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ORIGINAL ARTICLE

Comparison between hemodynamic effects of propofol and thiopental during general anesthesia induction with remifentanil infusion: a double-blind, age-stratified, randomized study

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Abstract

Purpose Propofol is commonly used with remifentanil for induction of general anesthesia (GA); however, it often leads to hypotension. Intraoperative hypotension is associated with postoperative adverse events. By contrast, thiopental has less negative inotropic effects on hemodynamics compared to propofol, which could be suitable to prevent hypotension during GA induction. In the present age-stratified, randomized, assessor-blinded study, using the ClearSight® system, we compared the hemodynamic effects of propofol and thiopental during GA induction under remifentanil infusion in non-cardiac surgery.

Methods Patients were divided into young (20–40 year), middle (41–70 year), and elderly (> 70 year) groups ($n = 20$, each group). General anesthesia was induced with remifentanil 0.3 μg/kg/min, followed by propofol (2.0, 1.5, and 1.2 mg/kg) or thiopental (5.0, 4.0, and 3.0 mg/kg) in the young, middle, and elderly groups, respectively. The primary outcome was the difference in the decrease in mean arterial blood pressure between patients receiving propofol and thiopental in each age group. The secondary outcomes included other hemodynamic parameters and minimal bispectral index values measured up to 10 min after tracheal intubation.

Results The decrease in mean arterial blood pressure was greater in patients receiving propofol than those receiving thiopental (− 45.4 vs − 26.6 mmHg and − 45.7 vs − 28.9 mmHg, $P = 0.003$ and 0.007, respectively), whereas no significant difference was observed in the young age group ($P = 0.96$).

Conclusions Thiopental is a more suitable agent than propofol for avoiding hypotension during GA induction under remifentanil infusion in the middle and elderly patients.

Keywords Propofol · Thiopental · ClearSight® system

Introduction

General anesthesia (GA) is most commonly induced with hypnotic, analgesic (e.g. opioids), and neuromuscular blocking agents. The administration of hypnotics, however, often causes hypotension during GA induction, especially when potent analgesic agents such as propofol are co-administered [1]. A previous report states that the incidence of severe hypotension during GA induction is 9% in non-cardiac surgeries [2]. Moreover, intraoperative hypotension, resulting from even a slight decrease in blood pressure, is associated with postoperative complications: acute kidney injury, major adverse cardiac events, and stroke, among others [3–6]. The stabilization of hemodynamics during surgery under GA is critical, especially for elderly patients because of their relatively low cardiopulmonary reserve [7]. Although various techniques of GA induction for maintaining stable hemodynamics have been proposed, no definitive protocol has been developed so far.

Propofol is currently the most commonly used hypnotic agent for GA induction; however, the administration of 2–2.5 mg/kg propofol leads to a 25–40% decrease in systolic blood pressure and cardiac output [8]. Thiopental has less negative inotropic effect, with a smaller degree of

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suppression of sympathetic activity in response to tracheal intubation compared with propofol [9]. Remifentanil is a relatively new opioid with a higher potency in analgesia and in suppressing stress responses to tracheal intubation than fentanyl [10]. It is quickly eliminated with a short duration of action and is a commonly used opioid during GA induction. Therefore, GA induction with propofol and remifentanil may cause profound hypotension in patients with predisposing factors such as advanced age, whereas the combination of thiopental and remifentanil may have less risk.

At present, there are no reports comparing the hemodynamic effects of propofol with those of thiopental during GA induction under remifentanil infusion in different age groups. Thus, the present age-stratified, randomized, assessor-blinded study was conducted to compare the hemodynamics between propofol and thiopental during GA induction under remifentanil infusion using the ClearSight® system (Edwards Lifesciences Corporation, Irvine, CA, USA), which can non-invasively measure various hemodynamic parameters. Our primary endpoint was the difference in the decrease in MAP, which was defined as the difference between MAP measured in the ward and the minimal MAP during the study protocol, resulting from the use of the two hypnotic agents during GA induction under remifentanil infusion.

