโรคจิตที่ดื้อต่อยา หรือมีอาการรุนแรงถึงขั้นทำร้ายตัวเองหรือผู้อื่น ในโรงพยาบาลบางแห่งให้การรักษาด้วยการช็อคไฟฟ้าแบบหลายครั้งติดต่อกันในคราวเดียว พบว่าการตอบสนองจะเร็วขึ้นและลดระยะเวลาในการนอนโรงพยาบาลลง ส่วนใหญ่จะลดความรุนแรงของการชักโดยใช้ยาหย่อนกล้ามเนื้อที่มีฤทธิ์สั้นคือซัคซินิลโคลีนเพียงหนึ่งครั้ง บางครั้งฤทธิ์ของยาสั้นเกินไปไม่พอสำหรับการชักครั้งหลังทำให้ชักรุนแรงจนอาจเกิดอันตรายได้ การศึกษานี้เปรียบเทียบการให้ยาซัคซินิลโคลีนหนึ่งครั้งแบบเดิมกับการแบ่งให้ยาแบบสองครั้ง*

รูปแบบการศึกษา : *เปรียบเทียบในผู้ป่วยคนเดียวกัน คราวแรกจะสุ่มว่าผู้ป่วยจะได้รับยาวิธีใดก่อนการรักษาในคราวต่อไปจะสลับให้ยาอีกวิธีหนึ่ง ผู้ศึกษาและผู้ป่วยไม่ทราบว่าเป็นยาวิธีใด*

สถานที่ : *แผนกจิตเวช โรงพยาบาลจุฬาลงกรณ์*

ประชากร : *ศึกษาในผู้ป่วยโรคจิต 40 รายที่มารับการรักษานี้ที่โรงพยาบาลจุฬาลงกรณ์*

วิธีการ : *ถ้าเป็นวิธีให้ยาครั้งเดียวหลังจากนำสลบแล้วผู้ป่วยจะได้รับยาซัคซินิลโคลีน 1 มก/กก สำหรับการกระตุ้นด้วยไฟฟ้าสองครั้งห่างกัน 3 นาที ถ้าเป็นวิธีแบ่งให้จะให้ยาซัคซินิลโคลีน 0.75 มก/กก ก่อนการกระตุ้นครั้งแรก และ 0.25 มก/กก ก่อนการกระตุ้นครั้งที่สอง*

การประเมินผล : *เปรียบเทียบความรุนแรงการชักของขาสองข้าง ข้างหนึ่งรัดต้นขาไม่ให้ยาซัคซินิลโคลีนเข้าไปได้ ถ้าขาสองข้างชักรุนแรงเท่ากันแสดงว่ายาไม่ได้ผลในการลดความรุนแรงของการชัก*

ผลการศึกษา : *การแบ่งให้ซัคซินิลโคลีนจะลดการชักที่ควบคุมได้ไม่ดีลงจากร้อยละ 43.6 เหลือเพียงร้อยละ 10.3 ($p=0.004$) โดยที่ระยะเวลาเฉลี่ยในการฟื้นของกล้ามเนื้อยาวนานขึ้นจาก 125 วินาที เป็น 183 วินาที ($p=0.001$)*

สรุป : *การแบ่งให้ซัคซินิลโคลีนเหมาะสมสำหรับการลดความรุนแรงของการชักจากการรักษาด้วยการช็อคไฟฟ้าแบบหลายครั้งติดต่อกัน*

คำสำคัญ : *ซัคซินิลโคลีน, การช็อคไฟฟ้า*

Electroconvulsive therapy (ECT) is a modality of treatment in psychiatric practice for depressive states, acute schizophrenia and some manic states.[1-4] It is effective in the patients who fail medical treatment or have severe manifestation.[5-8] While the electrical seizure activity in the brain has therapeutic effect on psychiatric symptoms, motor seizure in the body causes only harmful effects to the patients. Currently modified ECT is used with suitable muscle relaxation to attenuate the severity of convulsion and then minimizes the injury during the therapy.[9]

Multiple monitored electroconvulsive therapy (MMECT), which stimulated more than one convulsion in one treatment session, has been recommended to yield a better outcome than single therapy.[10-14] But several convulsions in one session increase the chance of injury and also extend the time of vulnerable period. There is relatively refractory period following each seizure, which prevents subsequent stimuli from eliciting convulsive activity. Thus the minimum interval between convulsions should be three minutes.[10] This causes a problem for appropriate muscle relaxant administration. A single dose of succinylcholine, a short acting muscle relaxant, is usually used and the effect is frequently inadequate to modify the seizure severity of the latter convulsion. The injury may occur even when the first convulsion is adequately modified but the following one is not. Sometimes supplemental dose of succinylcholine is given with individual judgment when the first convulsion seems to be too violent. We propose that a small dose of succinylcholine should always be given after the first convulsion to minimize the risk of injury from subsequent convulsion. This is the proposal of split dose administration. The objective of this study is to compare the effect of split dose with the conventional single dose of succinylcholine for modification of motor seizure activity during multiple monitored electroconvulsive therapy.

