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Predictive factors of unacceptable movement and motor-evoked potentials during intraoperative neurophysiological monitoring in adult patients undergoing brain surgery
A retrospective study

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Abstract

Motor-evoked potential (MEP) monitoring is an essential monitoring for clinicians to improve outcomes. Although unacceptable movement during MEP is a rare complication but it can lead to terrible results. The aim of this study was to evaluate the risk factors associated with unacceptable movements in patients undergoing brain surgery with MEP monitoring.

We performed a retrospective observational study of patients who underwent brain surgery with MEP monitoring under general anesthesia while using a partial neuromuscular blocker in a tertiary care hospital from January 2014 to August 2017. Unacceptable movement was defined as a condition in which MEP stimulation induced vigorous movement of patient hindered the smooth progress of the operation. We compared the baseline patient characteristics and laboratory results according to unacceptable movements during surgery to identify factors associated with unacceptable movement during MEP monitoring.

768 patients were included in this analysis, and unacceptable movements were observed in 278 patients (36.2%). A multivariate logistic regression analysis revealed that an increase in ionized calcium was associated with the most strongly unpredictable movement during surgery [odds ratio (OR): 1.79, 95% confidence interval (CI): 1.37–2.36, $P < .001$]. In addition, age (OR, 0.98; 95% CI, 0.96–0.99; $P = .001$), male sex (OR, 1.59; 95% CI, 1.09-2.33; $P = .017$), and body mass index (OR, 0.90; 95% CI, 0.86-0.95; $P < 0.0010$) were also associated with unacceptable movement. Serum ionized calcium concentration was the best predictor associated with unacceptable movement with MEP monitoring under general anesthesia.

Serum ionized calcium concentration was the best predictor associated with unacceptable movement with MEP monitoring under general anesthesia.

Abbreviations: BMI = body mass index, CI = confidence interval, MEP = motor-evoked potential, NMB = neuromuscular blocker, OR = odds ratio.

Keywords: Intraoperative complication. Motor-evoked potential, Risk Factors, Train-of-four, Unacceptable movements

1. Introduction

Despite the advances in neurovascular techniques, several complications can occur during brain surgery. Among them, 1 of the most catastrophic complication is a postoperative motor deficit within or adjacent to the motor areas.[1] Motor-evoked potential (MEP) monitoring is an intraoperative method that has been recently introduced to improve the outcomes regarding postoperative motor deficits.[2] MEP monitoring has high diagnostic accuracy of about 90% in predicting postoperative motor deficit.[3] MEP monitoring is a clinically safe and essential

monitoring device when used carefully by experts.[4] However, if unacceptable movements occur, it can cause inadvertently harm to patients.[5,6]

The incidence of unacceptable movements is relatively low.[6] However, the results are so disastrous that they can cause injuries that can require rigid pin fixation of the head, cervical spine injuries, excessive surgical field movement, and deterioration of surgical outcome. Thus, partial neuromuscular blockade is often used to prevent unacceptable patient movement [7] because full omission of the neuromuscular blocker (NMB) may cause unacceptable patient movement. However, the risk factors associated with unacceptable movement remain unclear. If the risk factors are identified in advance, the patient can be kept safe and the surgical results will be improved.

Therefore, this retrospective study evaluated the risk factors associated with unacceptable movement in patients undergoing brain surgery with MEP monitoring under general anesthesia while using a partial NMB.

2. Materials and methods

2.1. Study design and inclusion criteria

This study was approved by the Institutional Review Board of Seoul National University Bundang Hospital (Seongnam-si, South Korea; approval on January, 2018, B-1801-444-102) and was registered at ClinicalTrials.gov (NCT03489785). We retrospectively analyzed electronic medical data collected from consecutive patients with American Society of Anesthesiologists physical status classes 1–2, aged 19–74 years who underwent brain surgery with MEP monitoring under general anesthesia while using a partial NMB at Seoul National University Bundang Hospital from January 2014 to August 2016.

