의학석사 학위논문

Effect of thiopental or propofol continuous infusion on serum potassium disturbance in patients with increased intracranial pressure

두개내압이 높은 환자에서 thiopental 또는 propofol 지속 정주가 혈중 칼륨 농도 이상에 미치는 영향

2014 년 2 월

서울대학교 대학원

의학과 마취통증의학 전공

김 태 경

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2014

김태경

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4cm

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A thesis of the Degree of Master of Medicine

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February 2014

The Department of Medicine
Seoul National University
College of Medicine
Tae Kyong Kim

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지도 교수 박 희 평

이 논문을 의학석사 학위논문으로 제출함
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서울대학교 대학원
의학과 마취통증의학 전공
김 태 경

김태경의 의학석사 학위논문을 인준함
2013년 12월

위 원 장 _____ (인)
부위원장 _____ (인)
위 원 _____ (인)

Effect of thiopental or propofol continuous infusion on serum potassium disturbance in patients with increased intracranial pressure

by
Tae Kyong Kim

A thesis submitted to the Department of Medicine in partial fulfillment of the requirements for the Degree of Master of Science in Medicine (Anesthesiology and Pain Medicine) at Seoul National University College of Medicine

December 2013

Approved by Thesis Committee:

Professor _____Chairman

Professor _____Vice chairman

Professor _____

학위논문 원문제공 서비스에 대한 동의서

본인의 학위논문에 대하여 서울대학교가 아래와 같이 학위논문 제공하는 것에 동의합니다.

1. 동의사항
① 본인의 논문을 보존이나 인터넷 등을 통한 온라인 서비스 목적으로 복제할 경우 저작물의 내용을 변경하지 않는 범위 내에서의 복제를 허용합니다.
② 본인의 논문을 디지털화하여 인터넷 등 정보통신망을 통한 논문의 일부 또는 전부의 복제.배포 및 전송 시 무료로 제공하는 것에 동의합니다.

2. 개인(저작자)의 의무
본 논문의 저작권을 타인에게 양도하거나 또는 출판을 허락하는 등 동의 내용을 변경하고자 할 때는 소속대학(원)에 공개의 유보 또는 해지를 즉시 통보하겠습니다.

3. 서울대학교의 의무
① 서울대학교는 본 논문을 외부에 제공할 경우 저작권 보호장치(DRM)를 사용하여야 합니다.
② 서울대학교는 본 논문에 대한 공개의 유보나 해지 신청 시 즉시 처리해야 합니다.

논문 제목: Effect of thiopental or propofol continuous infusion on serum potassium disturbance in patients with increased intracranial pressure

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ABSTRACT

Introduction: Thiopental continuous infusion is associated with hypokalemia and rebound hyperkalemia. However, the effect of propofol continuous infusion on serum potassium levels has not been investigated extensively. We retrospectively compared the effects of thiopental and propofol on serum potassium levels during continuous infusion.

Methods: We reviewed the medical records of 60 consecutive patients who received coma therapy or deep sedation for intracranial pressure control using either thiopental (n=37) or propofol (n=23) between January 2010 and January 2012.

Results: Thirty-three (89.2%) patients in the thiopental group and nineteen (82.6%) patients in the propofol group had hypokalemia (serum potassium <3.5 mmol/L) following the induction of therapy (p=0.468). The incidence of moderate to severe hypokalemia (serum potassium <3.0 mmol/L) following the induction of therapy was significantly higher in the thiopental group than in the propofol group (51.4 vs. 13.0%, p=0.003). The lowest serum potassium level averaged 2.9 ± 0.6 mmol/L in the thiopental group and 3.2 ± 0.4 mmol/L in the propofol group (p<0.05). The patients in the thiopental group required greater potassium replacement than the propofol group patients (0.08 ± 0.04 vs. 0.02 ± 0.01 mEq/kg/hr, p<0.001). On multivariate analysis, thiopental (odds ratio, 95% confidence interval, 7.31 [1.78-27.81]; p=0.005) was associated with moderate to severe hypokalemia during continuous infusion. The incidence of rebound hyperkalemia (serum potassium >5.0 mmol/L) after the cessation of therapy was higher in the thiopental group than in the propofol group (32.4 vs. 4.3%; p<0.05). The average peak serum potassium

concentration was 4.8 ± 1.1 and 4.2 ± 1.1 mmol/L in the thiopental and propofol groups, respectively ($p<0.05$). On multivariate analysis, thiopental (8.821 [1.000-77.811]; p=0.049) and duration of continuous infusion (1.021 [1.004-1.039]; p=0.016) were associated with rebound hyperkalemia once therapy was discontinued.

Conclusions: When continuous infusion was used to relieve intracranial hypertension, propofol was less frequently associated with moderate to severe hypokalemia after induction and rebound hyperkalemia following the cessation of continuous infusion than thiopental.