Materials and Methods

The institutional review board of Faculty of Medicine, Chulalongkorn University had approved the study protocol. The participants consisted of 40 adult psychiatric patients who were scheduled to receive more than one session of multiple monitored electroconvulsive therapy. The sample size was estimated from pilot data calculated with effect size 30 %, type I error at 0.05, and power of 0.8.[15] The informed consent was obtained from the patients and their responsible relatives. All patients were older than 15 years and agreed to participate. The patients who had contraindication to electroconvulsive therapy or the medication used in the study and those having history of systemic or neuromuscular problems or receiving medication that might interact with succinylcholine were excluded.

Each patient received one treatment, either single dose or split dose, in the first session according to randomization by a computer. Then he or she would get the other dosage regimen in the following therapy session. The interval between therapy sessions was at least 48 hours to ensure that the effect of succinylcholine was completely washed out.

For allocation concealment, the numbers were secured in the consecutive sealed opaque envelopes. Only one person, the drug dispenser, knew the code after the enrollment of the patient.

Anesthesia started after preparation for intravenous access and baseline monitoring for EKG,

EEG, nerve stimulator, and pulse oximetry. Thiopental 3 mg/kg was given for induction. If the patient was not unconscious after 1 minute, supplemental dose of thiopental would be given as necessary and recorded. The anesthetist, blind to the treatment allocation, manually ventilated the patients and tried to avoid the condition of hyperventilation. Then the patients received succinylcholine regimen according to the randomization number.

For single dose regimen, 1.0 mg/kg of succinylcholine was injected intravenously after the patient was unconscious (Fig. 1). One minute later, an electrical stimulation for seizure was given by MECTA SR (MECTRA Corporation, Portland, Ore.). A responsible psychiatrist determined the proper stimulus parameter and tried to keep it constant, if possible, throughout the study. Every change of stimulus between sessions was recorded. Two minutes after termination of the first convulsion, the patient received an intravenous injection of placebo. One minute later, the patient would receive the second electrical stimulation. In case of failure to induce seizure, additional electrical stimulus might be given by the psychiatrist's judgment and recorded.

