



Initial Seizure Threshold in Brief-Pulse Bilateral Electroconvulsive Therapy in Patients with Schizophrenia or Schizoaffective Disorder

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Objective The present study aimed to report the initial seizure threshold (IST) of a brief-pulse bilateral electroconvulsive therapy (BP-BL ECT) in Korean patients with schizophrenia/schizoaffective disorder and to identify IST predictors.

Methods Among 67 patients who received ECT and diagnosed with schizophrenia/schizoaffective disorder based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision, we included 56 patients who received 1-millisecond BP-BL ECT after anesthesia with sodium thiopental between March 2012 and June 2018. Demographic and clinical information was gathered from electronic medical records, and a multiple regression analysis was conducted to identify predictors of the IST.

Results The mean age of the patients was 36.9 ± 12.0 years and 30 (53.6%) patients were male. The mean and median IST were 105.9 ± 54.5 and 96 millicoulombs (mC), respectively. The IST was predicted by age, gender, and dose (mg/kg) of sodium thiopental. Other physical and clinical variables were not associated with the IST.

Conclusion The present study demonstrated that the IST of 1-ms BP-BL ECT following sodium thiopental anesthesia in Korean patients was comparable to those reported in previous literature. The IST was associated with age, gender, and dose of sodium thiopental.

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Key Words Schizophrenia, Schizoaffective disorder, Initial seizure threshold, Electroconvulsive therapy, Brief-pulse width, Bilateral electrode placement.

INTRODUCTION

Electroconvulsive therapy (ECT) is a safe and effective treatment for various psychiatric disorders and conditions.^{1,2} The successful induction of a generalized seizure requires an adequate dose of electricity that exceeds the seizure threshold, which is defined as the minimal electrical intensity necessary to produce a seizure.^{3,4} The initial seizure threshold (IST) determined at the first ECT session guides the electrical doses for

the entire following sessions, and thus, considered to be one of the most important parameters of ECT procedure.⁵ Because unnecessary exposure to higher electrical doses produces more severe cognitive impairment,⁶⁻⁸ determining IST is particularly important for ECT optimization with better clinical efficacy and minimal cognitive side effect.^{9,10}

However, IST determination is not a straightforward task, as it varies up to 40 times for different individuals.^{11,12} IST is known to be associated with patients' own characteristics (age, sex, body mass index, etc.) and/or treatment factors (ECT parameters, anesthetics, concomitant medication, etc.).^{3,13-17} For example, the IST is higher in older age,^{3,13,16} in male,^{3,13,16} in bilateral electrode placement,^{14,15,17,18} and following the use of certain anesthetic agents.¹⁹ On the other hand, the effects of severity or duration of illness, presence of psychosis, or the use of concomitant medications remain controversial or largely irrelevant.^{10,20-24}

Several methods of IST determination have been proposed,

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including age-based, half-age-based, fixed-high, and empirical titration methods.^{4,8,25,26} These methods can be categorized into two approaches: 1) the administration of a predetermined fixed-dose modified by the above variables and 2) the titration by repeated trials in which the dose is incrementally raised until a satisfactory seizure appears. However, controversy remains regarding which of these is the most desirable method.²⁷

The influence of race and ethnicity on IST is not yet clear.²¹ Most studies on IST had been conducted in Western populations and only a handful of studies reported IST values in Asian populations.^{23,24,28-30} For example, Yasuda et al.²³ assessed IST in Japanese patients (age range of 20–83 years) using 0.5-ms pulse with Thymatron SYSTEM IV ECT apparatus. They found that the IST was equal or slightly higher than those reported in other ethnic groups. In contrast, Lee et al.³¹ reported that the IST of Korean patients (age range of 20–73 years) using 1.4-ms pulse with MECTA SR-1 model was lower than that of Western populations. These findings were not directly comparable to each other due to differences in the used pulse width, ECT devices, titration schedules, and age distributions. However, considering ethnicity may still be important in estimating IST in actual clinical practice.^{23,32,33}

