



Factors Affecting the Time Taken to Determine Brain Death in Patients with Impending Brain Death

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Background and Purpose The increased demand for donor organs has made it crucial to keep the organs of patients with impending brain death (PWIBDs) suitable for transplantation during the process of determining brain death. This study aimed to identify the time taken to determine brain death (TT-BD) in PWIBDs and the associated influencing factors.

Methods This study analyzed data collected by the Korean Organ Donation Agency from 15 hospitals in the Yeongnam region of South Korea. There were 414 PWIBDs eligible for inclusion in this study. The data consisted of the TT-BD for PWIBDs and the potential variables influencing the TT-BD.

Results The mean age of the 414 PWIBDs was 48.9 years, and 120 of them were female (29.0%). The mean TT-BD was 8.5 days. The presence of spontaneous movements (SMs) and craniotomy significantly affected the TT-BD. The mean TT-BDs were 13.9 and 8.2 days in the PWIBDs with and without SMs, respectively, and 9.8 and 8.0 days in the PWIBDs with and without craniotomy, respectively.

Conclusions The SMs in PWIBDs and a craniotomy performed immediately before starting the process of determining brain death seem to be related to lengthening the TT-BD.

Key Words brain death, organ transplantation, time, movement, craniotomy.

INTRODUCTION

The donor organs used in organ transplantation are primarily sourced from living donors, but their supply is not meeting the present need. Although constituting a relatively small number compared to the organs from living donors, more transplantations are being performed using organs from brain-dead donors. The demand for organs from brain-death donors is also increasing due to the difficulty of increasing the number of organs from living donors.^{1,2} This increased demand makes it crucial to keep the organs appropriate for transplantation in patients with impending brain death (PWIBDs) until brain death has been confirmed.

Given the need to keep organs from brain-death donors in an appropriate state for transplantation, clinicians have been investigating methods to reduce the delay to the decision about brain death in PWIBDs. There has been an opinion that the reflex movements (RMs) and spontaneous movements (SMs) observed in PWIBDs may have a psychological impact on clinicians responsible for confirming brain death, thereby delaying the time taken to determine brain death (TT-BD).³ However, there have been no systemic evaluations of such effects.

PWIBDs exhibit complex characteristics, and there may be specific factors affecting the TT-BD. Knowledge of the factors influencing the TT-BD in PWIBDs may help clinicians to

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maintain organs from brain-death donors in the proper state for transplantation. This study aimed to identify the factors influencing the TT-BD in PWIBDs.

METHODS

Study design

The Yeongnam region is a vast area in the southeast of South Korea that comprises Gyeongsangbuk-do, Gyeongsangnam-do, Busan Metropolitan City, Daegu Metropolitan City, and Ulsan Metropolitan City. This retrospective study used data collected in the Yeongnam region from January 2013 to December 2016 by the Korean Organ Donation Agency (KODA).

The following 15 hospitals (listed in alphabetical order) in the Yeongnam region provided data to the KODA: Bong Seng Memorial Hospital, Changwon Fatima Hospital, Daegu Catholic University Medical Center, Dong-A University Hospital, Gyeongsang National University Hospital, Inje University Busan Paik Hospital, Inje University Haeundae Paik Hospital, Keimyung University Dongsan Medical Center, Kosin University Gospel Hospital, Kyungpook National University Hospital, Pusan National University Hospital, Pusan National University Yangsan Hospital, Samsung Changwon Hospital, Ulsan University Hospital, and Yeungnam University Medical Center. According to information from the Health Insurance Review and Assessment Service of South Korea, there are 100 general hospitals in the Yeongnam region.⁴ The above-listed 15 hospitals are general hospitals selected by the Korea Centers for Disease Control and Prevention as having the potential to determine brain death, and 13 of them are university hospitals. For PWIBDs at hospitals not selected by the Korea Centers for Disease Control and Prevention, there is a system to transfer them to the selected hospitals after notifying them to the KODA.

The present authors previously performed a prospective study that examined the RMs and SMs observed in 436 PWIBDs during the decision process about brain death.⁵ The present study excluded 22 of those 436 PWIBDs, and so enrolled 414 PWIBDs who were the objects of the previous research. Sixteen of the 22 excluded PWIBDs had missing information on hypertension, diabetes mellitus, cardiac disease, smoking, and alcohol drinking, while the other 6 patients were excluded since the causative disease for brain death was not appropriate or there was only 1 case for 1 etiology: the KODA registry described the etiology of brain death as arteriovenous malformation, brain abscess, diffuse astrocytoma, encephalopathy, toxic encephalopathy, and unruptured aneurysm.

