Original Article

The Efficacy of Single-Dose Aescin in Preventing Postoperative Sore Throat Compared to Placebos: A Double-Blinded, Randomized Controlled Trial

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Background: Postoperative sore throat (POST) is a common complication found in surgical patients undergoing general anesthesia with endotracheal tube (ETT). Its severity varies and may affect postoperative outcomes and patient satisfaction. Aescin is an extract from horse chestnut (Aesculus Hippocastanum) that possesses the anti-inflammatory, venous decongestion, and anti-edema property with few side effects.

Objective: To demonstrate the reduction of incidence and severity of POST in patients undergoing general anesthesia with ETT.

Materials and Methods: One hundred and seventeen patients, ASA I and II undergoing general anesthesia with ETT with elective surgery (abdominal, breast, gynecological, orthopedics) in a university hospital were enrolled and allocated randomly to aescin (A) or placebo (P) group. Patients, investigators, and research assistants were blinded to the allocation. Patients in A group (n=58) received aescin (Reparil®) 40 mg orally 2 to 6 hours prior to surgery and P group (n=59) received placebo. Anesthesia care was identical and under blinded staff anesthesiologist's discretion. The presence/absence of POST, numerical pain score of POST, adverse events and cumulative analgesics consumption were recorded postoperatively at 30, 60 minutes, 2, 4, and 24 hours.

Results: Thirty-seven and 34 patients in A and P group, respectively, developed POST which was not different significantly at all time points. Numerical pain score at all time points did not differ between groups statistically. However, log-rank test analysis revealed that A group had a slightly more rapid recovery from POST than P group (0.0013 vs. 0.0007 case/person-minute, p=0.03). Side effects and analgesics consumption did not differ between groups.

Conclusion: Single 40 mg oral dose of aescin preoperatively, compare to placebo, did not reduce the incidence or severity of POST in the first 24 postoperative hours. Aescin, however, hastened the speed of recovery of POST compare to placebo with statistical significance.

Keywords: Aescin; Incidence; Postoperative sore throat; Reparil

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Post-Operative Sore Throat (POST) is a common complication in intubated patients under general anesthesia with the incidence ranging from 14.5 to 50%[1]. In a large survey, it was the second most common complication among 12,000 surgical patients[2]. POST is not the most deleterious adverse event to avoid[3]. On the contrary, it is an adverse event that could easily be significantly decreased or even potentially eliminated with reasonable measures. The presence of sore throat after anesthesia can contribute to patients' dissatisfaction with anesthesia[4]. In an animal study, Sinha et al found that even in a short-term intubation period tracheal mucosal injury could occur. Microscopically, the inflammation caused 1) neutrophilic migration to epithelium 2) lamina propria and submucosal edema and 3) epithelial flattening and ulceration[5].

Many studies have been dedicated to identify measures to reduce POST incidence and severity. Many of which has not clearly demonstrated the promising results. For example, oral premedication with 150 mcg clonidine did not prevent POST or hoarseness, and may have exacerbated these symptoms[6]. The use of topical lidocaine appeared to confer no benefit and might, in fact, make POST worse[7,8]. Medications to reduce POST have been categorized into 2 types; steroid and non-steroidal anti-inflammatory drugs. The former has been known to cause numerous serious side effects.

Aescin is the extract of horse chestnut (*Aesculus hippocastanum*). It is a commercially over-the-counter drug

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available under the trade name Reparil®. It is widely used to reduce tissue edema, inflammation and venous congestion. The mechanism of this drug is facilitating calcium ion channel and, consequently, reduction of inflammatory mediators[9]. It is therefore a non-steroidal anti-inflammatory drug. An animal study reported that aescin could reduce inflammation in bowel mucosa[10]. From alternative medicine's viewpoint, horse chestnut bark is a remedy for severe sore throat whereas its seed could improve tissue healing and blood stagnation[11]. Pharmacokinetics of oral aescin tablets include T_{max} of 2 hours with $T_{1/2}$ 6 to 8 hours and better absorption after the meals[12].