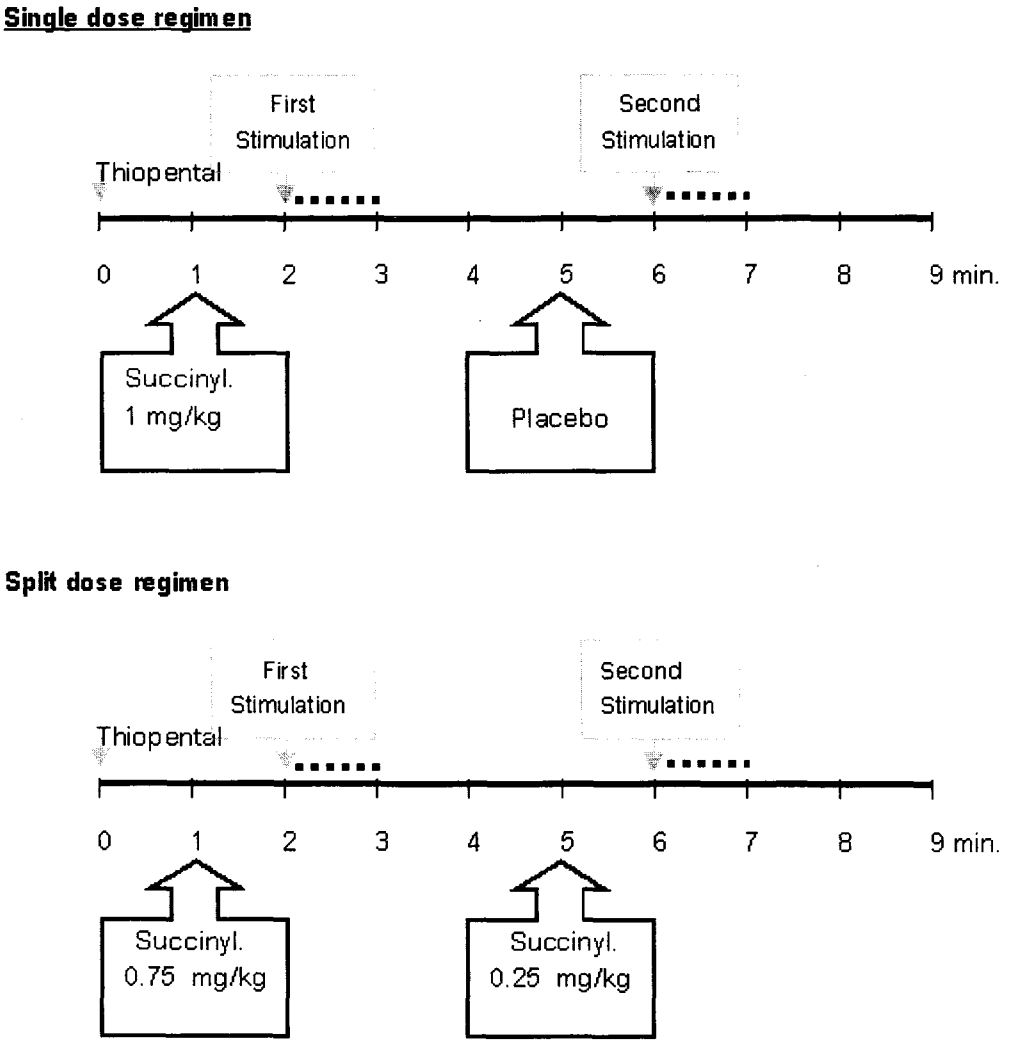

Figure 1. Intervention plan.

For split dose regimen, 0.75 mg/kg of succinylcholine was administered first and then 0.25 mg/kg after the first convulsion instead of placebo. The administration of electrical stimulation was the same as in the single dose regimen.

The preparation of the study drug in both regimens varied in concentration of the medication according to the patient's body weight but its volume and characteristic were the same. Nobody could distinguish from its appearance. So everybody, except the drug dispenser, was blind to the treatment regimen.

We evaluated the modification of motor seizure by a pressure cuff to occlude one leg, so that succinylcholine could not enter that leg, and then compared the convulsion with other parts of the body. One observer, who was blind to treatment and not involved in the treatment, assessed grading score for convulsion severity (Table 1). The score at 5 meant that succinylcholine was very effective in attenuation of motor convulsion in every part of the body except the limb that we occluded with a pressure cuff. The convulsion could be seen only in the cuffed limb and in the electroencephalogram monitoring brain electrical activity. The score from first or second convulsion less than 3 indicated poor modification [16,17] because the limbs that received succinylcholine, or not, had equal intensity of convulsion. This situation denoted that the dose of succinylcholine was not effective.

When there were clinical signs of forceful respiration or strong motor movement one minute after administration of the study drug but before any electrical stimulation, inadequate muscle relaxation was possible. Confirmed by muscle twitch height more than 20 %, this situation then required a rescue dose, 0.5 mg/kg, of open-label succinylcholine. The result was recorded and classified as a poor outcome for modification of electroconvulsive therapy.

An accelerometer (TOFwatch, Organon, USA) was used for neuromuscular function monitoring from ulnar nerve stimulation with 0.1 Hz single twitch. An assistant recorded the time from the end of the convulsion to 20 % recovery of twitch height, considered as an indicator of adequate respiration. He would disclose the reading of twitch height to other personnel only when there were clinical signs of inadequate relaxation and the twitch height was more than 20 % before seizure stimulation, which required rescue succinylcholine.

Table 1. Seizure modification score assessment.

Score	Convulsion
1	Violent as unmodified electroconvulsive therapy
2	Bilateral motor convulsions equal intensity both cuffed & uncuffed limbs
3	Bilateral motor convulsions, and the intensity was clearly more in cuffed limb when compared with corresponding uncuffed limb
4	Motor convulsion in cuffed limb and face
5	Motor convulsion only in cuffed limb

Statistical Analysis

At the end of the study, we tabulated the outcomes by the period and the sequence of the treatments to illustrate the period effect, sequence effect, and carry-over effect. [18] The statistical analysis, by SPSS version 7.5 software, consisted of McNemar test for seizure modification status and Wilcoxon signed rank test for recovery time using statistical significance level at $p<0.05$.