Keywords: intracranial hypertension; thiopental; propofol; dyskalemia

Student number: 2009-21781

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intracranial pressure (ICP)

cerebral metabolic rate of oxygen ($CMRO_2$)

propofol-related infusion syndrome (PRIS).

intensive care unit (ICU)

Glasgow coma scale (GCS)

acute physiology and chronic health evaluation II (APACHE II)

INTRODUCTION

Barbiturates are widely used to control refractory intracranial hypertension. They indirectly lower intracranial pressure (ICP) via a coupled reduction in cerebral metabolic rate of oxygen ($CMRO_2$) and cerebral blood flow. The maximum decrease (roughly 50%) in $CMRO_2$ occurs when the electroencephalographic readings become isoelectric (1, 2). Barbiturate therapy, however, is associated with adverse effects, including hypotension and immunosuppression (3). Additionally, barbiturates can induce hypokalemia after the induction of coma therapy and cause rebound hyperkalemia after the cessation of therapy (4-8).

The incidence of hypokalemia after thiopental induction ranges between 82 and 89.4% (4, 5). A case series reported that 34% of patients had rebound hyperkalemia after stopping thiopental coma therapy (4). There have also been several reports of serious adverse events due to hypokalemia and rebound hyperkalemia (6, 8-10). Dyskalemia is life-threatening and a major obstacle to barbiturate coma therapy.

Propofol has been demonstrated to be an effective drug for the regulation of ICP (11, 12). It decreases ICP in normal subjects and as well as in patients with an elevated ICP (12). It reduces the cerebral metabolic rate by 40% in a dose-dependent fashion and decreases cerebral blood flow by metabolism-flow coupling (13, 14). Propofol is known to cause hypotension, hypertriglyceridemia, and propofol-related infusion syndrome (PRIS) (15-18). Unlike thiopental, however, research has not fully evaluated the effect of propofol continuous infusion on serum potassium levels, especially when used for the regulation of ICP.

In this study, we compared the effects of thiopental or propofol continuous infusion on serum potassium levels in patients with increased intracranial pressure.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Seoul National University Hospital (Seoul, Korea). Patients who were consecutively admitted to the surgical intensive care unit (ICU) to receive coma therapy for the treatment of refractory intracranial hypertension or deep sedation for the prevention of a further increase in ICP from January 2010 to January 2012 were included. Patients without ICP monitoring were excluded from the analysis.

Group assignment

In this study, head elevation, deep sedation, analgesia, use of osmotic agents, and cerebrospinal fluid drainage were used as the first-tier methods to control ICP in patients with elevated ICP. Coma therapy was used when the first-tier therapies failed to reduce ICP to 25 mmHg.

The patients received one of two regimens for the regulation of ICP, including thiopental (n=37) or propofol (n=23). In those using thiopental continuous infusion, a loading dose (250 mg) was administrated for about 30 min, followed by a continuous infusion of 3-7 mg/kg/h. In those using propofol continuous infusion, a loading dose (100-150 mg) was administrated for about 30 min, followed by a continuous infusion of 3-7 mg/kg/h. During both treatments, the cerebral perfusion pressure was maintained at 60-80 mmHg. Once no further increases in ICP from baseline were detected for 9-18 h in patients with a baseline ICP of <25 mmHg, in whom deep sedation was needed for ICP control, or if the ICP decreased to ≤24 mmHg and the decrease in ICP was maintained for 24-36 h in patients with refractory intracranial hypertension, both treatments were slowly weaned over 3-12 h.

Definition

Hypokalemia (defined as a serum potassium level <3.5 mmol/L) was managed by potassium replacement (target serum potassium >3.0 mmol/L), while hyperkalemia (defined as a serum potassium level >5.0 mmol/L) was managed with conservative methods such as sodium bicarbonate, insulin, and diuretics. Mild hypokalemia was defined as a serum potassium level of 3.0-3.5 mmol/L. Moderate hypokalemia was defined as a serum potassium level of 2.5-3.0 mmol/L and severe hypokalemia was defined as a level less than 2.5 mmol/L. Hypothermia was defined as a core temperature <35°C. Refractory intracranial hypertension was defined as ICP >25 mmHg despite the use of first-tier therapies for ICP control. Good and poor clinical outcome was defined as 1-3 points and 4-6 points on modified Rankin scale at discharge respectively.

Measurement

In all patients, serum potassium was measured before therapy. Serum potassium was measured with various intervals (3-8 hr) during and after therapy. The same protocol was applied to both groups. The primary measurement in this study was the incidence of hypokalemia during thiopental or propofol continuous infusion. The secondary measurement was the incidence of hyperkalemia after the cessation of thiopental or propofol therapy.

Data collection

Electronic medical records were used to extract and analyze the following parameters: patient's age, sex, past medical history, duration and dose of both therapies, serum potassium level, ICP, modified Rankin scale at hospital discharge, Glasgow coma scale (GCS) score prior to and two days after therapy, acute

physiology and chronic health evaluation II (APACHE II) score, light reflex prior to therapy, motor weakness before therapy, complications during the ICU stay, hospital mortality, and duration of ICU stay. Variables that possibly contributed to dyskalemia, including urine output, body temperature, vasopressors, inotropes, insulin, mannitol, diuretics, and transfusion, were also extracted and analyzed.