With the evidence of local mucosal inflammation in intubated animals and the efficacy of aescin to reduce edema as well as tissue inflammation, we hypothesize that preemptive single-dose aescin extract could reduce POST in surgical patients either its incidence or severity in the first 24 hours postoperatively.

Materials and Methods

This is a prospective randomized, controlled trial conducted in a single university hospital. It was approved by The Institutional Review Board of Srinakharinwirot University No. SWUEC/F-467/2561 and was registered with the Thai Clinical Trial Registry No. TCTR20190903005. Patients age 18 to 64 years with ASA physical status I and II who were undergoing elective gynecologic, intra-abdominal, breast, and orthopedic surgery under general anesthesia with orotracheal tube were enrolled. The operations were done in supine position and the operative time between 1 to 6 hours.

Exclusion criteria included non-consent, known allergy to aescin, known glucose or galactose or fructose intolerance, pregnancy, preexisting sore throat, CKD stage III-IV or end stage renal disease, history of upper respiratory tract infection within 2 weeks, pulmonary disease, psychiatric disorders, history of or suspected difficult airway, planned naso- or orogastric tube insertion, nasopharyngeal temperature probe insertion, and patients with indwelled endotracheal tube prior to surgery. Operative procedures to be excluded were those with the insertion of equipment into oral cavity or below, for example, panendoscopy, endoscopic retrograde pancreato-duodenoscopy (ERCP), esophago-gastroduodenoscopy, or esophageal dilatation. Patients were withdrawn from the study if there was allergic reaction to aescin, preemptive aescin taken more than 6 hours prior to anesthesia and intubation due to delayed schedule, more than one attempt of intubation, excessive manipulation of external larynx during intubation, unexpected prolonged operation >6 hours, unplanned non-extubation, and other serious postoperative complications that precluded the study protocol compliance.

The n4Studies Program was used to calculate sample size with a category of randomized controlled trial with binary outcome (absence or presence of POST). From March 1, 2018 to February 28, 2019 the incidence of POST in intubated patients undergoing general anesthesia at HRH Princess Maha Chakri Sirindhorn Medical Center, Srinakharinwirot University had been 29%. With the aim to reduce half of the incidence (14.5%) with α 0.5 and test power β 90%, the calculated sample size was 140 in each group. Additional participants were considered for 10% dropout or withdrawn resulting in the final sample size of 154 in each group.

All participants were unaware of the group allocation and fully informed before consent was obtained. NPO at least 8 hours was assured except for study drugs before surgery. All eligible participants were computerized randomly (simple randomization) allocated to either Aescin (A group) or placebo (P group) using sealed envelopes. The envelopes were opened by the research assistant who was not involved in the study at the time of premedication visit in the afternoon prior to operative day. The same nurse then handed the opaque sachet of 2 pills of aescin or placebo to the blinded anesthesia residents or another nurse anesthetist who was assigned to make the premedication visit. Each participant in A group received 2 tablets of aescin (20 mg tab) while in the P group received 2 placebo tabs of similar color, size and shape. The timing of the drugs taken was between 2 to 6 hours before operation otherwise the individual would be withdrawn from the study. The research assistant was the only person to prepare the drugs in opaque envelope and was not involved in the whole study process.

Upon operating room (OR) arrival, the patient received standard anesthesia care and monitoring according to the Royal College of Anesthesiologists of Thailand (RCAT) guidelines which include ECG, NIBP, HR, and pulse oximetry. Anesthesiologists and nurse anesthetists were unaware of the allocated group. Anesthesia started with preoxygenation via face mask 3 to 5 minutes followed by midazolam 0.03 to 0.04 mg/kg, fentanyl 2 mcg/kg and thiopental 3 to 5 mg/kg IV. After loss of eyelash reflex, ventilation via face mask was done followed by cisatracurium 0.15 kg/kg IV. Three minutes later, intubation was done by qualified anesthesiologists or nurse anesthetists with work experience of at least 3 months. Teleflex Rusch® Safety Clear® Plus Endotracheal (ET) tube size was 8.0 mm for men and 7.5 for women. ET tube was not lubricated or sprayed with local anesthetics. After successful intubation with depth of ET tube 20 to 22 cm, balloon cuff was inflated with intracuff pressure between 20 to 30 cmH_2O measured by portable manometer at the distal pilot tube.