The present retrospective study based on chart-review aimed to report the distribution of IST values in Korean patients following a specific protocol. Especially, this study had focused on patients diagnosed with either schizophrenia or schizoaffective disorder. To date, studies on IST done with psychotic patients were hard to find.^{28,34} However, schizophrenia and other psychotic illnesses are another important indication for ECT, especially in treatment-resistant groups.³⁵⁻³⁷ The protocol used in this study required that all the study participants received 1-millisecond (ms) brief-pulse bilateral (BP-BL) ECT following general anesthesia with sodium thiopental. The IST was empirically titrated by incrementally increasing the stimulus intensity, according to a predefined schedule. Additionally, the present study evaluated the association of IST with various demographic and clinical characteristics to identify factors that may be predictive of IST. A multiple regression model was built using those characteristics as potential predictors. The obtained results would provide valuable information in conducting ECT in patients with schizophrenia and schizoaffective disorder, especially in patients whose physical condition does not allow empirical titration procedure.^{38,39}

METHODS

Subjects

Patients who underwent an acute course of ECT under the diagnosis of schizophrenia or schizoaffective disorder from March 2012 to June 2018 at the ECT center of Dongguk Uni-

versity International Hospital were identified as eligible subjects. Diagnoses were confirmed by the physician-in-charge and one of the authors (CIW) after the chart review in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).

In an effort to report the IST distribution following a specific protocol, only the patients who had received 1-ms BP-BL ECT after anesthesia with sodium thiopental were selected, which constituted the majority of the all eligible subjects. Information on demographic characteristics, clinical characteristics, ECT history, and use of concomitant medications (antipsychotics, anticonvulsants, antidepressants, and benzodiazepines) was obtained from electronic medical records (EMR). The study proposal was approved by the Institutional Review Board of Dongguk University International Hospital (2018-10-003).

ECT procedure

The ECT session was commenced only after completion of psychiatric and medical work-ups. The administration of anticonvulsants and/or benzodiazepines was stopped or reduced the day before the ECT session in all patients. The MECTA spECTrum 5,000Q (MECTA Corp; Lake Oswego, OR, USA) was used to deliver the electrical stimulus, and BP-BL ECT was the primary recommendation if there were no concerns about memory or cognitive impairments. The seizure was monitored in three ways: electroencephalography (EEG), electrocardiography (ECG), and motor movement measuring by an optical motion sensor (OMS) under the tourniquet method. The anesthesia and muscle relaxation procedures were described in detail in a previous report issued by our research group.³⁷ All patients were continuously monitored until full recovery of consciousness and the return of stable vital signs.

IST measurement

The IST was measured at the first ECT session by empirical titration method. The stimulus intensity was increased according to a predetermined schedule (Table 1), which had been modified from the recommended dose table by Coffey et al.,⁴⁰ and those of Seoul National University Hospital and University of Pittsburgh Medical Center (UPMC).³⁷ The electrical dose was increased from the lowest level up to five times until an adequate seizure appeared. Adequate seizure duration was considered to be ≥ 25 sec according to EEG or ≥ 20 sec according to OMS, and seizure quality was evaluated by three EEG patterns of polyspike activity, three spikes and wave activity, and post-ictal suppression.⁴¹

Statistical analysis

The demographic and clinical characteristics of the patients are presented in Table 1. To compare genders, continuous vari-

ables were assessed with Student t-tests, and categorical variables were assessed with chi-square tests. A multiple regression analysis was conducted to identify the relevant predictors of IST; the candidate predictors included demographic variables (age, gender, duration of illness, family history of psychiatric illness), physical variables (weight, height, and BMI), ECT procedure variables (anesthetic agent dose) and variables related to medication use (use of clozapine/anticonvulsants/antidepressants/benzodiazepines, and chlorpromazine-equivalent doses of antipsychotic medication). A stepwise variable selection procedure was employed to identify the most parsimonious set of relevant predictors. The finding strategy was set to “both directions,” and the criteria for the best model were Akaike’s Information Criteria (AIC). After the best model was obtained, more complicated models were built in consideration of the possible interactions among the identified predictors. The significance levels of the interactions were determined based on the F-test values obtained in comparisons between the more complicated models and the base model. The p-values of less than 0.05 were considered to indicate statistical significance. All statistical analyses were performed using SPSS ver. 23.0 for Windows (IBM Corp, Armonk, NY, USA) and an open-source statistical program R (ver. 3.2.4: R Project for Statistical Computing, Vienna, Austria).⁴²