Statistical analyses

Statistical analyses were performed using SPSS 19.0 (SPSS, Chicago, IL, USA). All data are summarized as the mean ± standard deviation or median (interquartile range). Categorical and continuous data were compared using the chi-square and Student's *t*-test, respectively. To determine risk factors for hypokalemia and rebound hyperkalemia, univariate analyses were performed and only variables with $p<0.2$ were entered into the binary logistic analysis with a forward stepwise condition. All tests were two-tailed; $p<0.05$ was considered statistically significant.

RESULTS

Seventy-one patients were admitted to the surgical ICU from January 2010 to January 2012 for coma therapy to control refractory intracranial hypertension or for deep sedation to prevent a further increase in ICP. A total of 11 patients without ICP monitoring were excluded; thus, 60 patients were included in this study. Thiopental was used in 37 patients and propofol was used in 23 patients.

There were no statistically significant differences between the two patient groups with respect to age, sex, weight, APACHE II score, neurologic status before therapy, ICP before therapy, and the number of patients having refractory intracranial hypertension (Table 1). A total of 23 (62.2%) patients in the thiopental group had a vascular problem and 15 (65.2%) patients in the propofol group had a tumor.

Changes in serum potassium during and after thiopental or propofol continuous infusion

The overall changes in serum potassium level during thiopental or propofol continuous infusion are shown in Figure 1. The initial serum potassium level prior to therapy (3.9 ± 0.6 vs. 3.9 ± 0.5 mmol/L, p=0.800), total dose administered (5.3 ± 1.5 vs. 5.3 ± 1.8 mg/kg/hr, p=0.913), and therapy duration (60.2 ± 46.3 vs. 44.1 ± 32.3 hr, p=0.150) were comparable between thiopental and propofol group. A total of 11 patients had initial serum potassium level less than 3.5 mmol/L (8 in thiopental group vs. 3 in propofol group, p=0.506). The incidence of hypokalemia following the induction of therapy was not significantly differed in the thiopental group and propofol group. Meanwhile, the incidence of moderate to severe hypokalemia following the induction of therapy was significantly higher in the thiopental group than in the propofol group (51.4 vs. 13.0%, p=0.003). The minimum potassium level was lower in the thiopental group than in the propofol

group (p=0.020). The median time to the lowest serum potassium concentration was 18 (9-30) h in thiopental group and 15 (6-33) h in propofol group. The patients in the thiopental group required greater potassium replacement than the propofol group patients (p<0.001). No patient showed hyperkalemia during thiopental or propofol continuous infusion.

When therapy was discontinued, the serum potassium levels were 3.5 ± 0.8 mmol/L in the thiopental group and 3.6 ± 0.5 mmol/L in the propofol group (Figure 2). After continuous infusion was stopped, twelve patients in the thiopental group and one patient in propofol group experienced rebound hyperkalemia (p=0.010). Two patients in the thiopental group suffered from ventricular fibrillation and non-sustained ventricular tachycardia due to hyperkalemia. The average peak serum potassium level was higher in the thiopental group than in the propofol group (p=0.037). The median time to the highest serum potassium concentration was 33 (15-51) h in thiopental group and 41 (21-54) h in propofol group.

Clinical outcomes

Clinical outcomes such as ICU mortality, duration of the ICU stay, duration of the hospital stay, and the duration of mechanical ventilation were similar in both groups (Table 3). The GCS score measured on the second day after therapy was significantly higher in the propofol group than in the thiopental group (9.6 ± 4.5 vs. 3.8 ± 1.4, p<0.001).

Factors associated with hypokalemia or hyperkalemia

Based on a univariate analysis (Table 4) and binary logistic regression analysis, urine output (odds ratio, 95% confidence interval, 2.306 [1.059-5.024]; p=0.035) was associated with hypokalemia during continuous infusion. Only thiopental (odds

ratio, 95% confidence interval, 7.31 [1.78-27.81]; p=0.005) was associated with moderate to severe hypokalemia during continuous infusion (Table 5). A univariate analysis for rebound hyperkalemia development is shown in Table 6. According to a binary logistic regression analysis, thiopental (8.821[1.000-77.811]; p=0.049) and duration of continuous infusion (1.021[1.004-1.039]; p=0.016) were associated with rebound hyperkalemia once therapy was discontinued.

