The Effects of Propofol and Thiopental Continuous Infusion on Serum Potassium Disturbances in Neurosurgical Patients

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Objective : The potassium disturbance associated with thiopental continuous infusion in neurosurgical patients is well known. However, the effect of propofol continuous infusion on serum potassium levels has not been investigated extensively.

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

Results : The overall incidence of hypokalemia (K<3.5 mmol/L) was comparable between thiopental and propofol groups (89.2% vs. 82.6%). But, the incidence of moderate to severe hypokalemia (K<3.0 mmol/L) was significantly higher in thiopental group (51.4% vs. 13.0%, p=0.003). The lowest potassium level (2.9 mmol/L vs. 3.2 mmol/L, p=0.020) was lower in thiopental group. The patients in the thiopental group required greater potassium replacement than the propofol group patients (0.08 mmol/kg/h vs. 0.02 mmol/kg/h, 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 (K>5.0 mmol/L, 32.4% vs. 4.3%, p=0.010) and the peak potassium concentration (4.8 mmol/L vs. 4.2 mmol/L, p=0.037) after the cessation of therapy were higher in thiopental group. On multivariate analysis, thiopental [8.82 (1.00–77.81); p=0.049] and duration of continuous infusion [1.02 (1.00–1.04); p=0.016] were associated with rebound hyperkalemia once therapy was discontinued.

Conclusion : Propofol was less frequently associated with moderate to severe hypokalemia after induction and rebound hyperkalemia following the cessation of continuous infusion than thiopental.

Key Words : Intracranial hypertension · Thiopental · Propofol · Hypokalemia · Hyperkalemia.

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 (CMRO₂) and cerebral blood flow. The maximum decrease (roughly 50%) in CMRO₂ occurs when the electroencephalographic readings become isoelectric.²⁻¹⁷. Barbiturate therapy, however, is associated with adverse effects, including hypotension and immunosuppression.⁴⁻⁸. Additionally, barbiturates can induce hypokalemia after the induction of coma therapy and cause rebound hyperkalemia after the cessation of therapy.⁴⁻¹⁰,²⁴⁻³⁹. The incidence of hypokalemia after thiopental induction ranges between 82% and 89.4%.¹⁻¹³,³⁸⁻³⁹. A case series reported that 34% of patients had rebound hyperkalemia after stopping thiopental coma therapy.⁴⁻¹³. There have also been several reports of serious adverse events due to hypokalemia and rebound hyperkalemia.¹⁶⁻²⁵. 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.¹⁰⁻²². It decreases ICP in normal subjects and as well as in patients with an elevated ICP.²⁰⁻²⁴. It reduces the cerebral metabolic rate by 40% in a dose-dependent fashion and decreases cerebral blood flow by metabolism-flow coupling.²⁷⁻²⁹. Propofol is known to cause hypotension, hypertriglyceridemia, and propofol-related infusion syndrome (PRIS).⁻¹³,⁻²⁰. 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.

The aim of this study was to determine the effect of thiopental and propofol continuous infusion on serum potassium levels when used for ICP control.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Seoul National University Hospital (IRB no. H-1307-047-504) and was in accordance with the Declaration of Helsinki. 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 mm Hg.

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 infusions, a loading dose (250 mg) was administered for about 30 min, followed by a continuous infusion of 3–7 mg/kg/h. In those using propofol continuous infusions, a loading dose (100–150 mg) was administered 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 mm Hg. Once no further increases in ICP from baseline were detected for 9–18 h in patients with a baseline ICP of <25 mm Hg, in whom deep sedation was needed for ICP control, or if the ICP decreased to ≤24 mm Hg 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 mm Hg despite the use of first-tier therapies for ICP control.

Measurement

In all patients, serum potassium was measured before therapy. Serum potassium was measured with various intervals (3–8 h) during and after therapy. The same protocol was applied to both groups. The primary outcome in this study was the incidence of hypokalemia during thiopental or propofol continuous infusion. The secondary outcome 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, Glasgow Coma Scale score prior to therapy, acute physiology and chronic health evaluation II (APACHE II) score, light reflex prior to therapy, the length of ICU stay, ICU mortality, and duration of mechanical ventilation. 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 Inc., Chicago, IL, USA). All numerical data are summarized as the mean (standard deviation) or median (interquartile range). Categorical data were compared using the chi-square or Fisher’s exact test, if appropriate. Student’s t-test was used to compare continuous data. 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 during the study period 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 Fig. 1. The ini-
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Clinical outcomes such as ICU mortality, duration of the ICU stay, and the duration of mechanical ventilation were similar in both groups (Table 3).