RESULTS

Demographic and clinical characteristics

In total, 67 patients with schizophrenia or schizoaffective disorder received ECT during the study period. Among them, 56 (83.5%) had undergone a 1-ms BP-BL ECT after anesthesia with sodium thiopental. These patients were included in the present analysis. The excluded patients were 1) seven patients with the right unilateral electrode placement and 2) four patients with propofol-induced anesthesia.

The mean age of the study subjects was 36.9 ± 12.0 years, and 30 patients (53.6%) were male. There were no gender differences in educational level, occupation, family history, intelligence quotient (IQ) proportion and duration of illness, but the mean BMI of the male subjects (27.1 ± 5.4) was significantly higher than that of the female subjects (24.0 ± 5.3 ; $t=2.158$, $p=0.035$). The medication-related variables, such as chlorpromazine-equivalent dose, use of clozapine, and use of concomitant anticonvulsants, antidepressants, or benzodiazepines, did not differ between the male and female subjects (Table 1).

Distribution of IST values

The mean IST of the study subjects was 105.9 ± 54.5 millicoulomb (mC; range: 48–288 mC) (Table 1). The distribution was right-skewed with a mean value greater than median val-

Table 1. Summary of demographic, ECT, medication related variables and the estimated IST of the study subjects who underwent BP-BL ECT after anesthesia with sodium thiopental (N=56)

Variables	Total (N=56)	Male (N=30)	Female (N=26)	Male vs. female p-values
Demographic variables				
Age (years)	$36.9 \pm 12.0^*$	33.4 ± 11.5	40.9 ± 11.5	0.018
Weight (kg)	70.6 ± 18.1	79.7 ± 16.0	60.2 ± 14.5	<0.001
Height (cm)	165.5 ± 8.5	171.6 ± 4.9	158.4 ± 5.8	<0.001
BMI (kg/m ²)	25.6 ± 5.5	27.1 ± 5.4	24.0 ± 5.3	0.035
Duration of illness (years)	12.2 ± 7.8	12.5 ± 7.9	11.8 ± 7.8	0.729
ECT variables				
Thiopental dose (mg)	214.7 ± 62.5	240.8 ± 59.3	184.6 ± 52.5	<0.001
Thiopental dose/weight (mg/kg)	3.1 ± 0.6	3.0 ± 0.5	3.1 ± 0.7	0.725
IST (millicoulomb)	105.9 ± 54.5	115.2 ± 59.9	95.2 ± 46.3	0.174
Concomitant medications				
Chlorpromazine-equivalent dose of antipsychotics (mg)	667.2 ± 458.6	695.6 ± 430.8	634.4 ± 495.3	0.623
Clozapine use (yes/no)	40/16	20/10	20/6	0.102
Anticonvulsant use (yes/no)	27/29	16/14	11/15	0.579
Antidepressant use (yes/no)	14/42	8/22	6/20	1.000
Benzodiazepine use (yes/no)	39/17	16/10	23/7	0.349

*numbers are expressed as mean \pm standard deviation or as the frequency of yes/no. The difference between male and female subjects was statistically tested with Student t-tests for continuous variables and chi-square test for dichotomous variables. ECT: electroconvulsive therapy, IST: initial seizure threshold, BP-BL: Brief-pulse Bilateral, BMI: body mass index

ue (96 mC) (Figure 1). The mean IST of the males (115.2 ± 59.9 mC) appeared to be higher than that of the females (95.2 ± 46.3 mC), but this difference was not statistically significant. Also, the IST was not statistically different between patients taking clozapine (105.1 ± 50.1 mC) and those not (108.0 ± 66.0 mC). The mean daily clozapine dose in 40 patients treated with clozapine was 262.5 ± 126.3 mg (range: 37.5–450 mg).