2.2. Anesthesia and MEP monitoring

Surgical and anesthetic procedures were performed identically to our institutional protocol during the data collection period. Anesthesia was induced with propofol (effect-site concentration: 4–6 mg/mL), a continuous infusion of remifentanil (target effect-site concentration-controlled infusion 3 ng/mL), and rocuronium (0.6 mg/kg). A continuous infusion of propofol (effect-site concentration: 3–4 mg/mL) and remifentanil (target effect-site concentration-controlled infusion of 2–3 ng/mL) was maintained. Depth of anesthesia was monitored using a bispectral index score monitor and anesthetic agents were adjusted to keep the bispectral index score at 40-60. The lungs were mechanically ventilated with oxygen and medical air, and adjusted to maintain an end-tidal carbon dioxide tension of 35–40 mmHg. The temperature was measured with an esophageal stethoscope and maintained at least 35 °C.

After endotracheal intubation, no additional NMB was administered to obtain the baseline MEP signals. After obtaining the baseline signals, a continuous infusion of rocuronium (0.3 mg/kg/h) was started to achieve partial muscle relaxation of train-of-four (TOF) of 2-3 according to our institutional protocol. When an unacceptable movement was detected during surgery, the neurosurgeon informed the anesthesiologist and MEP specialist and recorded the event on the anesthesia record. Subsequently, the continuous infusion rate of rocuronium was increased by 0.1 mg/kg/h, which was also recorded on the anesthesia record. In addition, to avoid movement in the microsurgical field during a critical surgical procedure, the stimulus intensity and evoked potential responses were checked prior to the major surgical procedure.

MEPs were recorded using 32-channel and 16-channel Xltek Protektor. During MEP measurement, MEP is triggered using a voltage stimulus of about 100 to 400 V to prevent impulses from being degraded by resistance or spreading around. MEPs were recorded in 2 upper limbs and 2 lower limb muscles: Abductor policis brevis, Abductor digiti quinti, Abductor policis brevis, and Abductor digiti quinti. Most of the motor cortex had to be excited to record all of the upper and lower muscles. Thus, by controlling the stimulus intensity to the extent that stimulation is not transmitted to the opposite cerebral hemisphere, the stimulus is localized to 1 cerebral hemisphere. Although it is difficult to verify the voltage applied during the actual surgery time through the voltmeter, by using equipment proven to be reproducible and accurate, we kept the electrical stimulation and measurement consistent during surgery. During the quality control, the voltage generated by the equipment was measured using a quality control voltmeter to verify that the desired voltage is applied correctly. We standardized the equipment by stimulating the accurately measured Voltage to see if the amplitude is implemented in the equipment. During surgery, MEP records were conducted at 10ms/division. Amplification is μV and mV/division, and our hospital increases or decreases the amplitude depending on the size of the amplitude to facilitate monitoring as needed during surgery from 70 μV to 5 mV/division. All test results were digitized and stored in each individual's medical records. Neurosurgeons, anesthesiologists and MEP specialists of our institution have discussed the ideal intensity of MEP stimulation and rate of rocuronium infusion to establish an adequate degree of MEP monitoring to reduce false negatives and false positives. After obtaining baseline MEP data immediately after induction of anesthesia, rocuronium infusion of 0.3 mg/kg/h is initially started. If the patient's movement to the stimulus was too rough or if an unexpected movement is observed during the monitoring, the rate of infusion of rocuronium is increased by 0.1 mg/kg/h. On the contrary, if MEP record for stimulation was too small, we reduced the infusion rate of rocuronium by 0.1 mg/kg/h.

2.3. Data collection

We collected demographic data retrospectively, including age, sex, height, weight, body mass index (BMI, kg/m2), surgical procedure, position for surgery, duration of anesthesia and surgery, American Society of Anesthesiologists classification, preoperative comorbidities (e.g., hypertension, diabetes mellitus, neurological disease, chronic pulmonary disease), preoperative anti-convulsant usage, intraoperative propofol dosage (mg), and rocuronium dosage (mg). Laboratory data immediately after induction of anesthesia were collected from an arterial blood gas test and included hemoglobin (g/dL), sodium (mmol/L), potassium (mmol/L), glucose (mg/dL), ionized calcium (mmol/L), ionized magnesium (mmol/L), and lactate (mmol/L).

