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Original Article

Changes in postoperative cognitive function during off-pump coronary artery bypass graft surgery: dose response of propofol

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Abstract: To determine if concentration of propofol is related to the incidence of postoperative cognitive dysfunction (POCD) during off-pump coronary artery bypass grafting (OPCABG) surgery in geriatric patients. A total of 218 patients scheduled for elective OPCABG surgery were enrolled into three groups based on propofol dose, including TCI plasma concentration of 0.5-1.0 μg/ml (Group P1), 1.1-1.5 μg/ml (Group P2) and 1.6-2.0 μg/ml (Group P3). Neuropsychological testing was performed before surgery and at day 1, day 3, day 7, 3 months, and 6 months after surgery. S100-β and neuron-specific enolase (NSE) were measured at the startand end of surgery and at 6, 12, and 24 hours after surgery. As compared to groups P1 and P2, MMSE scores in group P3 decreased significantly at day 1 and day 3 postoperatively ($P<0.05$). S100-β protein and NSE were significantly differentin group P3 as compared to groups P1 and P2 ($P<0.05$). POCD incidence may correlate with concentration of propofol in patients undergoing OPCABG surgery.

Keywords: Propofol, postoperative cognitive dysfunction, off-pump coronary artery bypass grafting

Introduction

POCD is a well-recognized complication of CAB [1, 2]. The CABG surgery (off-pump or on-pump) impacts cognitive function for 3-6 months [3],with no major difference in POCD occurrence between OPCABG group (21% at 3 months and 30.8% at 12 months) and CPB group (29% at 3 months and 33.6% at 12 months) [4]. Total intravenous anesthesia (TIVA) is more suitable than inhalation anesthesia for senile patients [5]. The incidence of early POCD in patients under propofol anesthesia is lower than inhalation anesthesia [6]. Although many studies have investigated POCD after CABG surgery, the dose of the anesthetic is rarely mentioned. We investigate whether the dose of propofol is associated with POCD incidence during OPCABG surgery in geriatric patients.

Materials and methods

The duration of this prospective, randomized clinical study was eight months, from February to December 2013. Ethical approval was provided by the Clinical Research Ethics Committee (Approved ID: 2012KY-001-01). Informed written consent was obtained from all patients. The retrospective registration work was completed on www.chictr.org.cn (ChiCTR-OOC-15-005978).

Patients

The study was performed on 218 patients, between 60 and 75 years of age, ASA III, preoperative Euroscore 4-6 points, who were referred for elective OPCABG surgery. Patients were excluded if they met any of the following criteria: (1) emergency surgery; (2) preoperative cerebrovascular disease; (3) history of mental illness, long-term use of sedatives and antidepressants; (4) history of pneumothorax; (5) liver and kidney dysfunction; (6) secondary surgery; (7) ejection fraction <40%; (8) level of education <7 years; (9) serious visual, auditory and language barriers.

Grouping

Patients were randomly assigned to three propofol groups before anesthesia, including TCI plasma concentration of 0.5-1.0 μg/ml (Group