Factors associated with hypokalemia or hyperkalemia

Based on a univariate analysis, only urine output [odds ratio, 95% confidence interval, 2.31 (1.06–5.02); p=0.035] was associated with hypokalemia during continuous infusion. Thiopental and refractory intracranial hypertension were associated with moderate to severe hypokalemia during continuous infusion in univariate analysis (Table 4). Only thiopental [odds ratio, 95% confidence interval, 7.04 (1.78–27.81); p=0.005] was predictive of moderate to severe hypokalemia in binary logistic regression analysis after adjusting for the type of injury, refractory intracranial hypertension, beta agonist, hypothermia. A univariate analysis for rebound hyperkalemia development after stopping continuous infusion is shown in Table 5. According to a binary

### Table 1. Characteristics of patients

|                     | Thiopental (n=37) | Propofol (n=23) | p value |
|---------------------|-------------------|-----------------|---------|
| Age [yr, mean (range)] | 54 (19–82)       | 51 (19–82)     | 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)  |                   |                 | 0.001   |
| Trauma              | 7 (18.9%)         | 3 (13.0%)      |         |
| 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   |
| Cranectomy (n)      | 13 (35.1%)        | 10 (43.5%)     | 0.590   |
| Decompressive lobectomy (n) | 2 (5.4%) | 1 (4.3%) | >0.999 |
| GCS before therapy [median (IQR)] | 3 (3–4) | 3 (3–3) | 0.014   |
| No light reflex (n) | 10 (27.0%)        | 6 (26.1%)      | >0.999  |
| ICP before therapy (mm Hg) | 21.7 (15.4) | 19.6 (21.5) | 0.665   |
| Refractory intracranial hypertension (n) | 11 (29.7%) | 4 (17.4%) | 0.443   |

Data are presented as number (proportion) or mean (standard deviation) or median (IQR). IQR : interquartile range, APACHE : acute physiology and chronic health evaluation, GCS : Glasgow Coma Scale, ICP : intracranial pressure

Fig. 1. Mean (standard deviation) serum potassium against time after induction of thiopental or propofol continuous infusion.

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Clinical outcomes such as ICU mortality, duration of the ICU stay, and the duration of mechanical ventilation were similar in both groups (Table 3).

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In a recent study, the incidence of hypokalemia was 7.5% in patients admitted to an ICU after brain surgery\(^5\), whereas the incidence of hypokalemia was 80–90% in patients receiving thiopental coma therapy\(^{19,24}\). In the present study, hypokalemia developed in 89.2% of patients receiving thiopental therapy which was comparable with what has been previously reported. Interestingly, this study showed similar incidence of hypokalemia in thiopental and propofol-infused patients. However, the incidence of moderate to severe hypokalemia was lower in propofol-infused patients than in thiopental-infused patients.

Propofol has been demonstrated to be an effective drug for the regulation of ICP\(^{10,22}\). It has a short elimination half-life of <1 h and permits frequent and rapid titration. Also, propofol offers faster, more predictable awakenings, and earlier extubation than thiopental or other sedative agents\(^{7,9}\). Thus, it may be a useful

### 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 the thiopental group patients. Only thiopental was associated with moderate to severe hypokalemia and rebound hyperkalemia.

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### Table 2. Serum potassium change during and after thiopental or propofol continuous infusion

|                          | 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%)      | 0.034  |
| 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 (3.3%)        | 0.134  |
| Onset (h)                | 13.3 (11.2)      | 15.2 (12.9)     | 0.583  |
| Lowest level of potassium (mmol/L) | 2.8 (0.5)   | 3.1 (0.4)       | 0.009  |
| Total potassium replaced (mEq/kg/h) | 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%)        | 0.011  |
|  Severity (n)            |                  |                 |        |
| Mild (5.0≤K≤6.0 mmol/L)  | 7 (19.9%)        | 0 (0%)          | 0.037  |
| Moderate (6.0<K≤8.0 mmol/L) | 4 (10.8%)        | 1 (4.3%)        | 0.640  |
| Severe (K>8.0 mmol/L)    | 1 (2.7%)         | 0 (0%)          | >0.999 |
| Onset (h)                | 26.0 (27.3)      | 6               | 0.497  |
| Highest level of potassium (mmol/L) | 6.1 (1.1)     | 6.2             | 0.907  |

Data are presented as number (proportion) or mean (standard deviation)

### Fig. 2. Mean (standard deviation) serum potassium against time after cessation of thiopental or propofol continuous infusion.