We excluded cases that intraoperative rocuronium infusion was not continuously given or if there was a lack of medical records. Also adolescents under the age of 19 were excluded because they may have different responses to muscle relaxants.[8]

The primary outcome of this study was to uncover the risk factors associated with unacceptable movements during brain surgery with MEP monitoring under general anesthesia. To find out, we retrospectively divided patients into a groups: patients had been observed an unacceptable movement (movement

group) and patients had not been observed an unacceptable movement (no movement group). An unacceptable movement was defined as a condition in which the patient's vigorous movement hindered the smooth progress of the operation due to MEP stimulation, a movement that is unpredictable or a movement is thought to be dangerous for medical staff to judge. And it was judged to be meaningful only when there was an anesthetic record stating that the doctor complained about unacceptable movements, or the anesthesiologist declared that the movement was too large at the time of MEP, and an anesthetic record that indicated increased the rate of continuous infusion of neuromuscular relaxant. Only these cases were counted and included.

2.4. Statistical analysis

We compared the baseline patient characteristics and laboratory results between the 2 groups. The statistical values in analysis are either mean (standard deviation) or number (percent). The t-test for continuous variables and the chi-squared test for categorical variables were used to compare the 2 groups. A univariate logistic regression analysis was performed for the binary dependent variable (unacceptable movement) according to all variables. All variables with $P < .1$ in the univariate model were included in final multivariate logistic regression analysis. The results of the logistic regression analysis are presented as odds ratios (ORs) and 95% confidence intervals (CIs). All analyses were performed using IBM SPSS Statistics version 21.0 software (SPSS Inc., Chicago, IL), and a P-value $<.05$ was considered statistically significant.

3. Results

A total of 1789 patients underwent brain surgery with intraoperative monitoring from January 2014 to August 2016. Among them, 1010 patients were excluded for not receiving a continuous intraoperative rocuronium infusion, 1 patient due to age younger than 19 years, and 7 patients due to incomplete or missing medical records. Thus, 768 patients were included in the analysis, and unacceptable movements were observed in 278 patients (36.2%) (Fig. 1). The baseline characteristics of the 2 patient groups, assorted according to the presence of unacceptable movements, are showed in Table 1. Laboratory data immediately after induction of anesthesia in the 2 patient groups are presented in Table 2.

Table 3 shows the results of the univariate logistic regression analysis for the unacceptable movement during surgery according to all variables. The results of the final multivariate logistic regression analysis are presented in Table 4. An increase in ionized calcium was associated with an increase in unacceptable movements during surgery (OR: 1.79, 95% CI: 1.37–2.36, $<.001$). In addition, age (OR: 0.98, 95% CI: 0.96–0.99, $P=.001$), male sex (OR: 1.59, 95% CI: 1.09–2.33, $P=.017$), and BMI (OR: 0.90, 95% CI: 0.86–0.95, $P<0.001$), were also associated with unacceptable movements during surgery.

4. Discussion

As far as our knowledge, our study is the first study that tried to reveal the predictors of an unacceptable movement during MEP. This retrospective study found that age, male, BMI, and ionized calcium could be independent risk factors for unacceptable movement in patients undergoing brain surgery with MEP monitoring under general anesthesia while using a partial NMB.
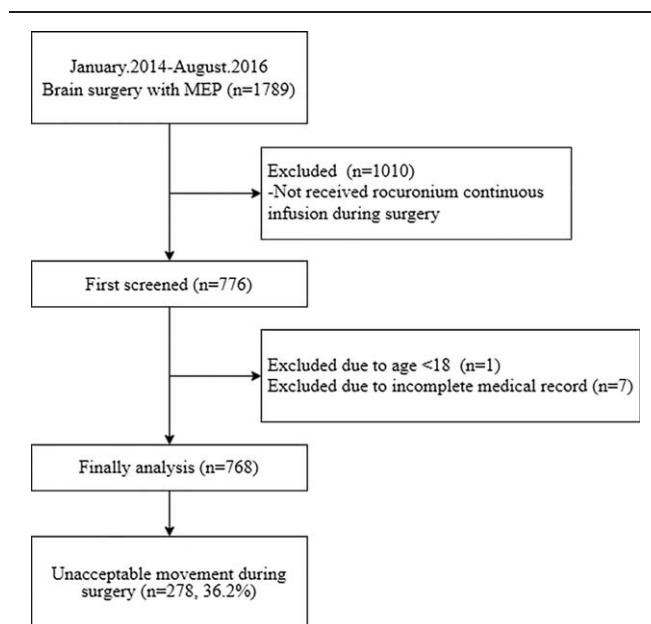

Figure 1. Flow chart of patient enrollment.

