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Relationship between the administration of nicardipine hydrochloride and the development of delirium in patients on mechanical ventilation

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A history of hypertension is a known risk factor for delirium in patients in intensive care units, but the effect of antihypertensive agents on delirium development is unclear. Nicardipine, a calcium channel blocker, is widely used in ICU as a treatment agent for hypertensive emergency. This study investigated the relationship between the administration of nicardipine hydrochloride and delirium development in patients under mechanical ventilation. We conducted a medical chart review of 103 patients, who were divided into two groups according to the use of nicardipine hydrochloride. The prevalence of delirium was compared with respect to factors such as age, sex, laboratory data, and medical history, by multivariate analysis. 21 patients (20.4 %) were treated with nicardipine hydrochloride in 103 patients. The treatment and non-treatment groups differed significantly in age (72 vs. 65 years) and history of high blood pressure (57% vs. 11%). Multivariate analysis revealed that patients in the treatment group developed delirium significantly less often than those in the non-treatment group (19% vs. 48%). These results suggested that treatment of high blood pressure with nicardipine hydrochloride is a possible method for preventing the development of delirium.

1. Introduction

Delirium develops acutely or sub-acutely and manifests as various cognitive dysfunction and psychological symptoms (Cavallazzi et al. 2012). The prevalence rate of delirium is between 12 and 31 % among in-patients of general hospitals and increases with age (Inouye et al. 1998; Edlund et al. 2006). Furthermore, the development of delirium is associated with increased mortality (Lin et al. 2004; Ely et al. 2004), worsened cognitive impairment (Girard et al. 2010; Pandharipande et al. 2013), and increased length of hospitalisation (Thomason et al. 2005; Ely et al. 2001a), as well as with poor prognosis. The development of delirium is also strongly associated with environmental factors (Van Rompaey et al. 2009), and its frequency in intensive care units (ICU) is high (Ely et al. 2001a).

Mechanical ventilation is often used for patients with severe pneumonia or respiratory failure, and 47–83 % of patients on mechanical ventilation are diagnosed with delirium (Micek et al. 2005; Ely et al. 2001b). Since delirium may cause self-removal of the endotracheal tube, it is important to investigate the causes underlying the development of delirium and to determine ways to prevent this in patients receiving mechanical ventilation.

A history of high blood pressure and cognitive impairment, age, presence of traumatic injury, metabolic acidosis, coma, and APACHE II score have been reported as significant risk factors for the development of delirium (Zaal et al. 2015). Additionally, as the development of delirium is reported to be high among the patients with high systolic blood pressure (Rahkonen et al. 2001), it is possible that high blood pressure may influence the development of delirium.

However, no studies have reported on the relationship between the use of antihypertensive agents for the purpose of blood pressure control and the development of delirium, and the effect of blood pressure control on delirium is not clear.

Nicardipine is a calcium channel blocker that is widely used in ICU for hypertensive emergency and similar events. In this study, we focused on nicardipine which is a representative anti-hypertensive agent in ICU, and investigated the relationship between administration of nicardipine hydrochloride for blood pressure control and the development of delirium with patients who received mechanical ventilation in the Okayama University Hospital Emergency Intensive Care Unit (EICU).

2. Investigations and results

2.1. Baseline characteristics of patients

In our retrospective chart review of 103 patients, 21 were treated with nicardipine hydrochloride and 82 did not receive treatment. The administration rate was 20.4%.

Patient characteristics for the two groups are presented in Table 1. Only age ($p = 0.009$), the history of hypertension ($p = 0.006$), serum CRP level ($p = 0.036$), and APACHE II score ($p = 0.002$) were significantly different between the two groups. The treatment

Table 1: Patient characteristics and prevalence of delirium

	Treatment group (n = 21)		Non-treatment group (n = 82)		p value
Prevalence of delirium, n (%)	4	(19)	39	(48)	
Age (year), median (interquartile range)	72.0	(62.0-81.0)	65.0	(47.0-74.0)	0.009[2]
Male, n (%)	10	(48)	53	(65)	0.153[1]
History of hypertension, n (%)	12	(57)	9	(11)	0.006[1]
Renal failure, n (%)	5	(24)	7	(9)	0.052[2]
Sepsis, n (%)	12	(57)	28	(34)	0.093[1]
Traumatic injury, n (%)	11	(52)	43	(52)	1.000[1]
Systolic blood pressure at 24 h after admission (mmHg), mean ± (S.D.)	137	(26)	126	(23)	0.096[3]
Highest value of PCT (ng/mL), median (interquartile range)	0.79	(0.14-1.23)	0.16	(0.06-1.06)	0.074[2]
Laboratory data at admission					
Alb (g/dL) , mean ± (S.D.)	3.3	(0.77)	3.4	(0.92)	0.981[3]
Cl (mEq/L) , median (interquartile range)	106	(105-109)	106	(103-108)	0.371[2]
K (mEq/L) , median (interquartile range)	3.9	(3.5-4.9)	4.15	(3.6-4.6)	0.427[2]
Na (mEq/L) , median (interquartile range)	140	(137-141)	139	(137-141)	0.899[2]
BNP (pg/mL) , median (interquartile range)	54.3	(22.2-399.8)	40.75	(14.0-141.1)	0.415[2]
CRP (mg/L) , median (interquartile range)	0.12	(0.05-0.28)	0.405	(0.10-5.66)	0.036[2]
APACHE score, mean ± (S.D.)	32.0	(8.3)	25.2	(8.6)	0.002[3]