A multiple regression analysis with stepwise variable selection procedure suggested that age, gender and the dose per body weight (mg/kg) of sodium thiopental were the most relevant and parsimonious set of predictors (Table 2). Interestingly, if the unadjusted dose (mg) of sodium thiopental were substituted for the per-kilogram dosage, BMI and height emerged as other potentially relevant predictors. Therefore, it was inferred that per kilogram dosage of anesthetics, not the absolute dosage, was important in determining IST. The final re-

gression model was highly significant ($F_{[3,52]}=4.806$, $p=0.005$), the adjusted R-squared value was 0.172, and each predictor (age, gender, and dose of sodium thiopental) was significant ($p=0.05$).

The relationship between IST and the set of relevant predictors (age, gender, and a dose of sodium thiopental) is depicted in Figure 2. For a visual representation, the dose of sodium thiopental was categorized into three non-overlapping ranges with equal numbers of patients. A positive relationship between age and IST was apparent in all subsets of the study patients, except for females receiving the middle range of the sodium thiopental dose (2.8–3.2 mg/kg) (Figure 2A). Additionally, higher IST values in males were clearly observed in those receiving the lower (2.0–2.8 mg/kg) and higher (3.2–5.0 mg/kg) ranges of sodium thiopental. The positive relationship between IST and sodium thiopental dose was more evident using another visual representation (Figure 2B) in which the dose of

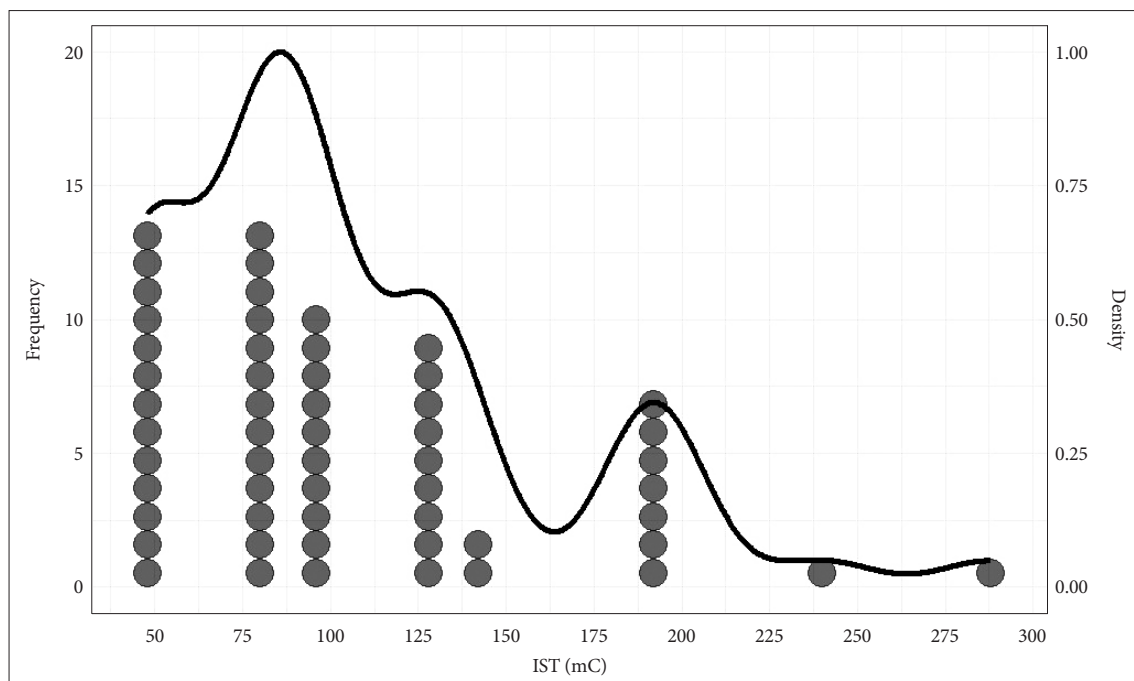


Figure 1. The distribution of IST after 1-millisecond pulse width BP-BL ECT. The IST values were estimated by empirical titration methods according to a predefined protocol. The subjects were 56 patients with schizophrenia and schizophreniform disorder. ECT was administered after anesthesia with sodium thiopental (gray dots are the actual cases and the thick black line is the estimated kernel density). IST: initial seizure threshold, BP-BL: brief-pulse bilateral, ECT: electroconvulsive therapy.