MEP monitoring is a reliable method that improves surgical outcomes of brain tumor surgeries,[9] cerebral aneurysm clippings,[3] and cerebrovascular surgeries, such as endarterectomy.[10] To strengthen the accuracy of the MEP monitoring, it is best not to use an NMB due to its false negative results.[7] Nonetheless, some

Table 1

Comparison of baseline patient characteristics according to unacceptable movements during surgery.

Variable	No movement group (n=490, 63.8%)	Movement group (n=278, 36.2%)	P-value
Age, yr	56.5 (11.6)	52.2 (12.1)	<.001
Sex: male	162 (33.1%)	127 (45.7%)	.001
Body mass index, kg/m^2	24.5 (3.4)	23.7 (3.3)	.001
Preoperative comorbidities			
ASA classification			.132
1	160 (32.7%)	99 (35.6%)	
2	303 (61.8%)	172 (61.9%)	
Hypertension	214 (43.8%)	103 (37.1%)	.070
Diabette mellitus	52 (10.6%)	19 (6.8%)	.082
Chronic pulmonary disease	12 (2.4%)	10 (3.6%)	.359
Neurologic disease	17 (3.5%)	2 (0.7%)	.018
Anti-convulsant user	461 (94.1%)	267 (96.0%)	.240
Duration of surgery, min	266.3 (106.1)	281.3 (106.0)	.060
Duration of anesthesia, min	338.3 (114.2)	351.5 (117.9)	.130
Type of surgery			.499
Vascular surgery	352 (71.8%)	206 (74.1%)	
Brain tumor	138 (28.2%)	72 (25.9%)	
Position for surgery			.778
Supine	461 (94.5%)	263 (94.9%)	
Prone or Lateral	27 (5.5%)	14 (5.1%)	
Intraoperative propofol dosage, mg	316.3 (115.2)	326.1 (132.2)	.020
Intraoperative rocuronium dosage, mg	230.9 (65.6)	236.1 (63.0)	.285

Values are mean (standard deviation) or number (percent).
ASA = American Society of Anesthesiologists.

Table 2

Laboratory data immediately after induction of anesthesia of total enrolled patients.

	No movement group (n = 490, 63.8%)	Movement group (n = 278, 36.2%)	P-value
Ionized calcium, mmol/L	1.12 (0.59)	1.14 (0.60)	<.001
Ionized magnesium, mmol/L	0.46 (0.52)	0.47 (0.52)	.147
pH	7.40 (0.38)	7.40 (0.35)	.342
pCO2,mmHg	36.40 (4.29)	36.47 (4.19)	.836
pO2,mmHg	231.77 (80.85)	241.30 (74.40)	.106
Serum Sodium, mmol/L	138.47 (2.57)	138.33 (2.39)	.442
Serum Potassium, mmol/L	3.68 (0.40)	3.73 (0.38)	.062
Serum Hemoglobin, g/dl	11.89 (1.18)	12.12 (1.21)	.011
Serum Glucose, mg/dl	109.34 (28.16)	106.95 (23.02)	.255
Serum Lactate, mmol/L	1.21 (0.63)	1.16 (0.63)	.352

Values are mean (standard deviation).
pCO2 = partial pressure of carbon dioxide; pO2 = partial pressure of oxygen.

institutions recommend the intraoperative infusion of partial NMB during MEP monitoring, as unacceptable movements cause fatal injuries.[11,12] In previous studies, the incidence rates of unacceptable movements during MEP monitoring with a partial NMB or no NMB were 3.2% to 10%. [6,7,13,14] However, in this study, the

Table 3

Univariable logistic regression analysis for unacceptable movement.