[1]Chi-square test
[2]Mann-Whitney test
[3]Welch's t test
S.D., standard deviation; BNP, brain natriuretic peptide; CRP, C-reactive protein; PCT, procalcitonin; APACHE, Acute Physiology and Chronic Health Evaluation
Age (p = 0.009), the history of hypertension (p = 0.006), serum CPR level (p = 0.036), and APACHE II score (p = 0.002) were significantly greater in treatment group compared with non-treatment group.

Table 2: Patient characteristics delirium/no-delirium groups

	Delirium group (n = 43)		**Non-delirium group (n = 60)**		**p value**
Age (year), median (interquartile range)	71.0	(63.0-81.0)	61.5	(44.8-72.5)	0.010[2]
Male, n (%)	28	(65)	35	(58)	0.623[1]
Administration of nicardipine, n (%)	5	(12)	16	(27)	0.105[1]
History of hypertension, n (%)	14	(33)	19	(32)	1.000[1]
Renal failure, n (%)	4	(9)	8	(13)	0.757[1]
Sepsis, n (%)	17	(40)	23	(38)	1.000[1]
Traumatic injury, n (%)	24	(56)	30	(50)	0.689[1]
Systolic blood pressure at 24 h after admission (mmHg), mean ± (S.D.)	132	(24)	126	(24)	0.168[3]
Highest value of PCT (ng/mL), median (interquartile range)	0.20	(0.09-0.88)	0.16	(0.05-1.50)	0.758[2]
Laboratory data at admission					
Alb (g/dL) , mean ± (S.D.)	3.4	(0.94)	3.3	(0.86)	0.744[3]
Cl (mEq/L) , median (interquartile range)	105	(103-109)	106	(104-108)	0.492[2]
K (mEq/L) , median (interquartile range)	4.0	(3.6-4.8)	4.0	(3.6-4.6)	0.955[2]
Na (mEq/L) , median (interquartile range)	139	(137-142)	139	(137-141)	0.997[2]
BNP (pg/mL) , median (interquartile range)	42.7	(15.0-131.7)	45.6	(15.2-204.8)	0.997[2]
CRP (mg/L) , median (interquartile range)	0.37	(0.11-5.29)	0.23	(0.07-1.87)	0.454[2]
APACHE II score, mean ± (S.D.)	26	(8)	27	(9)	0.382[3]

[1]Chi-square test
[2]Mann-Whitney test
[3]Welch's t test
S.D., standard deviation; PCT, procalcitonin; APACHE, Acute Physiology and Chronic Health Evaluation; BNP, brain natriuretic peptide; CRP, C-reactive protein
Age (p = 0.010) was significantly greater in delirium group compared with non-delirium group.

group had a higher mean age (72.0 years vs. 65.0 years) and a higher proportion of individuals with a history of high blood pressure (57% vs. 11%) than the Non-treatment group.

The patient characteristics when divided into two groups depending on whether delirium was developed or not is shown in Table 2. Age of delirium group patients was significantly greater than that of patients in the non-delirium group (71.0 years vs. 61.5 years, p = 0.010). Regarding the renal failure, BNP and APACHE II score, the Non-delirium group tended to be higher than the delirium group.

2.2. Results of multivariate logistic regression

Results of multivariate logistic regression with delirium are presented in Table 3. Significant differences were found between groups in terms of the age (odds ratio = 1.033, p = 0.013), administration of nicardipine (odds ratio = 0.164, p = 0.007), systolic blood pressure at 24 h after admission (odds ratio = 1.042, p = 0.004), and the highest PCT value (odds ratio = 3.538, p = 0.044). Odds ratios of age, systolic blood pressure at 24 h after admission, and the highest PCT value were over 1.0. On the other hand, that of administration of nicardipine was under 1.0.

Table 3: Multivariate logistic regression for risk factors of delirium

	Odds ratio	95 % CI	p value
Age	1.033	(1.007) - (1.061)	0.013
Administration of nicardipine	0.164	(0.044) - (0.616)	0.007
Systolic blood pressure at 24 h after admission	1.042	(1.014) - (1.071)	0.004
Renal failure	3.538	(1.033) - (12.122)	0.044

CI, confidence interval
Significant defferences were found in age (p = 0.013), administration of nicardipine (p = 0.007), systolic blood pressure at 24 h after admission (p = 0.004), and renal failure (p = 0.044).

3. Discussion

Delirium is a serious condition in clinical situations, in terms of poor prognosis, worsening mortality rates (Lin et al. 2004; Ely et al. 2004), and lengthened hospitalization periods (Thomason et al. 2005; Ely et al. 2001a). Since a history of hypertension has been recognized as a significant risk factor for delirium development and that many patients with high systolic blood pressure have experienced delirium, blood pressure and delirium appear to be related. In this study, we found that nicardipine hydrochloride, administered for control of blood pressure, had a suppressing effect on the development of delirium.