Table 2. The final output of multiple regression analysis with IST as the dependent variable after the stepwise variable selection procedure

Predictors*	β estimate	Standardized β	Standard error	t-value	p-value
Age	1.63	0.354	0.59	2.76	0.008
Gender	-33.65	-0.337	14.03	-2.40	0.020
Thiopental dose per weight (mg/kg)	27.35	0.291	11.53	2.37	0.021
Overall F-statistic: 4.81 (3,52)	$p=0.005$		$R^2=0.217$		Adjusted $R^2=0.172$

*these predictors were selected as the most parsimonious set of influential predictors for predicting IST. The most optimal model was chosen based on AIC. All predictors contained in the model significantly predicted IST values at p-values <0.05 . The model explained 21.7% of the total variance. IST: initial seizure threshold, AIC: Akaike's Information Criteria

sodium thiopental had a clear effect on IST, except in male subjects older than 42 years of age. Visual inspections were indicative of a potential interaction among the relevant variables. In order to verify the consistency of the pairwise associations

across different strata of other covariates, complex interaction models were evaluated. However, the interaction was not statistically significant in any of the models.

Other clinical variables related to the use of concurrent med-

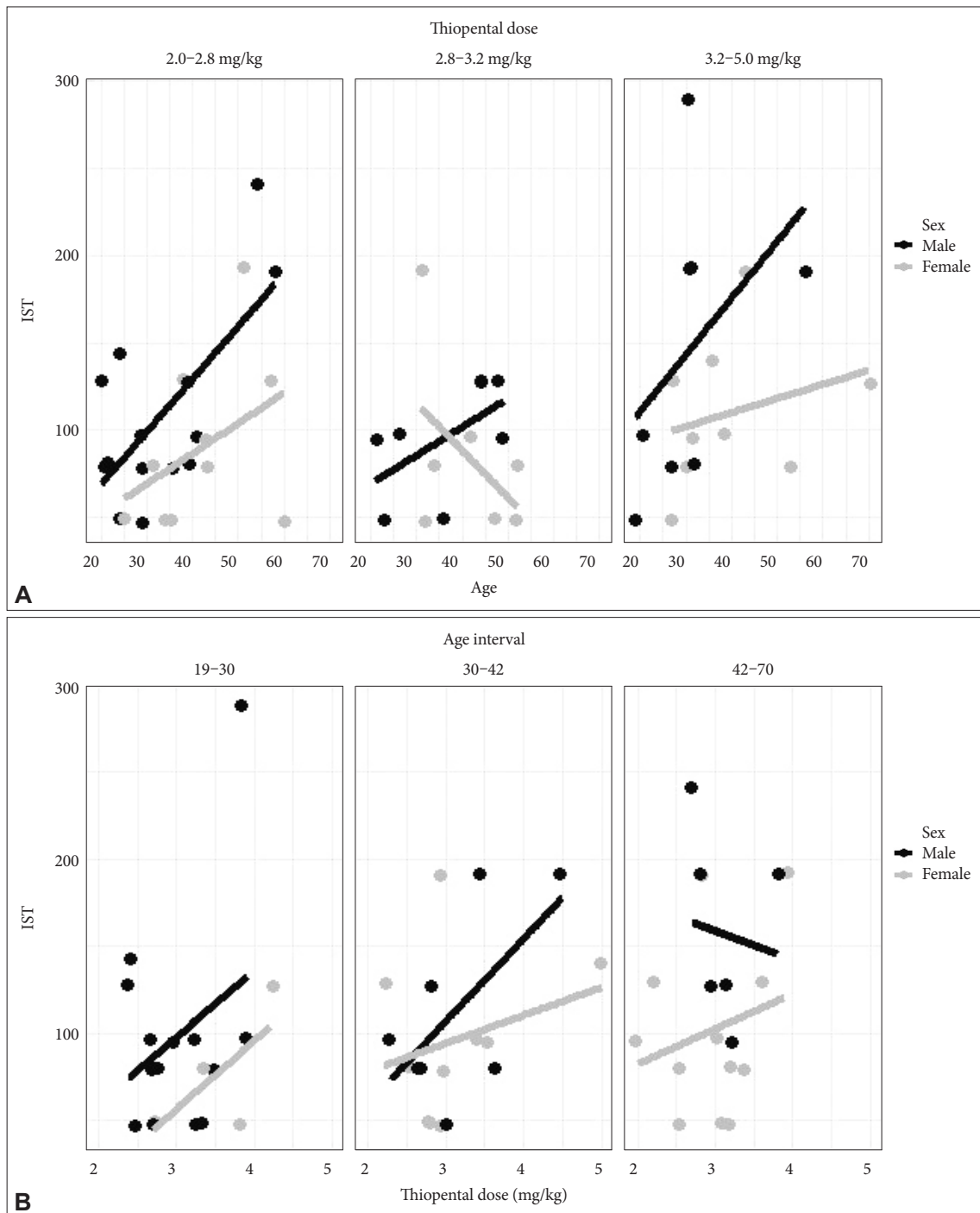


Figure 2. Relationships between IST and age, gender, and dose of sodium thiopental in patients who underwent BP-BL ECT after anesthesia with sodium thiopental. The overlaid lines represent the linear regression lines through respective subsets of study subjects. A: Relationship between IST and age stratified by gender and dose (mg/kg) of sodium thiopental using an arbitrary categorization of dose into three non-overlapping ranges with equal numbers of patients. B: Relationship between IST and dose (mg/kg) of sodium thiopental stratified by gender and age using an arbitrary categorization of age into three non-overlapping ranges with equal numbers of patients. IST: initial seizure threshold, BP-BL: brief-pulse bilateral, ECT: electroconvulsive therapy.