Variable	Univariable model OR (95% CI)	P-value
Age, year	0.97 (0.96, 0.98)	<.001
Sex: male	1.70 (1.26, 2.30)	.001
Body mass index, kg/m^2	0.93 (0.89, 0.97)	.001
ASA classification		
1	1	
2	0.92 (0.67, 1.25)	.589
Hypertension	0.76 (0.56, 1.02)	.070
Diabette mellitus	0.62 (0.36, 1.07)	.085
Chronic pulmonary disease	1.49 (0.63, 3.49)	.362
Neurologic disease	0.20 (0.05, 0.88)	.033
Anti-convulsant user	1.53 (0.75, 3.11)	.243
Duration of surgery, hour	1.08 (1.00, 1.17)	.061
Type of surgery		
Vascular surgery	1	
Brain tumor	0.89 (0.64, 1.24)	.499
Position for surgery		
Supine	1	
Prone or Lateral	0.91 (0.47, 1.76)	.778
Intraoperative propofol dosage, per 10 mg	1.01 (1.00, 1.02)	.285
Intraoperative rocuronium dosage, per 10 mg	1.01 (0.99, 1.04)	.285
Ionized calcium, per 0.1 mmol/L	1.85 (1.43, 2.40)	<.001
Ionized magnesium, per 0.1 mmol/L	1.23 (0.93, 1.63)	.148
pH	7.14 (0.13, 409.45)	.341
pCO2,mm Hg	1.00 (1.00, 1.04)	.836
pO2,mm Hg	1.00 (1.00, 1.00)	.107
Serum Sodium, mmol/L	0.98 (0.92, 1.04)	.442
Serum Potassium, mmol/L	1.42 (0.97, 2.08)	.071
Serum hemoglobin, g/dL	1.18 (1.04, 1.34)	.012
Serum Glucose, mg/dL	1.00 (0.99, 1.00)	.365
Serum Lactate, mmol/L	0.90 (0.70, 1.15)	.390

All variables of P < .1 were included in final mutivariable logistc regression model.
ASA = American Society of Anesthesiologists; pCO2 = partial pressure of carbon dioxide; pO2 = partial pressure of oxygen.

Table 4

Multivariable logistic regression analysis for unacceptable movement.

Variable	Multivariable model OR (95% CI)	P-value
Age, year	0.98 (0.96, 0.99)	.001
Sex: male	1.59 (1.09, 2.33)	.017
Body mass index, kg/m^2	0.90 (0.86, 0.95)	<.001
ASA classification		
1	1	
2	0.93 (0.67, 1.30)	.666
Hypertension	1.10 (0.77, 1.55)	.613
Diabette mellitus	0.68 (0.38, 1.24)	.214
Neurologic disease	0.23 (0.05, 1.02)	.053
Duration of surgery, h	1.05 (0.96, 1.15)	.253
Ionized calcium, per 0.1 mmol/L	1.79 (1.37, 2.36)	<.001
Serum Potassium, mmol/L	1.04 (0.68, 1.58)	.865
Serum Hemoglobin, g/dL	1.08 (0.91, 1.27)	.383

All variables of P < .1 in univariable model were included in final mutivariable logistc regression model.
ASA = American Society of Anesthesiologists.

incidence of unacceptable movement was about 38%. This was because we defined unacceptable movements with wider range of movements, including movements that could be considered little dangerous. For example, previous studies included only nociception-induced movements such as coughing or limb movements, and large head movements observed by both surgeons and anesthesiologists. In this study, even if there was no movement of the head, the case that the surgical field seen through the microscope by the operator was greatly shaken due to the MEP was included as an unacceptable movement. Since the usual incidence rate of unacceptable movements is relatively low, we thought that it would be easier to find the risk factors if we included wider range of movements as a definition.

In this study, no additional NMB was used after the 0.6 mg/kg of rocuronium for intubation until the baseline signals of MEP was obtained. Then, continuous infusion of rocuronium (0.3 mg/kg/hr) was initiated for partial neuromuscular blockade. The infusion rate was adjusted depending on the occurrence of an unacceptable movement. This allowed us to maintain a consistent degree of neuromuscular block, train-of-4 (TOF) 2/4–3/4 in almost all enrolled patients. According to previous studies,[7,10,15–20] appropriate degree of partial neuromuscular blockade has been reported variously from first evoked response of TOF between 5% and 50% of baseline or 1 or 2 twitches in TOF electrical stimulation to 0.5 twitch height of the second evoked response of TOF stimulation compared with the baseline control twitch. Compared with previous studies above, degree of partial neuromuscular block in our study was considered to have maintained the middle degree of the block presented above. In addition, although the comparison of SSEP and MEP is very limited, the degree of partial neuromuscular blocking used in this study did not seem to negatively affect the specificity or sensitivity based on our institute SSEP data.[21]