Table 1. Patients' characteristics

	Thiopental (n=37)	Propofol (n=23)	*p* value
Age (yr)	54 ± 14	51 ± 16	0.378
Sex (M)	20 (54.1%)	13 (56.5%)	0.852
Weight (Kg)	60.9 ± 1.7	61.9 ± 2.2	0.712
Type of injury (n)			
Trauma	7 (18.9%)	3 (13.0%)	0.001
Tumor	7 (18.9%)	15 (65.2%)	
Vascular	23 (62.2%)	5 (21.7%)	
APACHE II score	23.2 ± 5.2	22.6 ± 5.9	0.683
Craniectomy (n)	13 (35.1%)	10 (43.5%)	0.590
Decompressive lobectomy (n)	2 (5.4%)	1 (4.3%)	1.0
GCS before therapy [median(IQR)]	3 (3-4)	3 (3-3)	0.014
ICP before therapy [mmHg, median(IQR)]	22 (9-30)	13 (8-23)	0.678
Refractory intracranial hypertension (n)	11 (32.4%)	4 (22.2%)	0.443

Data are presented as a number (%) or mean ± SD. IQR, interquartile range; APACHE, acute physiology and chronic health care; GCS, Glasgow Coma Scale; ICP, intracranial pressure.

Table 2. Serum potassium change during and after therapy

	Thiopental (n=37)	Propofol (n=23)	*p* value
During therapy			
Baseline serum potassium (mmol/L)	3.9 ± 0.6	3.9 ± 0.5	0.800
Hypokalemia (K <3.5 mmol/L, n)	33 (89.2%)	19 (82.6%)	0.468
Severity (n)			
Mild (3.0≤K<3.5 mmol/L)	14 (37.8%)	16 (69.6%)	0.033
Moderate (2.5≤K <3.0 mmol/L)	11 (29.7%)	2 (8.7%)	0.105
Severe (K <2.5 mmol/L)	8 (21.6%)	1 (4.3%)	0.134
Onset [hr, median(IQR)]	9 (6-18)	9 (6-27)	0.583
The lowest level of potassium (mmol/L)	2.9 ± 0.6	3.2 ± 0.4	0.020
Total potassium replaced (mEq/kg/hr)	0.08 ± 0.04	0.02 ± 0.01	<0.001
After therapy			
Serum potassium when therapy ceased (mmol/L)	3.5 ± 0.8	3.6 ± 0.5	0.878
Hyperkalemia (K > 5.0 mmol/L, n)	12 (32.4%)	1 (4.3%)	0.010
Onset [hr, median(IQR)]	9 (6.0-58.5)	6	0.50
The highest level of potassium (mmol/L)	4.8 ± 1.1	4.2 ± 1.1	0.037

Data are presented as a number (%) or mean ± SD. IQR, interquartile range.

Table 3. Clinical outcomes

	Thiopental (n=37)	Propofol (n=23)	*p* value
GCS on post-therapy 2 day	3.8 ± 1.4	9.6 ± 4.5	<0.001
Mechanical ventilation duration (d)	12.2 ± 14.5	10.1 ± 20.1	0.634
Tracheostomy (n)	14 (37.8%)	4 (17.4%)	0.093
ICU mortality (n)	11 (29.7%)	4 (17.4%)	0.283
Duration of ICU stay [d, median(IQR)]	10.4 (6.7-22.9)	8.7 (4.9-12.8)	0.345
Duration of hospital stay [d, median(IQR)]	39.0 (17.5-80)	29.5 (17-74)	0.854
Clinical outcome (n)			
Good	9 (24.3%)	13 (56.5%)	0.015
Poor	28 (75.7%)	10 (43.5%)	

Data are presented as a number (%) or mean ± SD. IQR, interquartile range; GCS, Glasgow Coma Scale; ICU, intensive care unit.

Table 4. Comparison of variables associated with hypokalemia development.

	Hypokalemia		Univariate analysis			Multivariate analysis*		
	Yes (n=52)	No (n=8)	OR	CI	*p* value	OR	CI	*p* value
Drug (n)								
Thiopental	33 (63.5%)	4 (50.0%)	1.737	0.389-7.756	0.470			
Propofol	19 (36.5%)	4 50.0%)						
Type of injury (n)					0.942			
Trauma	9 (17.3%)	1 (12.5%)						
Tumor	19 (36.5%)	3 (37.5%)	1.500	0.147-15.284	0.732			
Vascular	24 (46.2%)	4 (50.0%)	1.056	0.210-5.299	0.948			
Renal disease (n)	2 (3.8%)	1 (12.5%)	3.571	0.285-44.718	0.324			
ICP before therapy (mmHg)	20.9 ± 15.8	30.2 ± 38.2	0.981	0.946-1.017	0.294			
K level before therapy (mEq)	3.9 ± 0.5	3.9 ± 0.4	0.973	0.233-4.063	0.970			
RBC transfusion (n)	17 (32.7%)	3 (37.5%)	1.235	0.264-5.786	0.789			
Urine output (ml/kg/hr)	4.6 ± 2.0	3.0 ± 0.8	2.306	1.059-5.024	0.035	2.306	1.059-5.024	0.035
Beta agonist (n)	31 (59.6%)	5 (62.5%)	0.886	0.191-4.110	0.877			
Insulin (n)	4 (7.7%)	2 (25.0%)	0.250	0.037-1.668	0.152			
Mannitol (n)	22 (42.3%)	3 (37.5%)	1.222	0.264-5.664	0.798			
Hypothermia (n)	32 (61.5%)	4 (50.0%)	0.625	0.140-2.785	0.538			

Data are presented as numbers or mean ± SD. OR, odds ratio, CI, confidence interval; GCS, Glasgow Coma Scale. *: adjusted for insulin use. Nagelkerke R^2 statistic was 0.209.