Materials and methods

This study was approved by the Osaka City University Hospital Research Ethics Review Board (no. 20367, March 31, 2017), registered with the University Hospital Medical Information Network Clinical Trials Registry (no. UMIN000026922, April 10, 2017), and performed in accordance with the Declaration of Helsinki. After obtaining written informed consent, a total of 72 patients aged 20 year or older with ASA physical status 1 or 2 and scheduled to undergo non-cardiac surgery were enrolled. The patients with the following characteristics were excluded: a predicted difficult airway, concomitant use of epidural anesthesia, a body mass index ≥ 30 kg/m^2, atrial fibrillation, bronchial asthma, regular use of hypnotic medication, a history of drug abuse, or porphyria.

Three groups were created and stratified according to the patients' ages: 'young' group (20–40 years old, $n=24$), 'middle' group (41–70 years old, $n=24$), and 'elderly' group (over 70 years old, $n=24$). The patients were then randomly assigned to one of two subgroups in each age group according to the anesthetic used for GA induction: propofol group or thiopental group. Anesthesia was induced by anesthetists who were not related to this study.

Medications used by the patients before the operation were continued except for angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and antihyperglycemic agents. On the other hand, no premedication was used. All patients received Ringer solution at 10 ml/min throughout the study. Further, electrocardiography, non-invasive blood pressure measurements, pulse oximetry, capnography, measurement of bispectral index (BIS), and monitoring using the ClearSight® system were performed. Simultaneously, preoxygenation (pure oxygen 6 l/min) and the infusion of remifentanil at 0.3 μg/kg/min were started. Five minutes after that, propofol (2.0, 1.5, and 1.2 mg/kg) or thiopental (5.0, 4.0, and 3.0 mg/kg) was administered over 30 s in young, middle and elderly patients, respectively. Additionally, rocuronium 0.8 mg/kg was administered to facilitate tracheal intubation, and the administration of sevoflurane at 1.5% was started after the patients lost consciousness. Tracheal intubation was performed with direct laryngoscopes. After tracheal intubation, the lungs were mechanically ventilated with an inspired oxygen concentration of 40% in the air to maintain the end-tidal CO_2 between 35 and 40 mmHg with a fresh gas flow of 6 l/min. Anesthesia was maintained with sevoflurane (1.5% end-tidal) and remifentanil 0.1 μg/kg/min, and the procedures were not begun until all necessary parameters were measured (Fig. 1).

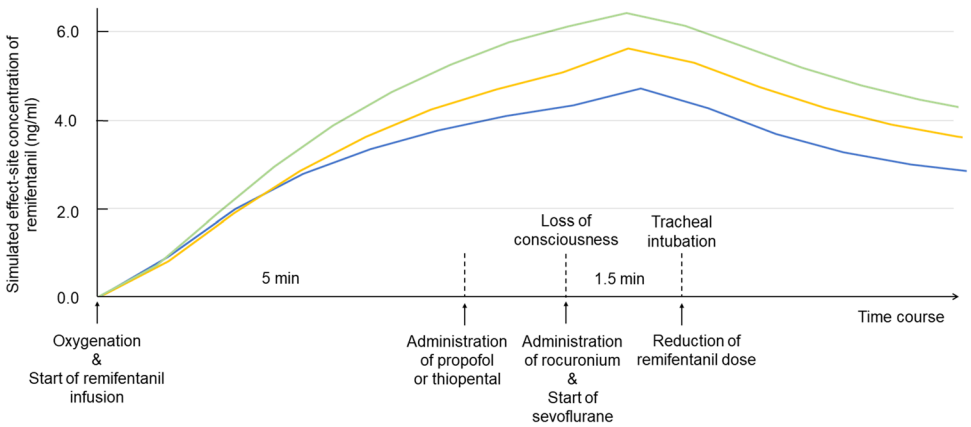

Fig. 1 Time course and the simulated effect-site concentrations of remifentanil in the young (blue line), middle (yellow line), and elderly (green line) patients. The horizontal axis indicates the time course of the study protocol and the vertical axis indicates the effect-site concentration of remifentanil

Hypotension (MAP < 55 mmHg over 2.5 min) was treated with the administration of ephedrine 5 mg or phenylephrine 50 μg at the discretion of the anesthesiologist.