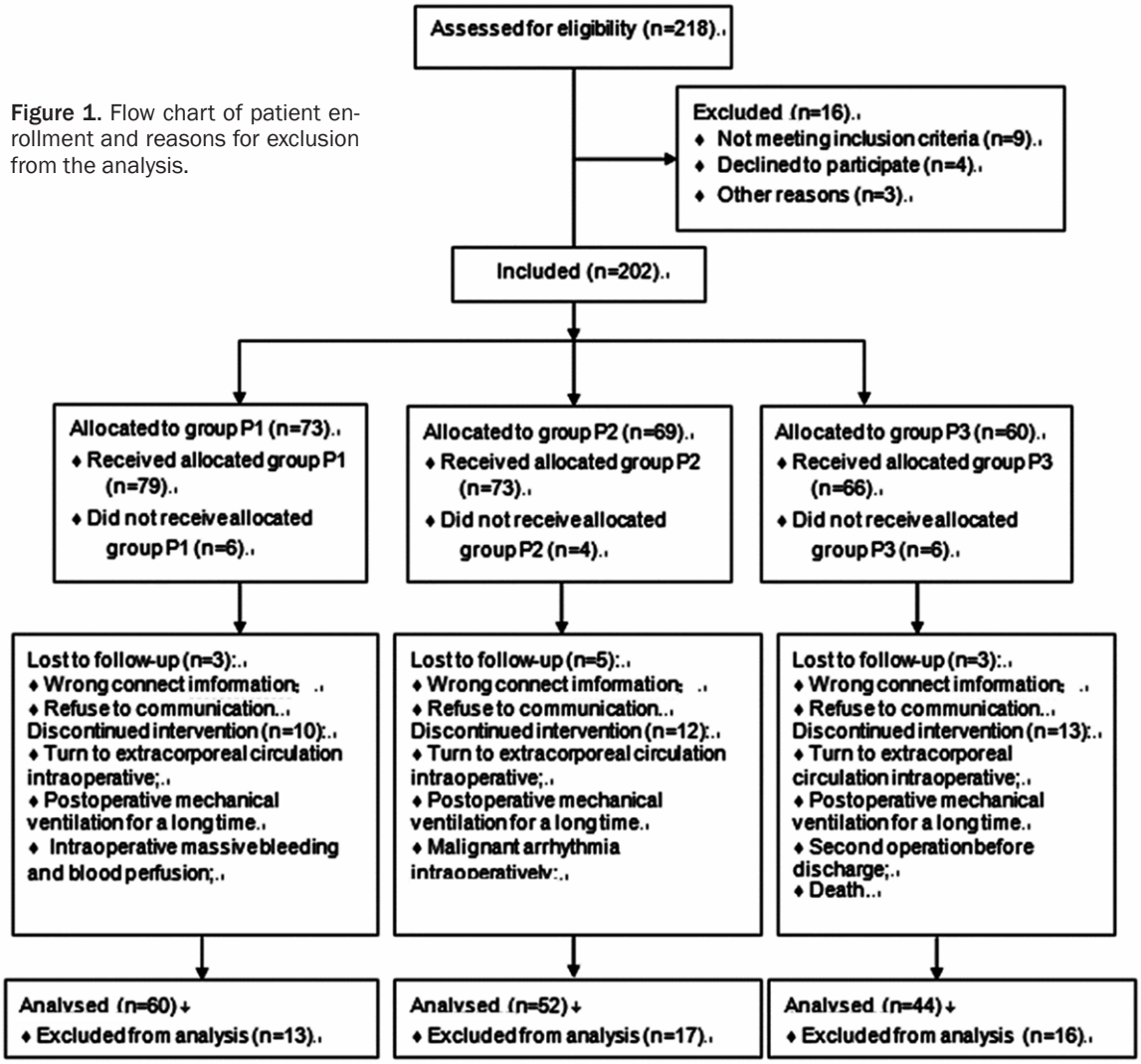

Figure 1. Flow chart of patient enrollment and reasons for exclusion from the analysis.

Table 1. Baseline characteristics

Variables	All patients (n=156)			*P* value
	Group P1 (n=60)	Group P2 (n=52)	Group P3 (n=44)	
Age (yr)	69±4.7	67±3.7	65±4.5	0.362
Education (yr)	10.5±3.2	10.6±3.5	11.0±3.5	0.462
Female gender	21 (35%)	16 (31%)	14 (32%)	0.563
Height (cm)	170±8.6	169±7.5	171±8.2	0.517
Weight (kg)	73±5.2	73±5.9	74±6.3	0.498
Hypertension	50 (83%)	45 (86%)	38 (86%)	0.221
Diabetes mellitus	35 (58%)	28 (53%)	22 (50%)	0.139
Old myocardial infarction	14 (23%)	10 (19%)	9 (20%)	0.235
Preoperative EF (%)	54±4.6	54±5.2	55±3.9	0.735
ASA classification	II (II~III)	II (II~III)	II (II~III)	0.869
Preoperative Euroscore	2.0±0.1	2.0±0.2	2.0±0.1	0.935

P1, n=73), 1.1-1.5 μg/ml (Group P2, n=69) and 1.6-2.0 μg/ml (Group P3, n=60).