![Fig. 2. Mean (standard deviation) serum potassium against time after cessation of thiopental or propofol continuous infusion.](image-url)
Table 3. Clinical outcomes of patients receiving thiopental or propofol continuous infusion for intracranial pressure regulation

|                          | Thiopental (n=37) | Propofol (n=23) | p value |
|--------------------------|------------------|----------------|---------|
| 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   |

Data are presented as number (proportion) or mean (standard deviation) or median (IQR). IQR : interquartile range, ICU : intensive care unit

Table 4. Comparison of variables associated with moderate to severe hypokalemia during thiopental or propofol continuous infusion

|                           | Moderate to severe hypokalemia | Univariate analysis |
|---------------------------|-------------------------------|---------------------|
|                           | Yes (n=22)             | No (n=38)   | OR     | 95% CI     | p value |
| Drug (n)                  |                               |                        |       |          |         |
| Thiopental                | 19 (86.4%)                | 18 (47.4%)    | 7.04   | 1.78–27.81| 0.005   |
| Propofol                  | 3 (13.6%)                 | 20 (52.6%)     |        |            |         |
| Type of injury (n)        |                               |                        |       |          |         |
| Trauma                    | 4 (18.2%)                 | 6 (15.8%)      | 0.33   | 0.06–1.76 | 0.196   |
| Tumor                     | 4 (18.2%)                 | 18 (47.4%)     | 1.50   | 0.35–6.50 | 0.588   |
| Vascular                  | 14 (63.6%)                | 14 (36.8%)     |        |            |         |
| Renal disease (n)         | 2 (9.1%)                  | 1 (2.6%)       | 0.27   | 0.02–3.17 | 0.999   |
| GCS before therapy        | 3.6 (1.2)                 | 3.4 (1.1)      | 0.83   | 0.52–1.32 | 0.421   |
| ICP before therapy (mm Hg)| 23.9 (14.1)               | 19.2 (19.7)    | 1.01   | 0.99–1.05 | 0.340   |
| Refractory intracranial hypertension (n) | 9 (40.9%)                | 6 (15.8%)      | 3.69   | 1.09–12.48| 0.035   |
| K level before therapy (mEq) | 3.9 (0.6)                 | 3.9 (0.5)      | 1.14   | 0.41–3.14 | 0.800   |
| RBC transfusion (n)       | 8 (36.4%)                 | 12 (31.6%)     | 0.81   | 0.27–2.44 | 0.705   |
| Urine output (mL/kg/h)    | 4.6 (1.9)                 | 4.3 (2.0)      | 1.09   | 0.83–1.42 | 0.535   |
| Beta agonist (n)          | 16 (72.7%)                | 20 (52.6%)     | 2.40   | 1.27–87.88| 0.029   |
| Insulin (n)               | 1 (4.5%)                  | 5 (13.2%)      | 0.33   | 0.03–2.88 | 0.306   |
| Mannitol (n)              | 10 (45.5%)                | 15 (39.5%)     | 1.28   | 0.44–3.70 | 0.651   |
| Hypothermia (n)           | 16 (72.7%)                | 20 (52.6%)     | 0.42   | 0.13–1.30 | 0.130   |

Data are presented as number (proportion) or mean (standard deviation). OR : odds ratio, CI : confidence interval, GCS : Glasgow Coma Scale, ICP : intracranial pressure, RBC : red blood cell

Table 5. Comparison of variables associated with hyperkalemia development after cessation of thiopental or propofol continuous infusion