Hemodynamic parameters were measured at the following time points: before GA induction (T0), just before tracheal intubation (T1), at tracheal intubation (T2), and 1–10 min after tracheal intubation (T3–T12) by the minute. The heart rate (HR), systolic arterial blood pressure (SAP), MAP, diastolic arterial blood pressure (DAP), cardiac index (CI), stroke volume index (SVI), systemic vascular resistance index (SVRI), and stroke volume variation (SVV) were measured using the ClearSight® system. The baseline blood pressure data were obtained from the ward medical records. The number of times vasopressors were used was also recorded. The minimal BIS values during the study protocols were obtained from the electronic anesthesia records. The effect-site remifentanil concentrations simulated by the Minto pharmacokinetic-pharmacodynamic model at tracheal intubation were also recorded.

Statistical analysis was performed with SigmaPlot (ver. 13.00, Systat Software, Inc., San Jose, California, USA) and StatFlex (ver. 6.0, Artech. Co., Ltd, Osaka, Japan). We conducted a preliminary study involving six patients with a mean age of 57.7 using the same protocol and found that MAP decrease caused by propofol was 33.1 ± 11.5 mmHg. To detect a 20 mmHg difference in MAP with a power of 0.80 and a type 1 error protection of 0.05, the sample size was calculated to be 10 for each group. An analysis of variance and Fisher's exact test were used to compare numerical and categorical data of the patient characteristics among the groups. After a normal distribution and an equal variance were confirmed with the Shapiro–Wilk and the Brown–Forsythe tests, respectively, a two-way ANOVA was used to compare MAP decrease among the groups. The Bonferroni *t* test was performed as a post hoc analysis. The hemodynamic parameters were analyzed with a split-plot design repeated-measures ANOVA. A *P* value < 0.05 was considered to indicate a significant difference.

Results

Of the 72 patients recruited, 6 declined to participate and the remaining 66 patients (20, 22, and 24 in the young, middle, and elderly groups, respectively) received random allocation. After 6 patients were excluded due to measuring errors, the remaining 60 patients ($n = 10$ in each group) were analyzed (Fig. 2). The patients' demographic data for the two subgroups and for each age group were similar (Table 1). Since two-way ANOVA indicated the possibility of GA agent × age interaction ($P = 0.067$), a post-hoc analysis was conducted. The post-hoc analysis with the Bonferroni *t* test unveiled that, in the middle and elderly groups, the MAP decrease was greater in the propofol group than in the thiopental group (− 45.4