Anesthesia

All preoperative cardiac medications except anticoagulants were administered until the morning of surgery. Diabetic patients on oral anti-diabetic agents were preoperatively switched to insulin therapy. All patients received a standard pre-operative treatment: 0.1 mg/kg morphine and 0.3 mg scopolamine by in tramuscular injection, 30 minutes before surgery. In the operating room, the patients were monitored with 5-lead electrocardiogram, oxygen saturation and electroencephalogram (BIS). A peripheral line was established through the left or right upper extremity vein, and blood pressure was measured through left

Table 2. Intraoperative vital signs

Variables	All patients (n=156)			*P* value
	Group P1 (n=60)	Group P2 (n=52)	Group P3 (n=44)	
Heart rate (bpm)	69±4.2	67±6.1	73±5.4	0.458
MAP (mmHg)	73±6.6	70±4.5	68±6.1	0.452
SpO_2 (%)	99±1.2	99±0.8	99±1.1	0.884
Bis	48±2.5	46±1.9	43±4.2	0.377
$ETCO_2$ (mmHg)	31±2.2	33±4.4	32±5.1	0.548

Table 3. Clinic record

Variables	All patients (n=156)			*P* value
	Group P1 (n=60)	Group P2 (n=52)	Group P3 (n=44)	
Number of graft	2 (2~3)	3 (2~4)	3 (2~4)	0.946
Anesthesia duration (hour)	3.5±0.5	4.1±0.7	4.0±0.6	0.645
ICU stay (day)	2.2±0.2	2.0±0.1	2.3±0.2	0.424
Hospital stay (day)	8.3±1.2	7.2±1.3	7.9±1.2	0.197

Table 4. Complication and drugs

Variables	All patients (n=156)			*P* value
	Group P1 (n=60)	Group P2 (n=52)	Group P3 (n=44)	
Premedication				
Morphine (mg/kg)	0.1	0.1	0.1	-
Scopolamine (mg)	0.3	0.3	0.3	-
Positive inotropic drugs				
Dopamine (mg/kg/min)	3.81±0.70	4.02±0.56	3.85±0.53	0.367
Milrinone (mg/kg/min)	0.46±0.05	0.43±0.06	0.44±0.03	0.202
Norepinephrine (ug/kg/min)	0.45±0.07	0.34±0.05	0.38±0.07	0.143

or right radial or brachial artery catheterization. Then, anesthesia was induced with etomidate 0.15-0.3 mg/kg, sufentanil 1.0-1.5 μg/kg, and rocuronium 0.6 mg/kg. Oralintubation was performed. The indices of ventilation were tidal volume 6-8 ml/kg; respiratory rate 12-15 breaths/min, and end-tidal carbon dioxide ($PETCO_2$) 30-40 mmHg. Central venous catheter was placed through the right internal jugular vein or subclavian vein, and a single cavity venous catheter was placed retrograde to the jugular vein bulb through the right internal jugular vein. A pulmonary artery catheter was inserted, when necessary. Anesthesia was maintained with propofol and BIS targeted between 40 and 60. During surgery, sufentanil (0.8-1.2 μg/mL) and cisatracurium (0.2-0.3 mg/kg/h) were continuously pumped. Intra-operative monitoring included electrocardiogram, arterial pressure, pulse oxygen saturation, end-tidal expiratory carbon dioxide, central venous pressure, nasopharyngeal temperature, and urine output. Nasopharyngeal temperature was maintained above 35°C, and systolic blood pressure above 60 mmHg.

OPCABG surgery was performed by the same group of surgeons. Sternotomy was performed at the midline and the number of bypass grafts was 2-4. Intravenous heparin (1.0 mg/kg) was administered and the activated clotting time (ACT) was controlled between 250-350 s and then lowered to 90-120 s after protamine neutralization. At the end of surgery, the patients were transferred to the Intensive Care Unit (ICU) without extubation. Subsequently, follow-up personnel recorded decannulation time, time back to the general ward, and discharge time.

Blood samples

Two ml blood sample was drawn from a catheter retrograde to the jugular vein bulb at the start and end of surgery, and 6, 12, and 24 hours after surgery to measure S100-β protein and NSE.

MMSE

All patients underwent neuropsychological testing using MMSE scale before surgery and at day 1, day 3, day 7, 3 months, and 6 months after surgery.