Table 5. Comparison of variables associated with moderate to severe hypokalemia development

	Moderate to severe hypokalemia		Univariate analysis			Multivariate analysis*		
	Yes (n=22)	No (n=38)	OR	CI	*p* value	OR	CI	*p* value
Drug (n)								
Thiopental	19 (86.4%)	18 (47.4%)	7.037	1.781-27.807	0.005	7.307	1.781-27.807	0.005
Propofol	3 (13.6%)	20 (52.6%)						
Type of injury (n)					0.080			
Trauma	4 (18.2%)	6 (15.8%)						
Tumor	4 (18.2%)	18 (47.4%)	0.333	0.063-1.763	0.196			
Vascular	14 (63.6%)	14 (36.8%)	1.500	0.346-6.498	0.588			
Renal disease (n)	2 (9.1%)	1 (2.6%)	0.270	0.023-3.168	0.999			
ICP before therapy (mmHg)	24.0 ± 14.5	20.5 ± 23.2	1.009	0.979-1.040	0.550			
K level before therapy (mEq)	3.9 ± 0.6	3.9 ± 0.5	1.140	0.414-3.137	0.800			
RBC transfusion (n)	8 (36.4%)	12 (31.6%)	0.808	0.267-2.440	0.705			
Urine output (ml/kg/hr)	4.6 ± 1.9	4.3 ± 2.0	1.088	0.833-1.422	0.535			
Beta agonist (n)	16 (72.7%)	20 (52.6%)	2.400	0.772-7.459	0.130			
Insulin (n)	1 (4.5%)	5 (13.2%)	0.314	0.034-2.881	0.306			
Mannitol (n)	10 (45.5%)	15 (39.5%)	1.278	0.442-3.695	0.651			
Hypothermia (n)	16 (72.7%)	20 (52.6%)	0.417	0.134-1.295	0.130			

Data are presented as numbers or mean ± SD. OR, odds ratio, CI, confidence interval. *: adjusted for type of injury, beta agonist use, hypothermia. Nagelkerke R^2 statistic was 0.206.

Table 6. Comparison of variables associated with hyperkalemia development

	Hyperkalemia		Univariate analysis			Multivariate analysis*		
	Yes (n=13)	No (n=47)	OR	CI	*p* value	OR	CI	*p* value
Drug (n)								
Thiopental	12 (92.3%)	25 (53.2%)	10.560	1.269-87.882	0.029	8.821	1.000-77.811	0.049
Propofol	1 (7.7%)	22 (46.8%)						
Type of injury (n)					0.109			
Trauma	3 (23.1%)	7 14.9%)						
Tumor	1 (7.7%)	21 (44.7%)	0.905	0.189-4.340	0.900			
Vascular	9 (69.2%)	19 (40.4%)	0.101	0.012-0.869	0.037			
Duration of therapy (hr)	86.8 ± 64.2	45.0 ± 28.2	1.023	1.007-1.039	0.005	1.021	1.004-1.039	0.016
Renal disease (n)	1 (7.7%)	2 (4.3%)	0.533	0.045-6.391	0.620			
GCS after therapy	4.2 ± 1.4	6.5 ± 4.5	0.817	0.643-1.038	0.098			
K level after cessation of the therapy (mEq)	3.5 ± 1.2	3.6 ± 0.5	0.800	0.320-2.002	0.633			
K replace during the therapy (mEq/kg/hr)	0.07 ± 0.03	0.05 ± 0.05	2.574	0.066-9.405	0.114			
RBC transfusion (n)	4 (30.8%)	16 (34.0%)	1.161	0.309-4.362	0.825			
Urine output (ml/kg/hr)	3.8 ± 1.2	4.5 ± 2.1	0.790	0.539-1.157	0.226			
Beta agonist (n)	10 (76.9%)	26 (55.3%)	2.692	0.656-11.056	0.169			
Insulin (n)	1 (7.7%)	5 (10.6%)	0.700	0.074-6.581	0.755			
Mannitol (n)	3 (23.1%)	22 (46.8%)	0.341	0.083-1.399	0.135			
Hypothermia (n)	10 (76.9%)	26 (55.3%)	0.371	0.090-1.525	0.169			

Data are presented as a number (%) or mean ± SD. OR, odds ratio, CI, confidence interval; GCS, Glasgow Coma Scale. *: adjusted for type of injury, GCS after therapy, K replace during the therapy, beta agonist, mannitol use, hypothermia. Nagelkerke R^2 statistic was 0.342.