Anesthesia was maintained by oxygen-air mixture with FiO_2 0.5 and sevoflurane 1.0 to 1.5 MAC. Simple bacterial filter without HME filter was used in the circle absorption anesthetic circuit in every case. Cisatracurium and fentanyl top-up doses were at the anesthesiologist's discretion. Inhalation anesthetics were tailed off before the end of operation. When the spontaneous breathing was noted reversal agents (atropine 0.02 mg/kg and neostigmine 0.05 mg/kg) were given. Endotracheal and oral suction was done gently, avoiding vigorous attempts. Extubation was done as appropriate by responsible anesthesiologist. Oxygen 10 L/min with humidifier via mask with reservoir bag was then applied during transfer to postanesthesia care unit (PACU). Operation time, time from intubation to extubation

(indwelled ET tube time), analgesics and opioids consumption, laryngoscopic view, the use of stylet in ET tube and the amount of blood-stained secretion during suction were recorded.

At PACU, each patient was assessed the degree of POST by PACU nurses who were blinded to the group allocation. Assessment included 1) the verbal numerical POST pain score from 0 to 10 where 0 = no pain, 1 to 3 = mild pain, 4 to 6 = moderate pain, 7 to 9 = severe pain, and 10 = worst pain and 2) aescin side effects, for example, dizziness, headache, abdominal cramp, itching, or rash at 30 minutes, 60 minutes, 2 hours, 4 hours and 24 hours postoperatively. POST at 2, 4 and 24 hours was assessed at the patient ward by research assistant who was blinded to the group allocation. Pain medications were given as per surgeon's order for surgical site pain and supplement by our POST pain regimen if not improved as follow: warm water sip for mild pain, parecoxib 40 mgIV for moderate pain, and fentanyl 25 to 50 mcg IV for severe and worst pain. Pain medications at PACU were recorded. PACU discharge was at PACU nurse discretion according to modified Aldrete's score. Primary outcome was the incidence of POST in each group where numeric POST pain score = 0 means absence and from 1 and above means presence. Secondary outcome was the severity of POST if presence, whether expressed as numeric score or level of severity (mild, moderate or severe) and the speed of recovery from POST over time.

Statistical analysis was done using STATA17.0 software. Continuous numerical data were presented in mean, standard deviation (SD) or median, interquartile range (IQR) depending on normality of distribution of data. Test for normality of data distribution was used by Kolmogorov-Smirnov equation. Comparison between groups was analyzed using Chi-square test for nominal data, unpaired t-test for continuous data. For non-parametric variables, Mann-Whitney U test was used to compare between groups. Survival analysis with Kaplan-Meier plot for POST recovery between groups was analyzed by log-rank test. Statistical significance was determined if p-value less than 0.05.

Results

Data collection was intended to be between August 1, 2019 to May 31, 2020. However, with the widespread of Covid-19 situation and the response of anesthesia procedure change according to The RCAT announcement in February 2020, general anesthesia in all elective cases must be done with rapid sequence induction and intubation with video laryngoscope. The announcement was made without the exact time period of end point. With the halt of data collection for 1 month, the authors decided to discontinue the study as the cumulative cases were 147, with n=72 in A group and n=75 in P group.

However, 14 patients in R group and 16 in P group were withdrawn from the study with the reasons as shown in Figure 1, resulting in total n=58 in A group and 59 in P group. In A group 4 patients were excluded because of inability to assess POST. Three of them were not fully awakened at 30 and 60 minutes. We decided to exclude them. Another one patient was sent to re-operation within 24 hours.