Statistical analysis

Data were presented as mean ± standard error of mean. The D'Agostino normality test was applied before performing the ANOVA test. Differences among the three groups at each time point were determined by one-way ANOVA followed by Newman-Keuls post hoc test. Differences across the six time points in each

Table 5. MMSE scores

Group	Preoperation	Postoperative 1st day	Postoperative 3rd day	Postoperative 7th day	Postoperative 3rd month	Postoperative 6th month
P1 (n=60)	28.88±0.93	26.12±1.25	27.14±1.35	28.20±2.78	29.38±0.71	29.43±0.53
P2 (n=52)	29.50±0.84	26.50±1.79	27.60±1.95	28.33±1.37	29.50±0.84	29.83±0.41
P3 (n=44)	29.00±0.99	23.13±1.51*,#	25.2±2.21*,#	27.75±0.98	28.38±0.74	29.38±0.75

Results are expressed as mean ± SEM of the whole groups. *P<0.05, ANOVA one-way, post hoc Newman-Keuls test. #P<0.05, ANOVA one-way and Tukey's, multi-comparison test.

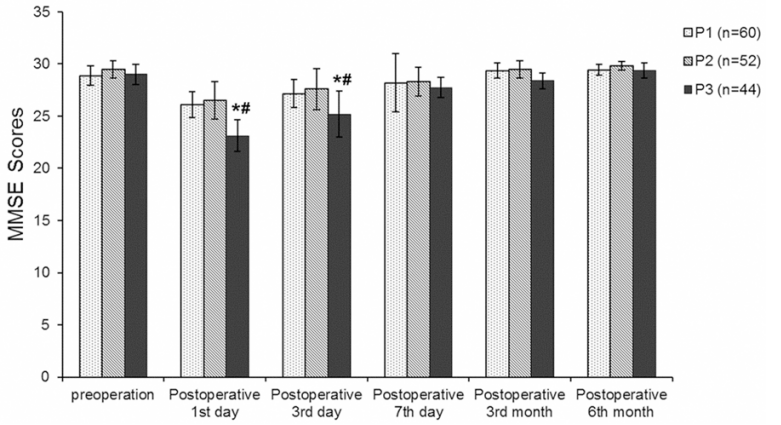

Figure 2. Differences in MMSE scores among the three groups before and after off-pump coronary artery bypass graft surgery. Error bars represent standard error. *P<0.05, ANOVA one-way post hoc Newman-Keuls test. #P<0.05, ANOVA one-way and Tukey's multi-comparison test. P1= propofol TCI 0.5-1.0 μg/ml; P2= propofol TCI 1.1-1.5 μg/ml; P3= propofol TCI 1.6-2.0 μg/ml.

group were assessed by repeated measures one-way ANOVA and Tukey'smulti-comparison test. P<0.05 was considered to be statistically significant.

Results

During the studyperiod, 218 patients were screened, of which 202 matched the criteria. Among the eligible patients, 46 were excluded due to the following reasons: (1) intraoperative finding of malignant arrhythmia; (2) intraoperativeswitched to extracorporeal circulation; (3) intraoperative massive bleeding and blood perfusion; (4) second surgery within short term after operation; (5) lengthy postoperative mechanical ventilation support; (6) lost to follow-up; and (7) death. Finally, 156 patients were enrolled in the study (**Figure 1**).

Analysis of general condition

There were no statistical differencesin epidemiological features, history, ASA classification, and preoperative Euroscore (**Table 1**). There were nosignificant differencesin the heart rate, MAP, SpO_2, BIS value, and $PETCO_2$ among the three groups (**Table 2**), and the number of grafts, anesthesia duration, ICU and hospital stay among the groups (**Table 3**). No differences were found between the groups in premedication and positive inotropic drugs support (**Table 4**). If cardiac adverse events (sudden cardiac death, congestive heart failure, angina, myocardial infarction, arrhythmia) and mortality existed, the patient was excluded.

MMSE scores

There was no significant difference in the preoperative MMSE scores among the three groups. As compared to groups P1 and P2, MMSE scores of group P3 were lower and significantly differenton day 1 and day 3 postoperation (P<0.05) by one-way ANOVA followed by Newman-Keuls post hoc test. The MMSE results of day 1 and day 3 were statistically different from other time points in group P3 (P<0.05) by repeated measures one-way ANOVA and Tukey's multi-comparison test. MMSE scores of patients in groups P1 and P2 were in the normal range during the entire postoperative follow-up period (P>0.05) (**Table 5**; **Figure 2**).