|                           | Hyperkalemia | Univariate analysis |
|---------------------------|--------------|---------------------|
|                           | Yes (n=13)   | No (n=47)   | OR     | 95% CI     | p value |
| Drug (n)                  |              |             |       |            |         |
| Thiopental                | 12 (92.3%)   | 25 (53.2%)  | 10.56 | 1.27–87.88| 0.029   |
| Propofol                  | 1 (7.7%)     | 22 (46.8%)  |        |            |         |
| Type of injury (n)        |              |             |       |            |         |
| Trauma                    | 3 (23.1%)    | 7 (14.9%)   | 0.92  | 0.09–8.8   | 0.447   |
| Tumor                     | 1 (7.7%)     | 21 (44.7%)  | 0.91  | 0.19–4.34 | 0.900   |
| Vascular                  | 9 (69.2%)    | 19 (40.4%)  | 0.10  | 0.01–0.87 | 0.037   |
| Duration of therapy (h)   | 86.8 (64.2)  | 45.0 (28.2) | 1.02  | 1.01–1.04 | 0.005   |
| Renal disease (n)         | 1 (7.7%)     | 2 (4.3%)    | 0.53  | 0.05–6.39 | 0.620   |
| Refractory intracranial hypertension (n) | 4 (30.8%)    | 11 (23.4%)  | 1.46  | 0.37–5.65 | 0.589   |
| K level after stopping the therapy (mmol) | 3.5 (1.2)      | 3.6 (0.5)    | 0.80  | 0.32–2.00 | 0.633   |
| K replace during the therapy (mmol/kg/h) | 0.07 (0.03) | 0.05 (0.05) | 2.57  | 0.07–9.41 | 0.114   |
| RBC transfusion (n)       | 4 (30.8%)    | 16 (34.0%)  | 1.16  | 0.31–4.36 | 0.825   |
| Urine output (mL/kg/h)    | 3.8 (1.2)    | 4.5 (2.1)   | 0.79  | 0.54–1.16 | 0.226   |
| Beta agonist (n)          | 10 (76.9%)   | 26 (55.3%)  | 2.69  | 0.66–11.06| 0.169   |
| Insulin (n)               | 1 (7.7%)     | 5 (10.6%)   | 0.70  | 0.07–6.58 | 0.755   |
| Mannitol (n)              | 3 (23.1%)    | 22 (46.8%)  | 0.34  | 0.08–1.40 | 0.135   |
| Hypothermia (n)           | 10 (76.9%)   | 26 (55.3%)  | 0.37  | 0.09–1.53 | 0.169   |

Data are presented as number (proportion) or mean (standard deviation). OR : odds ratio, CI : confidence interval, RBC : red blood cell
agent for serial neurological examinations in patients with intracranial hypertension. However, 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. In contrast, a previous case report showed that a sudden cardiac arrest due to hyperkalemia occurred after propofol single administration. Hyperkalemia has been reported as one of clinical manifestations in PRIS patients. PRIS is commonly associated with rhabdomyolysis, and hyperkalemia may have been due to rhabdomyolysis. Propofol can decrease beta-adrenoceptor responsiveness. Therefore, it may block the effect of beta agonists on the intracellular potassium shift. In this study, when propofol was continuously administered for ICP control, hypokalemia was common but the severity was low. We think that other factors rather than propofol caused hypokalemia in propofol continuous infusion group.

There are several 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. This study also showed that refractory intracranial hypertension was associated with moderate to severe hypokalemia in univariate analysis, although it was not an independent factor on binary logistic analysis. Second, hypokalemia can be induced by urinary potassium loss due to mannitol, diuretics or central diabetes insipidus. Our results also showed that urine output during continuous therapy was associated with hypokalemia. Urinary potassium loss and its combination with thiopental infusion can result in more severe hypokalemia. Third, vasopressor therapy, an insulin infusion, and hypothermia can also cause hypokalemia. But, these confounding variables were not associated with hypokalemia in this study.

In the present study, patients receiving thiopental had greater potassium supplementation than those receiving propofol during the infusion therapies. 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. 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.

The potassium disturbance associated with thiopental follows a relatively consistent biphasic pattern consisting of hypokalemia after induction and hyperkalemia after the cessation of therapy. In the previous studies, rebound hyperkalemia occurred within 6 h with sudden cessation, but occurred 31 h after cessation with gradual weaning of over 12–24 h. It is believed that the intracellular accumulation of potassium during thiopental therapy causes rebound hyperkalemia after the cessation of therapy. Our study showed that the incidence of rebound hyperkalemia was significantly higher in thiopental-infused patients than in propofol-infused patients. 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. 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.

There were several limitations to this study. Since this study was performed retrospectively, data collection was a limitation. The sample size was small. The type of surgery was also heterogeneous. But, our results showed that the type of surgery was not associated with hypokalemia development on the binary logistic analysis. In this study, we focused on serum potassium disturbances during and after the infusion of thiopental or propofol instead of clinical outcomes, because patients with refractory intracranial hypertension as well as patients with a baseline ICP of <25 mm Hg were included in the inclusion criteria.

CONCLUSION

When continuous infusion was used to control intracranial pressure, 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-h intervals.

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