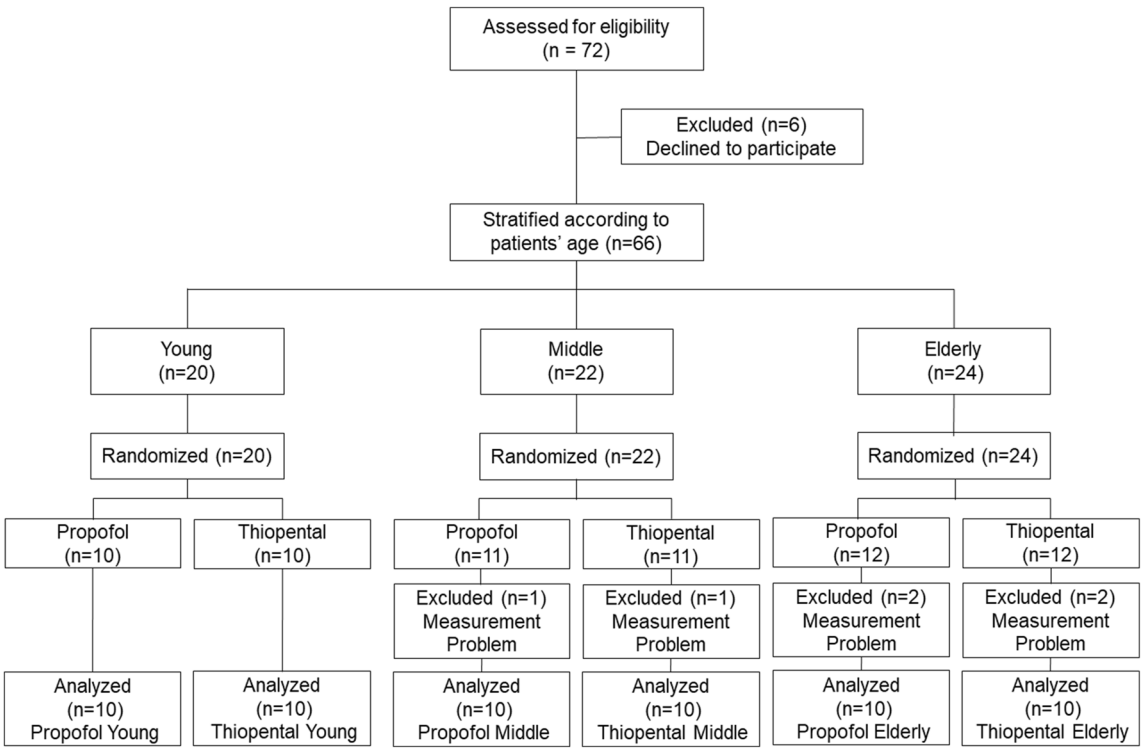

Fig. 2 CONSORT flowchart of patient recruitment

Table 1 Demographic data

	Propofol	Thiopental
Age, years		
All	56 (21)	54 (20)
Young	29 (7)	30 (7)
Middle	63 (7)	58 (10)
Elderly	76 (4)	75 (4)
Sex; male/female		
All	12/18	8/22
Young	4/6	2/8
Middle	4/6	3/7
Elderly	4/6	5/5
Height, cm		
All	157.5 (10.3)	158.3 (9.9)
Young	160.7 (9.4)	163.7 (8.1)
Middle	159.6 (10.8)	153.4 (8.3)
Elderly	152.1 (9.5)	157.7 (11.0)
Weight, kg		
All	54.7 (10.1)	57.6 (9.5)
Young	54.9 (12.7)	61.6 (10.9)
Middle	54.9 (9.1)	53.0 (8.5)
Elderly	54.4 (9.1)	58.2 (7.8)
BMI, kg/m^2		
All	22.0 (3.0)	22.9 (2.6)
Young	21.0 (3.2)	22.9 (2.9)
Middle	21.5 (3.0)	22.5 (2.8)
Elderly	23.4 (2.2)	23.4 (2.3)
ASA physical status; 1/2		
All	7/23	8/22
Young	5/5	5/5
Middle	1/9	4/6
Elderly	1/9	0/10

Values are the number of patients or the mean (SD) of ten patients in the young, middle, and elderly groups. The average of all age groups ($n=30$) is indicated as "all"

vs − 26.6 mmHg, − 45.7 vs − 28.9 mmHg, $P=0.003$ and 0.007, respectively); no significant difference was observed in the young group ($P=0.96$, Table 2). In the split-plot design repeated-measures ANOVA for the hemodynamic changes in the young group, the HR, SAP, MAP, DAP, CI, SVI, SVV, and SVRI were all comparable between the two GA agent subgroups, and there were no GA agent × time course interactions in these parameters. However, even though there was no significant difference between the two GA agent subgroups, there were significant GA agent × time course interactions in the SVI of the middle group and in the HR, SAP, MAP, DAP, and CI of the elderly group (Table 3). There was a trend, although not a significant one, toward a lower SVRI in the propofol group compared to the thiopental group in the elderly age group throughout the time course ($P=0.083$) (Fig. S1).

Table 2 MAP decrease, number of vasopressor bolus doses, minimal BIS, and C_{Remi}

	Propofol	Thiopental	*P* value
MAP decrease, mmHg			
All	36 (19)	24 (14)	0.068[a]
Young	16 (12)	16 (12)	0.96[b]
Middle	45 (19)	27 (15)	0.003[b]
Elderly	46 (6)	29 (14)	0.007[b]
Number of cases needing vasopressors			
All	7/30 (E 7, P 1)	4/30 (E 4, P 0)	0.32
Young	0/10 (E 0, P 0)	0/10 (E 0, P 0)	1.0
Middle	1/10 (E 1, P 0)	2/10 (E 2, P 0)	0.53
Elderly	6/10 (E 6, P 1)	2/10 (E 2, P 0)	0.07
Minimal BIS			
All	44 (9)	47 (12)	0.333[a]
Young	40 (9)	37 (11)	0.422[b]
Middle	49 (9)	49 (9)	0.981[b]
Elderly	44 (9)	54 (7)	0.016[b]
C_{Remi}, ng/ml			
All	5.5 (1.1)	5.6 (0.9)	0.567[a]
Young	4.4 (0.9)	4.9 (0.6)	0.106[b]
Middle	5.7 (0.6)	5.4 (0.6)	0.429[b]
Elderly	6.4 (0.8)	6.5 (0.7)	0.879[b]