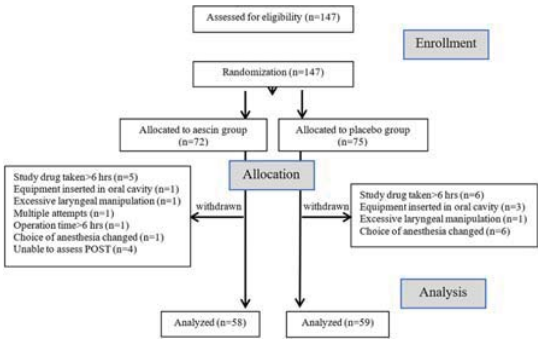

Figure 1. CONSORT diagram of the study.

Patient characteristics between groups were compared as shown in Table 1 without any significant difference except the operation time and indwelled ET time which were significantly longer in P group. The percentage of presence/absence of POST at 30 minutes, 60 minutes, 2, 4 and 24 hours was shown in Table 2. At each time point, there was no statistical significance in incidence difference between groups. Numerical POST pain score was assessed at each time point between groups. The mean score was shown in Table 3 in mean (SD) without statistical significance in difference.

Analgesics consumption according to surgeon's order and study protocol were cumulatively recorded within 24 hours postoperatively and was shown in Table 4. There was no significant different in analgesics consumption between groups.

The tally of cases who had developed POST in each group was performed. There were 37 patients in A group and 34 in P group who developed POST. At the end of the study (time point 1,410 minutes postoperatively) there were 10 patients and 19 patients in group A and P, respectively, who still experienced POST. Kaplan-Meier analysis to detect speed of recovery from POST in both groups was used. By head count, it took 90 minutes and 180 minutes to make 25% of patients in A group and P group, respectively, recover from POST. In A group, half of the patients recovered from POST within 210 minutes and 75% within 24 hours (Figure 2). However, only half of patients in P group recovered from POST by the end of the study leaving the other half with the persisting symptom. In other words, aescin group had a more rapid recovery from POST than in placebo group with statistical significance (p=0.03). The recovery speed was 0.0013 case/person-minute in A group and 0.0007 case/person-minute in P group (Table 5). The end point of the study was 24 hours from PACU arrival, therefore the duration to be analyzed in log-rank test was from the first POST score assessment (at 30 min) to 24 hours which was 1,410 minutes.

Table 1. Patient characteristics between groups

Patient characteristics	Aescin (n=58)	Placebo (n=59)	p-value
Sex			
Male, n (%)	9 (15.5)	7 (11.9)	0.560
Female, n (%)	49 (84.5)	52 (88.1)	
Age, years, mean (SD)	45.3 (11.4)	43.5 (10.8)	0.390
Weight, kg, mean (SD)	62.7 (10.7)	63.5 (13.8)	0.710
Height, cm, mean (SD)	159.1 (6.2)	159.6 (8.4)	0.670
ASA physical status			
1, n (%)	17 (29.3)	17 (28.8)	0.950
2, n (%)	41 (70.7)	42 (71.2)	
Premedication time, min, median (IQR)	185 (145 to 230)	180 (125 to 220)	0.160
Operation time, min, median (IQR)	132.5 (100 to 180)	160 (125 to 230)	0.020
Intubation time, min, median (IQR)	120 (90 to 165)	140 (115 to 200)	0.030
LV			
Grade I, n (%)	48 (82.8)	55 (93.2)	0.180
Grade II, n (%)	9 (15.5)	4 (6.7)	
Grade III, n (%)	1 (1.7)	0 (0.0)	
Stylet use			
No, n (%)	50 (86.2)	53 (89.8)	0.550
Yes, n (%)	8 (13.8)	6 (10.2)	
Blood stained secretion			
No, n (%)	43 (74.1)	49 (83.1)	0.300
Mild, n (%)	11 (19.0)	7 (11.9)	
Moderate, n (%)	2 (3.5)	3 (5.1)	
Fresh blood, n (%)	2 (3.5)	0 (0.0)	

Adverse events such as nausea, vomiting, dizziness and itching were reported in both groups without statistical difference as shown in Table 6.