The Institutional Review Board (IRB) of the Gyeongsang National University Hospital approved the present study (IRB Number 2016-12-018). The IRB waived the need to obtain

consent forms in the present study since it had a retrospective design.

The Ministry of Health and Welfare of Korea designated the KODA as an appointed agency to procure organs and tissues for transplantation and perform work related to organ donation. When patients in a state of potential brain death are detected in the emergency room or intensive-care unit of each hospital, a representative from each hospital reports to the organ procurement team of the KODA. The KODA registers and manages the patients as PWIBDs.

The PWIBDs in the KODA registry enter the process of confirming brain death through clinical observations and electroencephalography. If this process confirms the condition of a PWIBD as brain death, a brain-death decision committee of the applicable hospital formally determines the presence brain death. Each brain-death decision committee consists of four members to six members. The composition of the committee should include two or more medical specialists and one or more nonmedical members. The medical specialists must include at least one neurologist or neurosurgeon. The participation of more than half of the members and the consent of all of the attending members is mandatory for determining brain death.^{6,7} The organ procurement team is responsible for coordinating and managing the entire process of determining brain death.

The presence of brain death is determined in South Korea using the Korean Medical Association guideline for determining brain death.^{6,7} The contents of the guideline are described in brief as follows: the decision-making process of determining brain death begins with the precondition that the cause of brain dysfunction of the PWIBDs is irreversible. In PWIBDs that meet the prerequisites, the clinicians examine whether all functions of both the brain and brainstem are absent. The PWIBDs identified as being clinically brain dead are reevaluated 6 hours later if they are adults. When PWIBDs are confirmed to be clinically brain dead in the two sequential examinations, clinicians obtain an electroencephalogram or repeated electroencephalograms to provide an objective finding. After confirming electrical inactivity in the electroencephalograms, a committee for determining brain death finally decides about the presence of brain death. PWIBDs who were finally judged as brain death based on the guideline were included in this study.

Data extraction

The KODA creates the PWIBDs registry based on electronic medical records and physician observations, and the authors extracted the data used in this study from that PWIBDs registry. The TT-BD for PWIBDs was extracted from the registry as the dependent variable, and was defined as the time

period from the point of occurrence of brain diseases to the final determination of brain death. The independent variables possibly affecting the TT-BD from the KODA PWIBDs records were as follows: demographic variables (age and sex), clinical variables (etiology of brain death, SMs, RMs, craniotomy, inotropic agents, and cardiopulmonary resuscitation), and medical and social histories (hypertension, diabetes, heart disease, smoking, and alcohol drinking).

Monitoring and recording RMs and SMs

During the process of determining brain death, the KODA organ procurement team observed and recorded RMs and SMs in the PWIBDs. With the aid of the medical staff at each hospital, they applied the following standard protocol to elicit RMs in PWIBDs: 1) painful stimuli on the supraorbital area, sternum, and nail beds of the four limbs, 2) neck flexion, 3) tactile stimulation on the palms and soles, and 4) apnea test. The KODA organ procurement team captured those RMs and SMs in videos with medical staff's supervision as not to be omitted as possible. In PWIBDs for whom videos had not been captured, the medical staff checked whether there were RMs and SMs and recorded their types based on medical records. The two neurologists among the present authors reviewed the collected videos and classified RMs and SMs.⁵

Statistical analysis

The TT-BD and its potentially influencing variables were analyzed statistically. The first step involved determining coefficients for the correlations between the potential variables and the TT-BD, with the Spearman test used for factor variables and the Pearson test used for continuous variables. A multiple regression analysis with a generalized linear model was used to evaluate the factors affecting the TT-BD, which included the independent variables for which p was <0.1 in the correlation analyses. The significance cutoff for the regression analysis was defined as $p < 0.01$. All of the statistical analyses were performed using R software (version 3.6.3, The R Foundation for Statistical Computing, Vienna, Austria).⁸

RESULTS

Characteristics of the included patients

Table 1 presents the characteristics of the 414 PWIBDs included in this study. They were aged 48.9 ± 13.1 years (mean \pm standard deviation), their TT-BD was 8.5 ± 7.7 days, and they included 120 females (29.0%). The cause of impending brain death was traumatic brain injury in 128 PWIBDs (30.9%), hypoxic brain injury in 108 (26.1%), subarachnoid hemorrhage in 89 (21.5%), intracranial hemorrhage in 75 (18.1%), and ischemic stroke in 14 (3.4%). Movements were observed