Previous studies suggested age and hypertension as risk factors of delirium in the ICU setting (Zaal et al. 2015; Ouimet et al. 2007; Dubois et al. 2001; Pandharipande et al. 2006). In a comparison of the patient characteristics of the treatment and non-treatment groups, the treatment group had a higher mean age and a higher proportion of individuals with a history of high blood pressure than the non-treatment group. Thus the treatment group can be considered at high risk for delirium. However, the prevalence rate of delirium in the treatment group was 19%, which was lower than that in the non-treatment group (48%).

Multivariate analysis confirmed a significant difference in the development of delirium depending on the administration of nicardipine hydrochloride. Nicardipine hydrochloride is primarily used as an antihypertensive agent in hypertensive emergencies and similar events. As high blood pressure is a risk factor in the development of delirium (Zaal et al. 2015), our results suggest that blood pressure adjustment may be one way of preventing delirium. It has been suggested that chronic hypertension is also associated with a decline in cognitive function (Qiu et al. 2015; Staessen et al. 2007), and there are reports that treatment of hypertension suppress cognitive decline (Forette et al. 2002; Peters et al. 2015). Thus, treating hypertension may be able to decrease the risk of delirium onset.

We acknowledge that there are several limitations in this investigation. First, the known risk factor of delirium was not added as a covariate in multivariate analysis. In ICU setting, information such as medical history of patients was often not obtained, and in the retrospective study there were many missing values. Therefore, in this study, it was not possible to adjust by well-known risk factor of delirium such as dementia. However, as shown in Table 3, it was suggested that the known risk factors such as age and systolic blood pressure at 24 h after admission increased the risk of delirium. Second, because the present study is a retrospective analysis, there is a limitation to the quality management of the CAM-ICU evaluation. Previous studies have suggested that the Japanese version of CAM-ICU has a comparable inter-rater reliability as the English version CAM-ICU (Koga et al. 2015). However, since the CAM-ICU evaluation used in present study was collected within daily medical practice, quality control is insufficient. Third, the sample size of this study is small. It is necessary to investigate the effect of nicardipine on the onset of delirium by the large-scale study. Fourth, we could not collect information about disease and use of drugs like benzodiazepines, which are a well-known risk of delirium. In addition, data on intubated days was not collected in this study.

This study showed that administration of nicardipine hydrochloride may contribute to the suppression of delirium. Future studies investigating factors such as blood pressure, controlling blood pressure with antihypertensive agents, use of combination drugs may lead to improvements in treatment strategies and may contribute to the understanding of the underlying pharmacological mechanisms.

4. Experimental

4.1. Ethical approval of the study protocol

This study was conducted in keeping with the Ministry of Health, Labour, and Welfare's Ethical Guidelines for Epidemiological Research. This study was approved by the Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital Ethics Committee (No. 1702-013) and conformed to the tenets of the Declaration of Helsinki. Since this study was an observational study that did not involve treatment interventions and collection of human samples, obtainment of informed consent was exempted.

4.2. Subjects and review of medical records

This study included 103 patients who were provided mechanical ventilation at the EICU from April 1, 2013, to March 31, 2014. Patients aged < 20 years and those who were hospitalized for less than 4 days were excluded. Patients who hospitalized less than 4 days were excluded because these cases included many fatal cases. Patients who received nicardipine hydrochloride during hospitalisation were defined as the treatment group. If nicardipine hydrochloride was administered after the development of delirium, the patient was allocated to the non-treatment group. Medical records were reviewed to collect data on age, sex, blood pressure, medical history, APACHE II score, all other laboratory data. Renal failure was defined as eGFR is less than 15 mL/min/1.73 m^2. Evaluation of delirium was performed by the confusion assessment method for the ICU (CAM-ICU) (Ely et al. 2001b). It consists of four key CAM-ICU criteria; acute and fluctuating course, inattention, disorganized thinking, and altered level of consciousness (Ely et al. 2001b; McNicoll et al. 2003). Well trained nurses daily assessed and identified the four features of ICU delirium.

4.3. Statistical analysis

Continuous variables are presented as mean±standard deviation or median and interquartile range. A chi-square test was used for comparing categorical variables. Distribution normality was tested by Shapiro–Wilk test. Student's t-test or Welch's t test or Mann-Whitney U test was used for comparison of continuous variables. The level of significance was set at less than 5% ($p < 0.05$). Multivariate logistic regression analysis was conducted for the development of delirium. Age, systolic blood pressure at 24 h after admission, and highest PCT value (Zaal et al. 2015; McGrane et al. 2011), which are known risk factors of delirium, and administration of nicardipine hydrochloride were used as covariates. All statistical analyses were performed with IBM SPSS Statistics for Windows Version 21.0 (SPSS Inc. Chicago, IL).

Conflicts of interest: The authors report no relationships that could be construed as a conflict of interest.

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