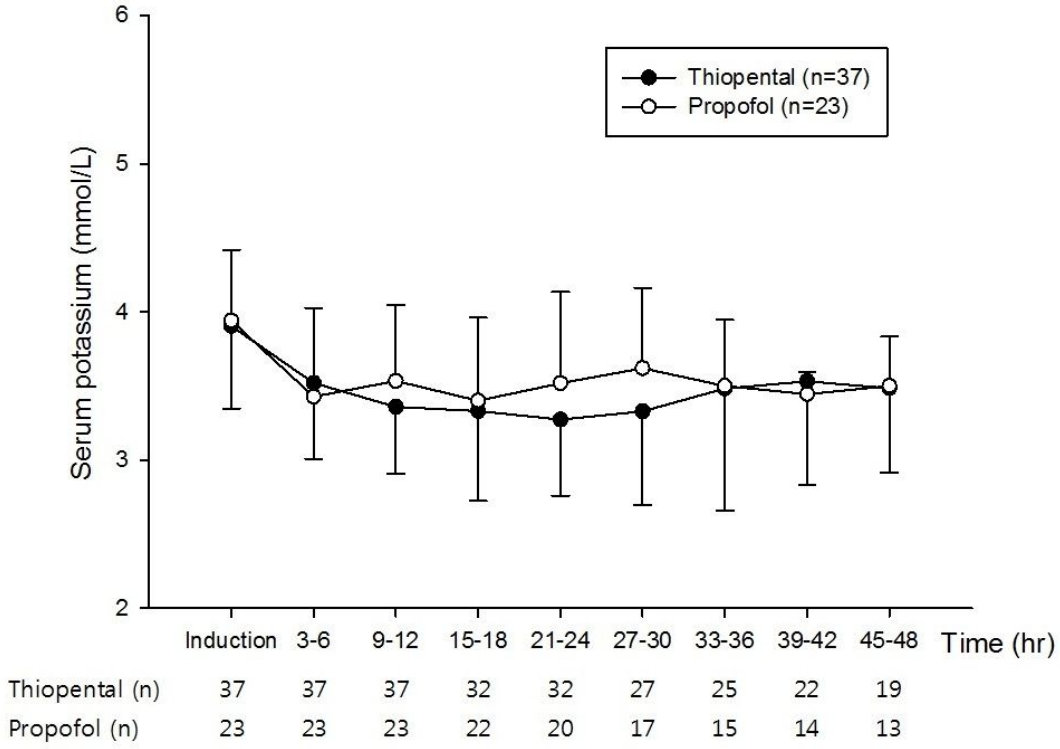

Figure 1. Mean (SD) serum potassium against time after thiopental or propofol induction. There is no significant difference in serum potassium level between thiopental and propofol groups.

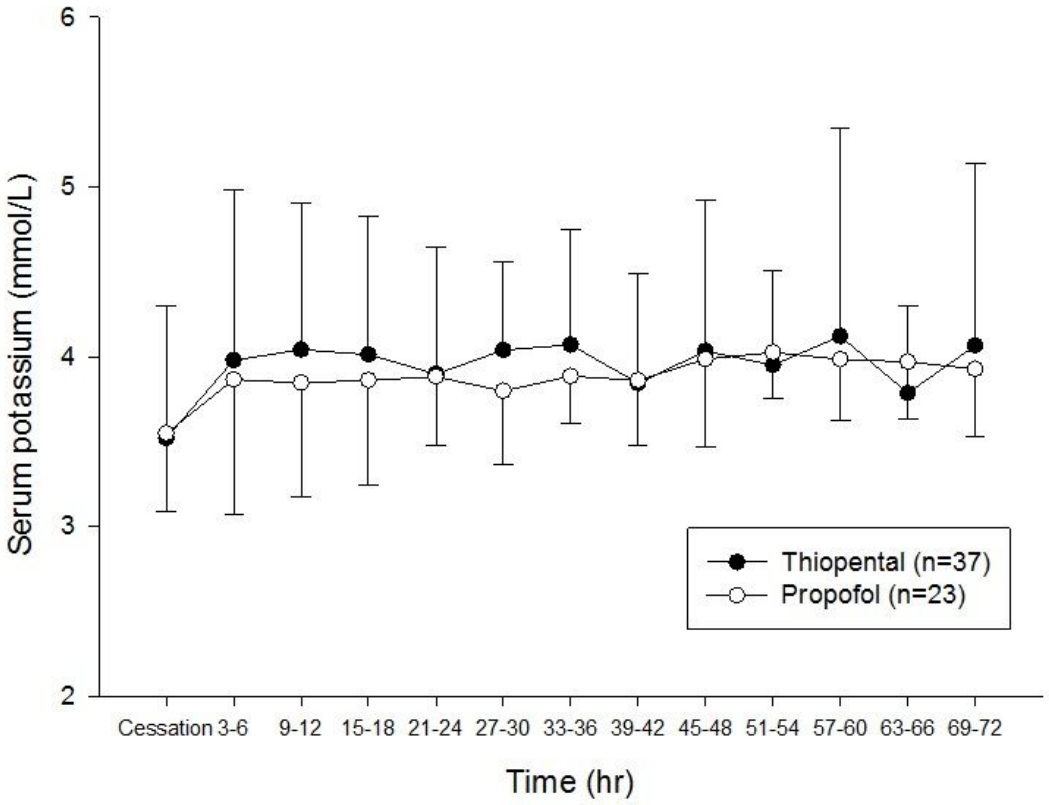

Figure 2. Mean (SD) serum potassium against time after cessation of thiopental or propofol infusion. There is no significant difference in serum potassium level between thiopental and propofol groups.