Table 1. Characteristics of patients with impending brain death ($n=414$)

Characteristic	Value
Age, years	48.9 \pm 13.1
Sex, female	120 (29.0)
Time taken to determine brain death, days	8.5 \pm 7.7
Etiology	
Traumatic brain injury	128 (30.9)
Hypoxic brain injury	108 (26.1)
Subarachnoid hemorrhage	89 (21.5)
Intracranial hemorrhage	75 (18.1)
Ischemic stroke	14 (3.4)
Movement type	
Reflex movements only	46 (11.1)
Spontaneous movements only	17 (4.1)
Both	8 (1.9)
Intervention	
Inotropic agents	386 (93.2)
Cardiopulmonary resuscitation	162 (39.1)
Craniotomy	126 (30.4)
Underlying disease	
Hypertension	104 (25.1)
Diabetes mellitus	44 (10.6)
Cardiac disease	12 (2.9)
Smoking	210 (50.7)
Alcohol drinking	246 (59.4)

Data are mean \pm standard-deviation or n (%) values.

in 71 (17.1%) of the 414 PWIBDs (17.1%): 46 (11.1%) with only RMs, 17 (4.1%) with only SMs, and 8 (1.9%) with both RMs and SMs; this meant that among the 71 PWIBDs with movements, 64.7% had only RMs, and 23.9% had only SMs, and 11.3% had both RMs and SMs.

Cardiopulmonary resuscitation was applied to 162 (39.1%) of the 414 PWIBDs, while 126 (30.4%) underwent craniotomy. Most ($n=386$, 93.2%) of the PWIBDs received treatment with inotropic agents during the process of determining brain death. The 414 PWIBDs included 104 (25.1%) with hypertension, 44 (10.6%) with diabetes, 12 (2.9%) with heart disease, 210 (50.7%) who smoked, and 246 (59.4%) who drank alcohol (Table 1).

Correlations

The p value was <0.1 for the correlations between the TT-BD and the following eight variables: sex ($r=-0.11$, $p=0.03$), etiology ($r=-0.13$, $p=0.01$), RMs ($r=0.10$, $p=0.05$), SMs ($r=0.19$, $p < 0.01$), craniotomy ($r=0.08$, $p=0.10$), inotropic agents ($r=-0.09$, $p=0.07$), smoking ($r=-0.12$, $p=0.01$), and alcohol drinking ($r=-0.20$, $p < 0.01$). The p value was ≥ 0.1 for cardiopulmonary resuscitation, hypertension history, diabetes mellitus history, and cardiac disease history (Table 2).

Generalized linear model

In an interaction plot between RMs and SMs versus the TT-BD, the two plot lines crossed each other, indicating the presence of an interaction effect between RMs and SMs (Fig. 1). RMs and SMs were merged into a single variable that was assigned four levels: 1) no movements, 2) RMs only, 3) SMs only, and 4) both RMs and SMs. A multiple regression analysis performing using a generalized linear model with seven independent variables (including the merged variable) showed that the presence of SMs only and craniotomy significantly affected the TT-BD (Table 3). The coefficient estimate for the SMs was 5.55 ($p<0.01$), and the corresponding

TT-BDs were 13.9 ± 10.4 and 8.2 ± 7.4 days in PWIBDs with and without SMs, respectively (Fig. 2A). The coefficient estimate for craniotomy was 2.47 ($p<0.01$), and the corresponding TT-BDs were 9.8 ± 10.4 and 8.0 ± 6.0 days in PWIBDs with and without craniotomy, respectively (Fig. 2B).

DISCUSSION

Few studies have investigated factors affecting the duration from the time point when the causative disease for impending brain death occurs to the time point when brain death actually occurs in PWIBDs. This study investigated factors af-

Table 2. Correlations of 13 factors with the time taken to determine brain death

Factor	Correlation coefficient	p
Sex*	-0.11	0.03
Age	-0.03	0.58
Etiology*	-0.13	0.01
Reflex movements*	0.10	0.05
Spontaneous movements*	0.19	<0.01
Craniotomy*	0.08	0.10
Inotropic agents*	-0.09	0.07
Cardiopulmonary resuscitation	-0.04	0.37
Hypertension	-0.06	0.25
Diabetes mellitus	-0.05	0.31
Cardiac disease	0.05	0.31
Smoking*	-0.12	0.01
Alcohol drinking*	-0.20	<0.01

* $p<0.1$.