Values are the number of patients or the mean (SD) of 10 patients in the young, middle, and elderly groups. The average of all age groups ($n=30$) is indicated as "all"

C_{Remi} simulated concentration of remifentanil, *E* ephedrine, *P* phenylephrine

[a]*P* value in comparison between the six groups in two-way ANOVA

[b]*P* value in comparison between the two groups in each age group in Bonferroni *t* test

Although patients in the propofol group in the elderly group were administered a vasopressor more often than the patients in the thiopental group, there was no significant difference among any of the age groups in the number times the vasopressor was used. The minimal BIS value was significantly lower in the propofol group than in the thiopental group in the elderly age group ($P=0.016$). Meanwhile, there was no significant difference in the minimal BIS values between the two GA agent subgroups in the middle and young age groups. The effect-site remifentanil concentrations simulated by the Minto model at tracheal intubation were not significantly different between the two GA agent subgroups in each age group (Fig. 1).

Discussion

In the present study, we found that the degree of decrease in MAP was greater with propofol than with thiopental during GA induction under remifentanil infusion in the middle and elderly patients. Our results were basically

Table 3 Comparison of hemodynamic parameters

Time	Young			Middle			Elderly		
	GA	Time	GA × time	GA	Time	GA × time	GA	Time	GA × time
HR, beat/min	0.82	< 0.001	0.92	0.65	< 0.001	0.84	0.97	< 0.001	0.021
SAP, mmHg	0.075	< 0.001	0.80	0.12	< 0.001	0.66	0.30	< 0.001	< 0.001
MAP, mmHg	0.23	< 0.001	0.97	0.25	< 0.001	0.83	0.18	< 0.001	< 0.001
DAP, mmHg	0.53	< 0.001	0.98	0.54	< 0.001	0.72	0.36	< 0.001	< 0.001
CI, l/min/m^2	0.71	< 0.001	0.84	0.46	< 0.001	0.16	0.79	< 0.001	0.0045
SVI, ml/m^2	0.61	0.18	0.85	0.65	< 0.001	0.002	0.81	< 0.001	0.20
SVRI, dyne s m^2/cm^5	0.93	< 0.001	0.98	0.89	< 0.001	0.18	0.083	0.14	0.33
SVV, %	0.10	< 0.001	0.41	0.28	< 0.001	0.45	0.96	< 0.001	0.49

Values are all *P* values of GA group differences, time-course differences, and GA group × time-course interactions

GA general anesthesia, *SAP* systolic arterial blood pressure, *MAP* mean arterial blood pressure, *DAP* diastolic arterial blood pressure, *CI* cardiac index, *SVI* stroke volume index, *SVRI* systemic vascular resistance index, *SVV* stroke volume variation

consistent with those reported previously [9, 11–13]. However, those studies did not use remifentanil nor investigate the effects of patients' ages on hemodynamics. We demonstrated the different effects of these agents according to the patients' ages and the causes of hemodynamic changes using the ClearSight® system.

We found that the decrease in the SVI contributed to a decrease in MAP in the middle age group. This result was in accordance with a previous study that indicated a more depressant cardiovascular effect of propofol than that of thiopental [13]. Kurokawa et al. reported that propofol attenuates beta-adrenoreceptor-mediated signal transduction in cardiomyocytes via the inhibition of cyclic adenosine monophosphate [14], which might have led to the decrease in the SVI observed in our study. The absence of a significant decrease in the CI despite a decrease in the SVI may be attributed to the study being statistically underpowered.