ications (clozapine, anticonvulsants, antidepressants, and benzodiazepines) were not significantly related to IST. Neither were they included in the final model nor any of the t-test for each variable revealed group difference.

DISCUSSION

This study explored the overall IST distribution in Korean patients with schizophrenia and schizoaffective disorder. The mean and median values of IST were 105.9 mC and 96 mC respectively. The distribution was highly right-skewed with about 80% of the study subjects below the IST value of 128 mC. The range was 48–288 mC and the variability was a six-fold difference. The obtained IST was much higher than those reported from unilateral electrode placement.^{19,43}

The largest studies so far which have explored IST values in representative samples of patients were done by Nitturkar et al.⁴⁴ in India and by Petrides et al.¹⁰ in the United States. Both studies also employed the BP-BL ECT but comparing these studies with the present study involved a variety of problems. The subjects' diagnoses in the previous two studies were mostly mood disorders, and only a part of them included subjects with schizophrenia. Besides, the US study used methohexital as anesthetic agent thus making the comparison difficult. On the other hand, the Indian study used thiopentone as in the present study. Despite having many aspects in common with the present study, the IST value reported by Nitturkar et al.⁴⁴ was higher (mean: 130.4 mC) than that in the present study (mean: 105.9 mC). They reported that IST values of 78.6% of the patients were equal or above 120 mC. The corresponding

percentage in the present study was only 35.7%. Petrides et al.¹⁰ also reported higher IST value (mean: 126.0 mC) and about 80% of patients were between 100 and 200 mC. The percentage belonging to this range in the present study was only 32%.