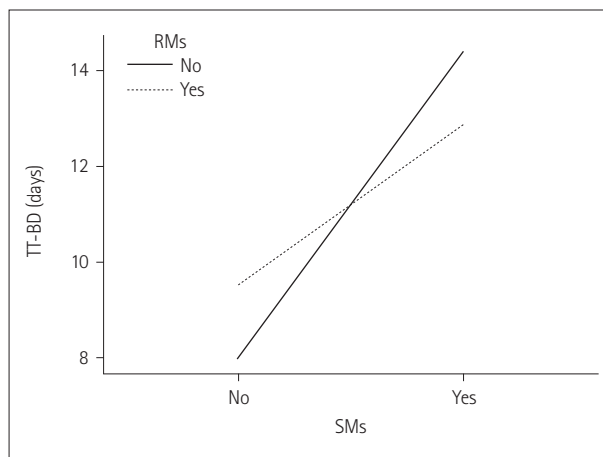


Fig. 1. Plot of interaction between RMs and SMs versus the TT-BD. There was an interaction effect between RMs and SMs because the two plot lines cross each other. RMs: reflex movements, SMs: spontaneous movements, TT-BD: time taken to determine brain death.

Table 3. Multiple regression analysis using a generalized linear model for the factors affecting the time taken to determine brain death

	Coefficient estimate	Standard error	t	p
Intercept	9.83	1.65	5.97	<0.01
Sex, male	-0.91	0.90	-1.00	0.32
Etiology				
Hypoxic brain injury, reference	0.00			
Intracranial hemorrhage	-0.82	1.22	-0.68	0.50
Ischemic stroke	0.15	2.18	0.07	0.94
Subarachnoid hemorrhage	-1.11	1.12	-0.99	0.32
Traumatic brain injury	-1.90	1.14	-1.66	0.10
Movements				
Neither, reference	0.00			
Reflex movements only	1.28	1.20	1.07	0.29
Spontaneous movements only*	5.55	1.91	2.90	<0.01
Both	4.40	2.72	1.62	0.11
Craniotomy, yes*	2.47	0.92	2.68	<0.01
Inotropic, yes	-0.53	1.49	-0.36	0.72
Smoking, yes	0.70	0.87	0.80	0.43
Alcohol drinking, yes	-1.28	0.90	-1.43	0.15

* $p<0.1$.

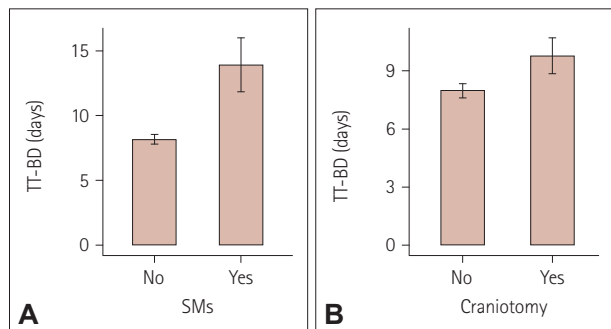


Fig. 2. Effects of SMs (A) and craniotomy (B) on the TT-BD in PWIBDs. SMs and craniotomy significantly affected the TT-BD in PWIBDs. The TT-BD was lengthened in the presence of SMs and when a craniotomy was performed immediately before the assessment process to determine brain death in PWIBDs. The mean TT-BDs were 13.9 and 8.2 days in PWIBDs with and without SMs, respectively, and 9.8 and 8.0 days in PWIBDs with and without craniotomy, respectively. PWIBDs: patients with impending brain death, RMs: reflex movements, SMs: spontaneous movements, TT-BD: time taken to determine brain death.

fecting the TT-BD using data collected by the KODA from PWIBDs confirmed as brain death in 15 hospitals in the Yeongnam region of South Korea. It was found that the two factors of SMs and craniotomy significantly affected the TT-BD in PWIBDs: the SMs in PWIBDs and a craniotomy performed immediately before the assessment process to determine brain death were related to lengthening the TT-BD. This information may help clinicians to predict the TT-BD of PWIBDs, thereby facilitating the preservation of organs procured from brain-death donors as adequate for transplantation.

The frequency of movements including RMs and SMs observed in PWIBDs has reportedly ranged from 17.0% to 75.0%.^{3,5,9-13} SMs reflect brain function while RMs reflect the function of the spinal cord, and so SMs do not appear in patients confirmed as brain death, whereas RMs such as spinal reflexes may appear in them.^{2,14} A multicenter study conducted in Argentina applied a standardized protocol of stimuli to elicit reflexes in PWIBDs before and after performing apnea tests in 107 PWIBDs, and observed various types of RMs.³ The most common RM was undulating toe flexion response, while the other RMs included triple flexion reflex, myoclonus of the arm and leg, quadriceps flexion, Lazarus sign, fasciculation, plantar response, facial myokymia, and pronator extension reflexes.