S100-β protein levels

We investigated the differences in S100-β between the three groups after surgery by one-way ANOVA. The average OD value of S100-β in group P3 significantly increased from the end of surgery to 24 hours postoperation (P<0.05), and were higher atthe end of surgery, and 6, 12, and 24 hours post operation in group P3

Table 6. S100-β protein OD value

Group	Post-introduction	Before the end of surgery	Postoperative 6th hour	Postoperative 12th hour	Postoperative 24th hour
P1 (n=60)	0.552±0.062	0.584±0.022#	0.627±0.043#	0.616±0.053#	0.573±0.022
P2 (n=52)	0.569±0.089	0.586±0.036#	0.619±0.080#	0.603±0.017#	0.568±0.027
P3 (n=44)	0.587±0.075	0.626±0.016#,*	0.693±0.078#,*	0.725±0.033#,*	0.650±0.033*

Results are expressed as mean ± SEM of the whole groups. *P<0.05, ANOVA one-way post hoc Newman-Keuls test. #P<0.05, ANOVA one-way and Tukey's multi-comparison test.

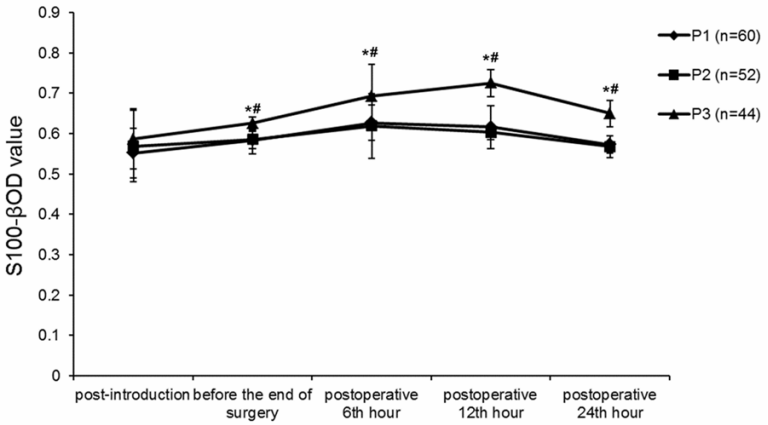

Figure 3. The plasma OD values of S100-β protein.Error bars represent standard error. *P<0.05, ANOVA one-way post hoc Newman-Keuls test. #P<0.05, ANOVA one-way and Tukey's multi-comparison test. P1= propofol TCI 0.5-1.0 μg/ml; P2= propofol TCI 1.1-1.5 μg/ml; P3= propofol TCI 1.6-2.0 μg/ml.

as compared to groups P1 and P2 (P<0.05). The values of group P1 were slightly higher than group P2 postoperation (P>0.05) (**Table 6**; **Figure 3**).

NSE levels

The OD values of NSE increased perioperatively and were statistically different between group P3 and the other two groups at 12 hours post-surgery (P<0.05) (**Table 7**; **Figure 4**).

Discussion

Age, as an independent factor, affects the mental state after anesthesia. This study selects geriatric patients (60-75 years) with coronary heart disease. A study proposes that decreasing age is a risk factor for early POCD [7], and the increasing age is a dominant potential risk factor for POCD, irrespective of gender [8]. Older patients are the most affected with POCD after surgery, based on risk factors and high-risk groups.

There is increasing evidence that long-term or permanent neuronal and neurological changes could occur following administration of anesthetics [9]. High-dose fentanyl is not associated with a difference in the incidence of POCD at 3 or 12 months after surgery. However, low-dose fentanyl is associated with a greater incidence of POCD, one week after surgery [10]. Sufentanil is stable for general anesthesia and has the least adverse effect on hemodynamics [11]. In our study, we use high-dose sufentanil as the analgesic, and findno significant difference amongthe three groups.

The internal jugular vein bulb is the initial part of the internal jugular vein, and can accurately reflect the relationship between cerebral oxygen supply and oxygen consumption. Therefore, we collect internal jugular venous blood to measure the biomarkers. Blood S100-β protein is a sensitive biomarker of blood-brain barrier damage [12]. POCD indeed correlates with the concentrations of peripheral inflammatory markers, particularly IL-6 and S-100β protein [13]. Therefore, S100-β protein content is closely related to the severity of brain damage, and can predict adverse neurological outcome. NSE may be an useful biomarker to identify patients with cognitive performance impairment [14].