This comparison gives the impression that the IST values from Korean subjects are rather low than from the American or Indian population. However, IST values reported in other small or medium-sized studies were in the lower or similar range as the present study irrespective of race or ethnicity (Table 3). Especially, the result from Chinese subjects was very close to our result.^{29,30} Above all, the only meta-analysis of IST conducted by van Waarde et al.⁴³ reported 111.6 mC as the weighted mean of past studies, which roughly corresponded to the present study. Another Korean study employing the same BP-BL ECT reported the mean IST values between 32.89–45.23 Joules (in different conditions) which corresponded to 186.7–257.9 mC.²⁴ The use of propofol as anesthetic agent might have caused the overall upward adjustment in this study. This range was even higher than those of Nitturkar et al.⁴⁴ and Petrides et al.¹⁰ Taken together, even though there remained a question of how to reconcile the differences in subject composition and employed ECT methodology, the ethnic difference seemed not to be greater than the differences between individual studies.

This study replicated the well-known fact that IST values are significantly associated with age and gender. Older age and being male predict a higher IST.^{3,15,18,26} Although the contribution of age and gender was only modest, the close relationship among these variables is the basis of the classical dose recommendation established by Coffey et al.¹⁵ Meanwhile, previous notion that concomitant medications, such as, mood stabiliz-

Table 3. Previous studies of the IST distributions in bilateral electroconvulsive therapy

Study	IST (Mean±SD)	Median	Range	Diagnosis	Anesthetics	Ethnicity	Number of participants
Coffey et al. ¹⁵	86.4±34.9			Affective disorder	Methohexital	American	25
Scott et al. ²⁰		75	50–200	Depressive disorder	Methohexitone	European	100
Chanpattana et al. ²⁸	91.3±31.2			Schizophrenia	Thiopental	Asian (Thai)	93
Chung and Wong ²⁹	117.4±65.6		48–403	Mixed	Thiopentone	Asian (Chinese)	54
Chung and Wong ³⁰	105.5±40.6		48–192	Mixed thiopentone		Asian (Chinese)	22
Chung ⁵⁶	115.1		48–403	Mixed	Thiopentone	Asian (Chinese)	105
Petrides et al. ¹⁰	126.0±69.7	100	25–400	Depressive disorder	Methohexital	American	402
van Waarde et al. ⁴³	111.6			Mixed	Mixed	Meta-analysis	1,116
Bennett et al. ⁵⁵		125	50–300	Depressive disorder	(Not informed)	European	62
van Waarde et al. ¹⁸	95.4±59.5			Depressive disorder	Etomidate	European	28
Yashuda et al. ²³	136		50.4–403	Major depressive disorder	Thiamylal	Asian (Japanese)	54
Nitturkar et al. ⁴⁴	130.4±52.0			Mixed	Thiopentone	Asian (Indian)	640
Chi et al. ²⁴	186.7±35.1			Mixed	Propofol	Asian (Korean)	43
Present study	105.9±54.5	96	48–288	Schizophrenia	Thiopental	Asian (Korean)	56

SD: standard deviation, IST: initial seizure threshold

ing agents, benzodiazepine, and antipsychotics (especially clozapine) may influence the seizure threshold was not verified in the present study. Quite a few preclinical studies have addressed the potential influence of psychotropic drugs on seizure physiology, but the actual ECT experience was inconsistent.⁴⁵⁻⁴⁷ Interaction among the psychotropic drugs themselves, complicated dose-response relationship, strong effect of anesthetic agent, or anticonvulsant effect of ECT itself may be some of the intricacies involved in these inconsistent results.¹⁸ Due to these intricacies and the small sample size of the present study, it would be premature to conclude that concomitant medications do not have any effects on IST.

Apart from this, another finding was the association between thiopental dose and IST. Traditionally, methohexital, etomidate, thiopental, and propofol have been used in ECT and there is no robust evidence to recommend a particular agent.^{48,49} An ideal induction agent should have a short half-life and have no interference with seizure duration or threshold. However, these anesthetics exhibit dose-dependent anti- or pro-convulsant activity and thus may change the seizure threshold.⁴⁹ Among these, propofol has the highest potential and thiopental/etomidate has the least potential.^{49,50} Although, the dose of anesthetic agent is rarely mentioned as a determinant of seizure threshold, a couple of authors stressed the importance of anesthetic dosage in seizure threshold.^{19,51} In the study by Boylan et al.,¹⁶ the obtained multivariate regression model only contained age, sex and methohexital dose, which was the same conclusion as the present study. Despite the methodological difference using right unilateral electrode placement, Galvez et al.¹⁹ also observed that age, the kind and dose of anesthetic agent significantly predicted the IST value.