Discussion

Postoperative sore throat (POST) is a common complications following general anesthesia with endotracheal tube. The severity of POST ranges from mild with self-limiting condition to severe with hoarseness and relief with medications. The precipitating factors of developing POST include not only endotracheal tube size, but also the dry anesthetic gases, intubation technique, intracuff pressure, anesthesia and indwelled ETT time, body positioning, succinylcholine use, orotracheal suctioning technique, gender, NG tube insertion, number of intubation attempts, the experience of intubation performer, and the application of local anesthetic spray.

We have reviewed the efficacy of aescin extract aforementioned which is commercially available over-the-counter in Thailand under the trade name Reparil®. It is widely used for leg discomfort relief in varicose veins, and edema relief from sports injury. We hypothesize that aescin could bear beneficial effects on local tissue edema in intubated patients undergoing general anesthesia.

In the present study single dose of oral 40 mg aescin has failed to show superiority compare to placebo in reducing the incidence of POST in the first 24 postoperative hours (Table 2). Also, it did not reduce the severity of POST as compared to placebo (Table 3) even though the operation time and indwelled ETT time was approximately 30 minutes longer in placebo group (Table 1). In aescin group the incidence at 60 minutes was slightly higher than 30 minutes. This might be due to the level of consciousness of some patients at 30 minutes when the numeric pain score was assessed or more pain perception at surgical site that might distract the POST assessment. Apparently, after 60 minutes the incidence was declining over time in A group. In P group, on the other hand, the incidence was increasing at 30, 60 minutes and 2 hours then started to decline at 4 hours. Apparently, Aescin seemed to hasten the recovery of self-limiting POST.

Despite statistically non-significant difference, there was a tendency of both incidence and severity reduction over time in aescin group. This tendency could probably be more statistically significant with a larger sample size. Furthermore, with comparable operation and indwelled ETT time the effect of POST recovery could have been more

Table 2. The incidence of POST between groups at each time point

Time	Aescin (n=58)	Placebo (n=59)	p-value
30 minutes			
Yes, n (%)	26 (44.8)	24 (40.7)	0.650
No, n (%)	32 (55.2)	35 (59.3)	
60 minutes			
Yes, n (%)	28 (48.3)	27 (45.8)	0.780
No, n (%)	30 (51.7)	32 (54.2)	
2 hours			
Yes, n (%)	19 (32.8)	28 (47.5)	0.100
No, n (%)	39 (67.2)	31 (52.5)	
4 hours			
Yes, n (%)	18 (31.0)	26 (44.1)	0.150
No, n (%)	40 (69.0)	33 (55.9)	
24 hours			
Yes, n (%)	10 (17.2)	14 (23.7)	0.390
No, n (%)	48 (82.8)	45 (76.3)	

Table 3. The comparison of severity POST between groups at each time point

Time	POST severity		p-value
	Aescin (n=58)	Placebo (n=59)	
30 minutes, mean (SD)	1.2 (1.7)	1.3 (2.1)	0.780
60 minutes, mean (SD)	1.2 (1.5)	1.3 (1.8)	0.750
2 hours, mean (SD)	0.8 (1.4)	1.1 (1.5)	0.310
4 hours, mean (SD)	0.7 (1.4)	0.9 (1.2)	0.570
24 hours, mean (SD)	0.3 (0.8)	0.3 (0.1)	0.870

significant.

There were 3 cases in A group who failed to awaken at 30 minutes to evaluate POST resulting in case withdrawal. This might simply be coincidence or the beneficial effect of aescin. Larger sample might reveal some insights.

Whether the severity of POST is reduced or not is an issue in the present study. As a matter of fact, most POST that is found in clinical practice is mild (score 1 to 3) and self-limited. From Table 3 patients who have sustained POST from the first 30 minutes postoperatively had the mean pain score of 1.2 in A group and 1.3 in P group. This was basically a mild symptom that increasing sample size might not differentiate the severity between groups and might not change the practice of anesthesia.