Whether a causal relationship existed between propofol dose and occurrence of POCD remains unknown. Although some anesthetics have shown neuroprotective effects in preclinical studies (cell culture systems or animal models of focal or global cerebral ischemia), the evidence in human studies has been inconsistent and controversial [15-18]. Non-sedative doses of propofol does not produce dyskinesia in rats [19]. We analyze why different doses of propofol anesthesia produce different levels of post-

Table 7. NSEOD value

Group	Post-introduction	Before the end of surgery	Postoperative 6th hour	Postoperative 12th hour	Postoperative 24th hour
P1 (n=60)	0.605±0.103	0.654±0.090	0.657±0.107#	0.609±0.100	0.578±0.092
P2 (n=52)	0.585±0.096	0.642±0.088	0.646±0.092#	0.595±0.105	0.565±0.101
P3 (n=44)	0.599±0.102	0.668±0.106	0.734±0.103*,#	0.627±0.093	0.608±0.104

Results are expressed as mean ± SEM of the whole groups. *P<0.05, ANOVA one-way post hoc Newman-Keuls test. #P<0.05, ANOVA one-way and Tukey's multi-comparison test.

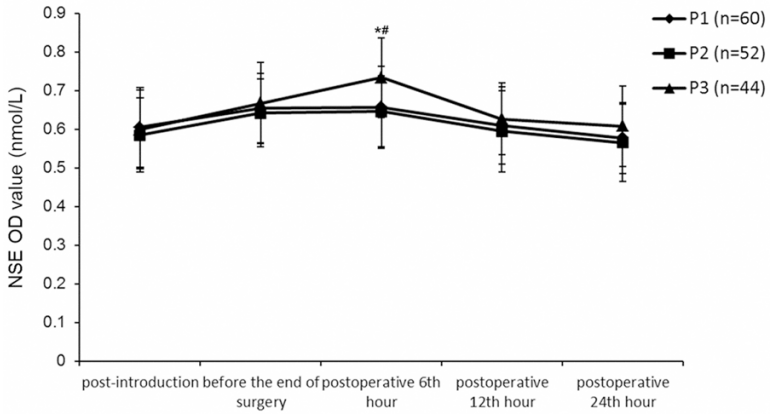

Figure 4. The concentrations of NSE. Error bars represent standard error. *P<0.05, ANOVA one-way post hoc Newman-Keuls test. #P<0.05, ANOVA one-way and Tukey's multi-comparison test. P1= propofol TCI 0.5-1.0 μg/ml; P2= propofol TCI 1.1-1.5 μg/ml; P3= propofol TCI 1.6-2.0 μg/ml.

operative cognitive function in this study, and the reasons maybe associated with the following:

The BIS values of the high-dose propofol group are slightly lower than the low-dose propofol groups during anesthesia. A report confirms the influence of extremely low BIS value on delirium by multivariate analysis [20]. Furthermore, high dose of propofol strengthens the function of GABAA receptors, inhibits synaptic prolonged enhanced expression of hippocampal cells and affects cognitive function. Additionally, an inflammatory response may be involved in the occurrence of POCD [21, 22]. Reasonable combination of sedative and analgesic drugs not only guarantees reduction of cerebral metabolism and blood flow but also hemodynamicstability to reduce the stress response.

The major limitation of the present study is the sample size of each group. Despite the power analysis to calculate the sample size, the effective group size was much smaller due to the inability of patients to perform cognitive tests and several missing values that had to be amended. On the other hand, the differences in the number of dropouts in the study groups have to be interpreted as results of the intervention.

Another limitation is the absence ofa standardizedtest to excludeddelirium as a global cerebral deficit. The CAM-ICU has been a suitable tool to detect hyper-and hypo-active delirium [23].

The patients in both groups receive sedation after operation in the ICU. This interference in the treatment cannot be avoided due to technical reasons.

POCD incidence may correspond with the concentration of propofol during OPCABG surgery.

Disclosure of conflict of interest

None.

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