Results

The participants included 19 men and 21 women. Their mean ± SD of age, weight, and height were 36 ± 11.9 yrs, 61.0 ± 14.8 kg, and 161.0 ± 9.4 cm, respectively. It was necessary to withdraw one female patient after the first session of the split dose therapy because of her amnesia, an adverse effect of the therapy. So the following sessions were changed to single ECT stimulation. In the 39 eligible patients, there were 17 sessions (43.6 %) of poor modification outcomes from the single dose regimen, and 4 sessions (10.3 %) from the split dose regimen. Nineteen patients had good results in both regimens, whereas one patient had poor results in both regimens (Table 2). The intrasubject comparison with McNemar test showed statistically significant difference between the results of the two regimens (p = 0.004, 2-sided Exact test). Absolute risk reduction for poor modification of seizure by the split dose regimen was 33.3%, with 95 % confidence interval from 14.1 % to 52.6 %. So the number needed to treat was 3, with 95 % confidence interval from 1.9 to 7.1.

When the numbers of poor outcome sessions were tabulated by treatment sequence and session period (Table 3), the period effect, sequence effect, and carryover effect could be evaluated. A comparison of the two row marginals (11 sessions in the first period compared with 10 sessions in the second period) did not show any period effect because the difference was small. A comparison of the column marginals (11 sessions in single-split sequence compared with 10 sessions in split-single sequence) also did not

Table 2. Outcome in each sequence of treatment.

Outcome	(Good, Good)	(Good, Poor)	(Poor, Good)	(Poor, Poor)
Single-Split Sequence	10	1	8*	1
Split-Single Sequence	9	8	2	0

p = 0.004, 2-sided Exact test

Table 3. Poor outcome session tabulated by period and sequence of treatment.

Poor outcome session	Single-split sequence	Split-single sequence	Total
Period 1	9 in 20	2 in 19	11 in 39
Period 2	2 in 20	8 in 19	10 in 39
Total	11 in 40	10 in 38	21 in 78

show any sequence effect. The median time between sessions for washout period in single-split sequence group was 3 days (range 2-42 days). The median time between sessions for washout period in split-single sequence group was 2.5 days (range 2-21 days).

Six patients during the single dose therapy required a rescue dose of open-label succinylcholine because of the clinical signs of inadequate muscle relaxation immediately before the electrical stimulation whereas three patients in the split dose regimen needed the rescue. After the rescue the convulsion showed good modification of seizure.

When the patients who received a rescue dose of succinylcholine were excluded from the analysis, there still were 11 sessions of poor modification outcome from the single dose regimen compared with 1 session in the split dose regimen (p=0.006, 2-sided Exact test).

The average time from the end of seizure to 20 % muscle twitch height recovery in the single dose and the split dose were 125 seconds and 183 seconds respectively. The difference was statistically significant (p=0.001, Wilcoxon signed rank test).

There were 2 patients in the single dose regimen and 1 patient in the split dose regimen who had poor modification of the first convulsion.

Discussion

By using split dose regimen, we could reduce the risk of poor modification of seizure from 43.6 % to 10.3 %. The patients might have average muscle recovery time extended from 125 seconds to 183 seconds. The mean of recovery time difference was less than one minute, which was not clinically significant.

Poor modification of seizure could result in morbidity or mortality, according to earlier reports on unmodified electroconvulsive therapy. Even though the tragic outcomes were rare, especially in the new trend of modified electroconvulsive therapy, and it was difficult to demonstrate the difference from muscle relaxant administration regimen [19,20], the strong convulsion itself was an unfavorable outcome for the patients. The inadequacy of the relaxation and violent seizure might lead to objection of the psychiatrists.[21]

The problems of period effect, sequence effect, and carryover effect were the major obstacle to interpret the outcome of a crossover trial. [18] The period effect was the change of responses due to the difference between the first and the second period of observation because each patient was observed twice. The sequence effect occurred whenever the order in which treatments were given produced a difference in the response. The carryover effect was the persistence of the effect of the first treatment extending beyond its period of application to influence the action of a subsequent treatment. The primary solution to overcome these problems was the selection of appropriate situation that should not produce such an effect by the nature of the diseases, the intervention, and the outcomes in the study. The response of our patients to electrical stimuli or succinylcholine and the short action of succinylcholine compared with the duration of washout period between sessions were appropriate for the crossover study.