DISCUSSION

The present study demonstrates that the incidence of hypokalemia was similar in patients receiving thiopental continuous infusion and in patients receiving propofol continuous infusion. However, the incidence of moderate to severe hypokalemia and rebound hyperkalemia were significantly higher in patients who received thiopental continuous infusion than in those who received propofol continuous infusion. Only thiopental was associated with hypokalemia and rebound hyperkalemia.

In a recent study, the incidence of hypokalemia was 7.5% in patients admitted to an ICU after brain surgery (19). In the present study, hypokalemia developed in 89.2% of patients receiving thiopental therapy. The incidence of hypokalemia in the present study was comparable with what has been previously reported, wherein hypokalemia developed in 80-90% of patients receiving thiopental coma therapy (3, 4). Moreover, the patients in our study who were administered thiopental had greater potassium supplementation than those receiving propofol during both treatments. Interestingly, however, the lowest serum potassium level was still significantly lower in patients receiving thiopental and the incidence of moderate to severe hypokalemia was significantly higher in this group. Such finding confirms the association between thiopental and hypokalemia.

There are several mechanisms that may explain the hypokalemia development in patients receiving thiopental continuous infusion. First, thiopental inhibits the voltage-dependent potassium current via sodium/potassium ATPase activity and induces the intracellular sequestration of potassium (20). Second, thiopental inhibits phosphofructokinase and reduces the intracellular production of pyruvate and lactate, thereby increasing the intracellular pH and inducing an extracellular to intracellular potassium shift (21).

In addition to thiopental administration, there are other possible causes of hypokalemia in neurosurgical patients. First, it is well known that hypokalemia is related to the sympathetic stress response and catecholamine surge in patients with a brain injury (22-25). Second, hypokalemia can be induced by urinary potassium loss due to mannitol or diuretics. Third, vasopressor therapy, an insulin infusion, and hypothermia can also cause hypokalemia. In this study, confounding variables such as the extent of head injury, urinary potassium loss, hypothermia, and the use of vasopressors or insulin were comparable in both groups, and a binary logistic regression analysis showed that such confounding variables were not associated with hypokalemia.

In our study, the median time to onset of hypokalemia was 9 h and the median time to the lowest serum potassium concentration for patient with hypokalemia was 21 h after the administration of thiopental. In a previous case series, the median time to onset of hypokalemia was 11 h and the median time to the lowest serum potassium level was 25 h after thiopental induction (4).

The potassium disturbance associated with thiopental follows a relatively consistent biphasic pattern consisting of hypokalemia after induction and hyperkalemia after the cessation of therapy (4-7). It is believed that the intracellular accumulation of potassium during thiopental therapy causes rebound hyperkalemia after the cessation of therapy (6). Only patients who showed hypokalemia during thiopental therapy had rebound hyperkalemia after the cessation of therapy (4). Rebound hyperkalemia occurred within 6 h with sudden cessation, and more slowly with gradual cessation (4-7). Similar to previous studies, our study showed that the incidence of rebound hyperkalemia was significantly higher in thiopental-infused patients than in propofol-infused patients, and the median time to onset of hyperkalemia was 9 h after discontinuing thiopental therapy. Moreover, this study

demonstrates that thiopental and the duration of therapy were significant predictors of rebound hyperkalemia after the cessation of therapy.

Dyskalemia associated with barbiturates can be life-threatening (5-8). Both hypokalemia and hyperkalemia are potentially fatal. In this study, one patient in the thiopental group suffered from ventricular fibrillation and another patient suffered from non-sustained ventricular tachycardia caused by rebound hyperkalemia. When thiopental is used to control ICP, clinicians should be aware of dyskalemia associated with barbiturate therapy, and serum potassium levels should be closely monitored.

Propofol has a short elimination half-life of <1 h and permits frequent and rapid titration. It may be a useful agent for serial neurological examinations in patients with intracranial hypertension. Propofol also offers faster, more predictable awakenings, and earlier extubation than thiopental or other sedative agents (26, 27). However, prolonged infusion should be used cautiously because of rare but fatal PRIS.