In this study, ionized calcium was the best predictor of unacceptable movement during MEP monitoring in patients undergoing brain surgery. This is because calcium has numerous regulatory functions, particularly in the neuromuscular junction, where it plays a significant role which is to trigger neuromuscular transmission.[22] Calcium channels are present in both presynaptic and postsynaptic membranes. Action potentials arriving at the presynaptic membrane open calcium channels, causing influx of calcium ions. Calcium triggers the release of neurotransmitters,

such as acetylcholine, from synaptic vesicles into the synaptic cleft. The neurotransmitter molecules bind to a membrane-bound receptor on the postsynaptic membrane, and triggers a postsynaptic response. The postsynaptic responses are excitatory or inhibitory. Receptors coupled to sodium or calcium channels are excitatory, whereas receptors coupled to chloride or potassium channels are inhibitory.[23–25] If the neurotransmitter binds to a receptor coupled to a calcium channel, it produces a depolarization of the postsynaptic membrane.

Several studies have investigated the overall effect of ionized calcium on neuromuscular transmission and neuromuscular blockade. In previous in vivo animal and in vitro experiments, calcium promoted desensitization of a depolarizing agent,[26] and reduced the affinity of the receptor for tubocurarine and pancuronium in the postsynaptic space.[27] Patients with hypercalcemia due to hyperparathyroidism show an upward tendency to increase the requirement for non-depolarizing muscle relaxants.[28] In addition, calcium coadministered with neostigmine for neuromuscular recovery enhances neuromuscular recovery from nondepolarizing neuromuscular blockade.[29] Overall, ionized calcium reverses neuromuscular blockade and with relatively high concentration, ionized calcium alters the effect of neuromuscular blocking agents and neuromuscular transmission. Therefore, it is thought that ionized calcium can affect the results of MEP monitoring or cause a jerky dangerous response to MEP stimulation despite a partial neuromuscular blockade.

In addition, the statistical results showed that age, male, and BMI could be predictors of unacceptable movements. This result is thought to be caused by the fact that the amount or strength of muscles varies depending on age, males, and BMI and the amount or strength of muscles affects the amplitude of movement. The muscle strength is proportional to the muscle mass, and men have larger type I fiber areas and mean fiber areas than women.[30] Furthermore, the muscle mass decreases with age, and people with high BMI will have limited physical activity, which will relatively tend to atrophy muscle fibers and increase fat tissue.[31] With larger muscle mass or muscle size, the movement could be better captured by the observer and movement strength and amplitude would be greater. These may have influenced to increase the incidence of dangerous movement.

This study had a few limitations. Firstly, because of the retrospective nature of study design, we could not fully exclude selection bias. Particularly observing movements may involve personal bias. Secondly, our study was conducted in a single center, which limits generalizability of the findings. Thirdly, naturally the etiology of the unacceptable movement is multifactorial and complex and the definition was broad and vague. Therefore, there might have been some unknown confounding factors the results of this study. Lastly, in our institution, we performed an arterial blood gas analysis test including electrolytes, glucose, and lactate in all patients to check preoperative baseline state immediately after induction of anesthesia. In addition, additional tests are conducted every 1 to 2 hours during surgery, or whenever necessary such as sudden massive bleeding. However, since this is a retrospective study, not all patients had blood test results immediately after unacceptable movement observed. Only the test results immediately after induction of anesthesia were collected, and other intraoperative test results were not included. In the future, if prospective and randomized studies comparing ionized calcium levels before and after unacceptable movement will conduct, clarify the relationship between ionized calcium levels and unacceptable movement will be cleared.

In conclusion, although it was a retrospective study, this was the first study to try to reveal the predictors of unacceptable movements during MEP monitoring, and our results showed that higher ionized calcium level could be an independent risk factor for unacceptable movements in patients undergoing brain surgery with MEP monitoring under general anesthesia while using a partial NMB. Furthermore, prospective and randomized study about unacceptable movement during MEP monitoring and the effect of calcium on MEP will be needed. We hope that this study will be helpful for future prospective and randomized studies to clarify the risk factors of unacceptable movements, as well as on the effects of calcium on MEP.

Author contributions

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