In addition, when the data were classified by the period and the sequence of treatment, the effect of these two factors could be estimated. If there was uniform carryover effect, affecting both treatments equally, it would appear as a period effect and would

not bias the estimate of treatment differences. If the carryover was not uniform, affecting the two treatments differently, then there would be a sequence effect, obscuring the true treatment differences. [18] Because the data did not demonstrate any period effect and sequence effect (Table 3), the assumption that there was no carryover effect was not violated.

Murali, *et al* [16] had shown that 1 mg/kg of succinylcholine was more effective in modifying the peripheral convulsion in the single electroconvulsive therapy than 0.5 mg/kg while our study used 0.75 mg/kg in the first portion of the split dose and it was adequate for modification of the first convulsion in most patients. If 1 mg/kg was used, instead of 0.75 mg/kg, the muscle relaxation might be a little better and sooner, but the recovery time would be prolonged. Our study also showed that 0.75 mg/kg of succinylcholine was effective in modifying the peripheral convulsion in the first convulsion, so it could be used in the single electroconvulsive therapy as well as 1 mg/kg.

There were some practices to administer the supplemental dose of succinylcholine depending on the result of the first convulsion and also on the clinical signs of inadequate muscle relaxation. Infrequently, a neuromuscular monitoring was used in guiding the succinylcholine administration. While these practices might rescue some patients, the rest of the patients still had high risk of poor modification of convulsion. Although neuromuscular monitoring might have some value in some patients, the discrepancy of relaxation of muscle in different parts of the body produced problems when we relied too much on the monitoring. Some patients had recovery of respiration while their muscle twitch was zero. In this condition, a stimulation might be given with a good outcome. In contrast, a few patients who had twitch height below 20 % before the stimulation had poor modification of seizure.

The issue of the rescue dose was a limitation to show more difference of the effect between the two regimens. If there was no rescue, the incidence of poor convulsion would have increased, but it was unethical and unpractical. In clinical practice, anesthesiologists would add more relaxant, should there be any clinical signs of inadequate muscle relaxation.

There was another clinical practice that gave only one dose of succinylcholine for two electrical stimulations. By inducing the second stimulation earlier, 45 seconds after the first convulsion, the second convulsion might occur within the duration of action of a single dose succinylcholine. With this practice one needed to increase the electrical current because the stimulation would fall on the relative refractory period. This meant that there was more electrical current reaching the brain and it might be more harmful to the brain. In addition, the failure rate of stimulation increased, and in this situation, another stimulation with higher level of current to the brain was retried until the adequate seizure occurred. [22] We suggested that the stimulation should be done in an appropriate period, beyond 3 minutes after the first stimulation, with the same setting of electrical stimulation as in the first stimulation. The stimulation could be done without concerning about inadequate duration of muscle relaxation by using the split dose regimen.

Multiple monitored electroconvulsive therapy employed in our institute usually consisted of two convulsions in one therapy session and the split

dose of succinylcholine is suitable for this situation. In other hospitals that used more than two convulsions in one session, the intermittent dose of succinylcholine for each convulsion should be adjusted. In the past, continuous succinylcholine infusion was recommended for multiple monitored electroconvulsive therapy but it is now not popular. [23] We need intermittent adequate relaxation just before each convulsion, so the intermittent dose would be more appropriate. With high dose of succinylcholine infusion to achieve intense relaxation throughout the procedure, it would result in complication such as abnormal phase II blockage.

Atracurium, an intermediate acting nondepolarizer, had been used successfully in multiple electroconvulsive therapy. However the dose of atracurium should be 0.5 mg/kg, instead of 0.3 mg/kg, to obtain effective modification of convulsion. [24] The duration of this larger dose was longer. Relaxation of respiratory muscle required assisted ventilation and relaxation of muscles of the upper airway might lead to obstruction or aspiration. Some patients required a reversal of muscle relaxant at the end of the procedure.

A potential replacement for succinylcholine was a short acting, nondepolarizing neuromuscular blocking agent, mivacurium. [25,26] It had fewer side effects and in low dose (0.08 mg/kg) might have no need for a reversal. However the quality of seizure modification was inadequate in 50 % of patients who received mivacurium compared with 12.5 % of patients who received succinylcholine. The study was terminated early due to objections of psychiatrists regarding the adequacy of seizure control. Therefore low dose of mivacurium was not recommended as a substitute for succinylcholine during electroconvulsive therapy. [21] A new nondepolarizing muscle relaxant, rapacuronium, was proposed for electroconvulsive therapy. [27] Further study should be done to compare it with succinylcholine.

In conclusion, we recommend that split dose of succinylcholine is suitable for modification of seizure during multiple monitored electroconvulsive therapy.

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