This study showed that hypokalemia was common but the incidence of moderate to severe hypokalemia was low when propofol was continuously administered for ICP control. No report has been demonstrated interaction between propofol and hypokalemia. We also think that other factors rather than propofol caused hypokalemia in propofol continuous infusion group. Indeed, urinary potassium loss was associated with development of overall hypokalemia in this study. The effect of propofol administration on serum potassium levels has not been widely researched, and results are inconsistent. For example, a previous study reported that the serum potassium level fell by 0.04 mmol/L at 5 min after induction with a propofol bolus injection (2.5 mg/kg), but recovered to the pre-induction level within 10 min (26). In contrast, a previous case report showed that a sudden cardiac arrest due to

hyperkalemia occurred after propofol single administration (28). Hyperkalemia has been reported as one of clinical manifestations in PRIS patients (29, 30). PRIS is commonly associated with rhabdomyolysis, and hyperkalemia may have been due to rhabdomyolysis (29). Propofol can decrease beta-adrenoceptor responsiveness (31). Therefore, it may block the effect of beta agonists on the intracellular potassium shift. Taken together, these findings suggest that the association of propofol with dyskalemia is not well established and its pathophysiology remains unclear. A large-scale study is necessary to verify the association between propofol infusions and serum potassium disturbances when used for the regulation of ICP.

There were several limitations to this study. Since this study was performed retrospectively, data collection was a limitation and the sample size was small. Not only patients with refractory intracranial hypertension, but patients with a baseline ICP of <25 mmHg were included in the inclusion criteria. The type of surgery was also heterogenous. But, baseline ICP and the type of surgery were not associated with hypokalemia development in the univariate analysis. We focused on serum potassium disturbances after the infusion of thiopental or propofol instead of clinical outcomes. In this study, although statistically not significant, patients in the thiopental treated group had more severe brain injuries at the outset. Therefore, a great caution to the interpretation of our result, especially clinical outcomes, is needed because a difference in the brain condition before therapy between two treatment groups can affect clinical outcomes. The doses of infused thiopental and propofol were based on clinical experience instead of burst suppression on an electroencephalogram.

In conclusion, when continuous infusion was used to relieve intracranial hypertension, propofol was less frequently associated with moderate to severe hypokalemia after induction and rebound hyperkalemia after cessation of therapy

than thiopental. Whenever thiopental is used to control intracranial hypertension, serum potassium levels should be closely monitored with at least 6-hr intervals.

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국문 초록

서론: Thiopental 지속 정주는 저칼륨혈증, 반동성 고칼륨혈증과 연관이 있다. 그러나 propofol 지속 정주가 혈중 칼륨 농도에 미치는 영향은 아직 많이 연구되지 않았다. 두개내압이 높은 환자에서 thiopental 과 propofol 지속 정주가 혈중 칼륨 농도에 미치는 영향을 후향적으로 비교하였다.

방법: 2010 년 1 월부터 2012 년 1 월까지 두개내압 조절을 위해 thiopental (n=37) 또는 propofol (n=23) 혼수요법 또는 깊은 진정 치료를 받은 60 명의 환자 의무기록을 검토하였다.

결과: Thiopental 군에서 33 명(89.2%)의 환자와 propofol 군에서 19 명(82.6%)의 환자에서 치료 시작 후 저칼륨혈증 (혈중 칼륨 농도 <3.5 mmol/L)이 있었다 (p=0.468). 치료 시작 후 중등도-중증 저칼륨혈증 (혈중 칼륨 농도 <3.0 mmol/L)의 발생은 propofol 군에 비해 thiopental 군에서 유의하게 높았다 (51.4 vs. 13.0%, p=0.003). 가장 낮은 혈증 칼륨 평균 농도는 thiopental 군에서 2.9 ± 0.6 mmol/L, propofol 군에서 3.2 ± 0.4 mmol/L 였다 (p<0.05). Thiopental 군 환자들이 propofol 군 환자들에 비해 더 많은 양의 칼륨 보충을 필요로 하였다 (0.08 ± 0.04 vs. 0.02 ± 0.01 mEq/kg/hr, p<0.001). 다변량분석에서 thiopental 은 지속 정주 중 중등도-중증

저칼륨혈증과 연관이 있었다 (odds ratio, 95% 신뢰구간, 7.31 [1.78-27.81]; p=0.005). 치료 종료 후 반동성 고칼륨혈증 (혈중 칼륨 농도 >5.0 mmol/L)의 발생은 thiopental 군에서 propofol 군에 비해 많았다 (32.4 vs. 4.3%; p<0.05). 최고 혈중 칼륨 평균 농도는 thiopental 군에서 4.8 ± 1.1 mmol/L, propofol 군에서 4.2 ± 1.1 mmol/L 였다 (p<0.05). 다변량분석에서 thiopental (odds ratio, 95% 신뢰구간, 8.821[1.000-77.811]; p=0.049)과 치료 기간(odds ratio, 95% 신뢰구간, 1.021[1.004-1.039]; p=0.016)은 치료 종료 후 반동성 고칼륨혈증과 연관이 있었다.

결론: 두개내압상승을 완화하기 위해 propofol 지속 정주를 하는 경우 thiopental 지속 정주를 하는 경우에 비해서 혼수요법 시작 후 중등도-중증 저칼륨혈증, 혼수요법 중단 후 고칼륨혈증의 연관이 적었다.

주요어 : 주요어 : 두개내압상승, thiopental, propofol, 칼륨농도이상

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