In an ECT center, an operation protocol is usually predefined according to the characteristics of the patient population and the ECT equipment. It dictates the employed ECT method, stimulus dose titration method, anesthesia-related procedures and policy on concomitant medication. In this case, estimating the IST distribution and finding the possible predictors of IST on that protocol would be important in several aspects. The Royal College of Psychiatrists recommends that the selection of the electrical dose should be individualized and contingent upon the IST value determined in the first session.⁵² They also pointed out that since IST cannot be reliably predicted based on demographic or clinical features, the empirical titration method is the preferred practice.⁵³ However, since this method estimates IST by starting from the lowest intensity and then incrementally increasing the stimulus, repeated exposure to subthreshold electrical stimuli might be an unintended consequence.²⁷ It may lead to cardiovascular complications, unwanted prolonged anesthesia, and more cognitive side effects.⁵⁴

Thus, the balance between harm and benefit of the empirical titration partly depends on the location and range of the expected IST value distribution. Past authors have had very different views on the extent of the IST variability. Some authors reported as high as 40-fold variation,^{3,11} while others suggested only 4–6 fold variability.^{13,16,30} The variability in the present study was 6-fold which is relatively narrow compared to previously known values. If the expected variability is narrow, the number of repeated trials would be small, and the risk of overexposure ignorable. However, in the opposite case, the number of unnecessary trials will increase beyond the allowed limit. Likewise, if the gap between the actual distribution of IST and the clinician's unwarranted expectation becomes wide, then the harmful effect of titration might exceed the potential benefit. In the latter two cases, efforts may have to be made to predict the IST value in advance before starting a titration procedure. Demographic and clinical variables associated with IST would be very useful in this situation even if the prediction is not precise.

The present study described an IST reference in Korean patients following a certain predefined protocol as an example. In order to successfully manage and to set up a procedure protocol of ECT, a preliminary determination of IST values stratified by sex, age and other variables may have to be defined based on past experience and accumulated data. In this case, the reference data described in the present study could be helpful in deciding whether the obtained IST values were within a comparable range and whether the similar variables could partly predict the individual IST values. Admittedly, the number of subjects in the present study was only modest for obtaining adequate generalizability and for properly investigating the determinants of IST with all their interactions. This may limit the value of the present findings. Undoubtedly, a universal reference which can be applied to every case is fundamentally unobtainable since every ECT center would deal with different patient populations and employ different ECT procedures. Minor changes in the implemented protocol may influence the overall distribution. Therefore, the data in the present study could only be used as a starting point to define each center's own reference guide suited to its own needs.

In conclusion, the present study reported an IST value distribution in Korean patients and replicated the previous finding that age and gender were independent predictors of IST. Additionally, it demonstrated that the dose of sodium thiopental per body weight was another predictor of IST. The described IST distribution was comparable to previous studies and the empirical titration method seemed appropriate to deal with most of the cases. Taken together, these findings may be used as a reference for estimating the IST in patients with schizophrenia or schizoaffective disorder. However, it has to

be mentioned that this result only applies to Korean patients who underwent 1-ms BP-BL ECT following sodium thiopental anesthesia. It may limit the generalizability of the study result.

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Conflicts of Interest

Dr. Kim YS received grants, research support and honoraria from Janssen, Otsuka, and Dainippon Sumitomo. Dr. Chung IW received research and educational grants from Janssen, Otsuka, Hanmi, Mecta, and Whanin. Dr. Youn T received research and educational grants from Otsuka, Eisai, Hanmi, Lundbeck, and Mecta. The others have nothing to declare.

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