In the elderly age group, the greater MAP decrease in the propofol group could be related to the decrease in the SVRI. A decrease in the SVRI is usually followed by an increase in the HR, which was not observed in the propofol group in the elderly age group. This might be attributed to the suppressive effects of remifentanil on sympathetic activity. In addition, there was a tendency toward a more frequent use of vasopressors in the propofol group. Thus, the difference in depressant effects between the propofol group and the thiopental group in the elderly age group may be underestimated. The effects of propofol and thiopental on the SVRI was in accordance with a previous study in which there was a larger decrease in the SVRI with propofol administration than with thiopental administration among patients with implanted artificial hearts [15]. On the other hand, other hemodynamic parameters, including SVI, in the elderly age group were recovered with ephedrine administration due to MAP decrease immediately after the protocol initiation.

Meanwhile, there were no differences in any of the hemodynamic changes between the GA agent subgroups in the young age group, unlike a previous report in which the SVR and MAP after tracheal intubation were lower with propofol than with thiopentone in young patients [12]. This discrepancy in the SVRI between our results and those of the previous report may be due to the difference in the opioid used in the respective studies. In Vohra's report, fentanyl 1.5 μg/kg was used and the SVRI increased after tracheal intubation in the thiopentone group, whereas we used a remifentanil infusion and the SVRI did not increase after tracheal intubation.

The induction doses of thiopental and propofol were determined based on previous reports [11, 16–18], and tailored according to the age groups due to age-related altered sensitivity to these agents and a slower distribution of these agents with age [17–21]. At first, we set the dose of propofol for the young group at 2.0 mg/kg and reduced the dose with increasing age within the range of usual induction doses [8]. The dose of thiopental for each age group was set in the consideration of the report that the hypnotic potency ratio of propofol to thiopental was reported to be 1:1.27–1:2.88 [16]. Patients in all groups lost consciousness immediately after GA induction. In spite of equivalent induction doses, the BIS value was lower in the propofol group in the elderly age group, though the BIS values in both GA agent subgroups were within the normal range. It has been reported that the onset of decrease in BIS is faster with thiopental than with propofol, although the minimal BIS value is lower for propofol despite comparable clinical signs of sleep onset (eye closure, ciliary reflex, and loss of grip) in elderly patients [11]. The effective concentrations of 50% (EC50) and of 95% (EC95) of remifentanil to block sympathetic responses to tracheal intubation were reported to be 4.6 and 6.0 ng/ml, respectively [22]. In the present study, the simulated remifentanil effect-site concentrations at GA

induction were not significantly different between the two subgroups in each age group, and all of the mean remifentanil concentrations for tracheal intubation were within proper analgesic ranges based on a previous report [22]. This may be one of the reasons that the inhibition of cardiovascular responses in the thiopental group in the young age group differed from a previous report [12].

Our study has some limitations. First, for ethical reasons, the patients enrolled in this study were those in relatively good health (ASA PS 1 or 2). Therefore, our findings might not be extrapolated to patients with severe comorbid disease who are at risk of hypotension during GA induction and have less cardiopulmonary reserve. However, our results conversely suggest that elderly patients with cardiovascular disease could develop severe hypotension with an anesthetic induction of propofol and remifentanil. Second, the measurement of hemodynamic parameters through directly inserted catheters (e.g. an arterial line, a pulmonary artery catheter) or echocardiography are established gold standards. However, in our study, these parameters were measured by the ClearSight® system. We chose this device because of its complete non-invasiveness, and its accuracy and precision in measuring these hemodynamic parameters [23, 24]. Third, the infusion protocol of remifentanil in this study resulted in relatively high effect-site concentrations in elderly patients, which might have contributed to the MAP decrease in the propofol group. This result suggests that using propofol risks causing unacceptable hypotension in elderly patients in the presence of an adequate dose of analgesic agents. Further studies using other infusion protocols, such as target-controlled infusion, will be required to investigate this issue.

In conclusion, we compared hemodynamic parameters measured during GA induction with propofol or thiopental under remifentanil infusion in the age-stratified populations. The hemodynamic effects of the GA agents in each of the age groups were different. We found that GA induction with thiopental was preferable in elderly patients to avoid severe hypotension. On the other hand, thiopental was comparable with propofol in young patients, which may have resulted from the remifentanil infusion. Therefore, GA induction with a combination of thiopental and remifentanil is more appropriate than a combination of propofol and remifentanil in terms of avoiding hypotension.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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