The present authors have previously reported on the RMs and SMs observed in 436 PWIBDs.⁵ Movements appeared in 74 (17%) of those 436 PWIBDs during the process of determining brain death: 60.8% had only RMs, 24.3% had only SMs, and 14.9% had both RMs and SMs. Flexor/extensor plantar responses and spinal myoclonus were the most common types of RMs. The movements occurred significantly more frequently when the etiology of brain death was hypoxic

brain injury. The systolic blood pressure was significantly higher when confirming brain death in PWIBDs who exhibited movements.

There has been an opinion that RMs and SMs observed in PWIBDs may have a psychological impact on clinicians that would increase the TT-BD. Therefore, recognizing the frequency and patterns of such movements could remove the psychological factors that interfere with determining brain death and supposedly increase the number of potential organ donors.³ The present study aimed to improve the understanding of how RMs and SMs affect the TT-BD in current clinical states. It was found that SMs significantly affected the TT-BD whereas RMs did not.

PWIBDs with SMs naturally require more time to reach a state of actual brain death, since these movements indicate the presence of remaining brain function. This study found that the mean TT-BD was 13.9 days in the PWIBDs with SMs and 8.2 days in those without SMs. On the other hand, RMs are spinal reflexes that can occur in the state of brain death. The present study found that RMs did not affect the TT-BD, meaning that even if RMs appear in PWIBDs, there is a low probability of such movements delaying the confirmation of brain death in the current clinical state.

One study has investigated the effect of decompressive craniectomy on brain perfusion scintigraphy in patients with suspected brain death.¹⁵ That study included 138 patients, of whom 15 had received decompressive craniectomy. Brain perfusion scintigraphy was performed in the 138 patients to confirm brain death. Patients with brain flow evident in the first scintigraphy examination were followed until their second or third scintigraphy examination. The proportion of negative brain flow was not low in patients with craniectomy than patients without that.¹⁵ Therefore, even if decompressive surgery reduces the intracranial pressure, this does not stop the process of reaching brain death.

The above-mentioned study did not provide information on the effect of craniectomy on the TT-BD in PWIBDs.¹⁵ Another study continuously monitored the intracranial pressure and cerebral perfusion pressure in 18 patients during the development of brain death.¹⁶ A few hours before confirming brain death in the patients, the intracranial pressures reached their highest values, while the cerebral perfusion pressure values were lowest. These observations meant that the intracranial pressure reaching the highest level and the cerebral perfusion pressure reaching the lowest level extinguished the brain perfusion. On that basis, surgery to lower the intracranial pressure could slow the progression to brain death, which is the state of negative brain flow caused by the highest intracranial pressure. Such a delay in progression may eventually increase the time it takes for PWIBDs to reach the

brain-death state. The present study found that craniotomy lengthened the TT-BD: from 8.0 days for PWIBDs not treated with craniotomy to 9.8 days for PWIBDs who underwent craniotomy.

This study had several limitations. The analyzed information came from the KODA in a particular format, which make it challenging to consider various variables that might affect the TT-BD. For example, the information about vital signs in the KODA database was from when brain death was confirmed rather than from when the process for determining brain death started, and so the vital signs could not have been potential variables affecting the TT-BD. Moreover, the KODA data did not provide information on disease severity or treatment intensity at the time of causative diseases occurring. Because these variables may also affect the TT-BD, as does a craniotomy, the lack of information about them represents a limitation of our research. The retrospective design of this study also resulted in the usual limitation of not being able to determine causality. Future prospective studies should fully consider various variables in order to provide more-reliable information.

Author Contributions

Conceptualization: Young-Soo Kim, Oh-Young Kwon. Data curation: Young-Soo Kim, Do-Hyung Kim, Tae-Won Yang, Minhwa Kim, Jeongrim Lee, Wonhyun Cho. Formal analysis: Young-Soo Kim, Oh-Young Kwon. Investigation: Young-Soo Kim, Oh-Young Kwon. Methodology: Young-Soo Kim, Oh-Young Kwon. Validation: Young-Soo Kim, Do-Hyung Kim, Tae-Won Yang, Oh-Young Kwon. Visualization: Oh-Young Kwon. Writing—original draft: Young-Soo Kim, Oh-Young Kwon. Writing—review & editing: Young-Soo Kim, Oh-Young Kwon.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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