The incidence of POST over 24 hours postoperatively was 63.7% (37 out of 58 cases) and 57.6%

Table 4. The analgesics consumption between groups

Analgesics	Dose*, mean (SD)		p-value
	Aescin (n=58)	Placebo (n=59)	
Morphine, IV, mg	9.4 (10.1)	8.7 (10.2)	0.700
Fentanyl, IV, mcg	15.6 (23.8)	21.2 (30.6)	0.270
Pethidine, IV, mg	0.3 (2.6)	1.3 (7.2)	0.360
Tramadol, IV, mg	2.6 (14.6)	5.1 (17.9)	0.410
Tramadol, PO, mg	0.9 (6.6)	5.1 (17.9)	0.090
Parecoxib, IV, mg	10.0 (21.6)	11.5 (23.6)	0.720
Meloxicam, PO, mg	1.2 (3.7)	0.8 (3.6)	0.550
Diclofenac, PO, mg	2.6 (12.1)	3.4 (18.8)	0.780
Ibuprofen, PO, mg	27.6 (126.8)	40.7 (160.9)	0.630
Paracetamol, PO, mg	179.3 (318.7)	222.4 (554.3)	0.610

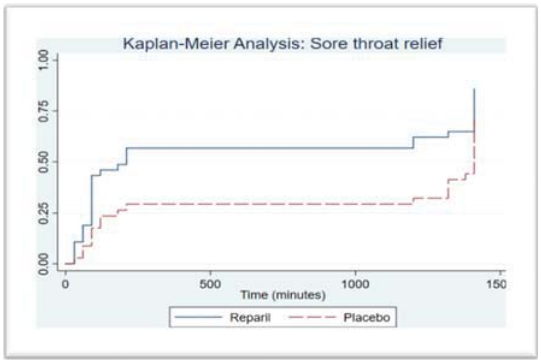

Figure 2. Log-rank curve of POST recovery.

(34 out of 59 cases) in A and P group respectively. Notably, it did not improve the incidence rate at our hospital. These 71 patients from 2 groups recovered from POST differently. The slightly more rapid recovery in A group suggested that aescin had a beneficial effect in easing the POST symptom. The recommended regimen of the drug is two tablets 3 times daily. However, we were unable to comply with this regimen for better outcomes since some patients were not allowed to have oral intake postoperatively particularly those who had undergone major intra-abdominal surgery. Further study should address this issue in patient selection.

POST recovery was analyzed using survival analysis model with log-rank test and the result was promising. The speed of recovery was almost twice in the aescin group even though the effect size might not large enough. Further study with larger sample size could improve the result. Considering that with single oral dose of 40 mg aescin could eliminate the symptom in 75% of cases in the first 24 hours,

Table 5. Log-rank test, Median times to recovery from POST

Treatment	Incidence rate	Subjects (n)	Survival time (min)			p-value
			0.250	50%	75%	
Aescin	0.0013	37	90	210	1,410	0.033
Placebo	0.0007	34	180	1,410	0	

Table 6. Adverse events between groups

Side effect	Treatment		p-value
	Aescin	Placebo	
Nausea & vomitting			
Yes, n (%)	9 (15.5)	10 (17.0)	0.838
No, n (%)	49 (84.5)	49 (83.1)	
Dizziness			
Yes, n (%)	9 (15.5)	12 (20.3)	0.503
No, n (%)	49 (84.5)	47 (79.7)	
Itching			
Yes, n (%)	1 (1.7)	3 (5.1)	0.326
No, n (%)	57 (98.3)	56 (94.9)	

the subsequent oral dose might have a benefit if the patient was allowed to resume eating and drinking postoperatively. Further study with protocol modification can make it more evident.

There were several limitations in the present study that might prompt further study for better and clearer results. First, the outbreak of COVID-19 precluded the compliance to the study protocol which led to unexpected smaller sample size. This study, therefore, was underpowered with the value of 0.47. The results, however, could provide an insight into this promising drug in POST relief regimen. Second, the timing of drug premedication could not be completely controlled within 2-6 hours before surgery, the clinical duration of the drug. Case cancellation, case postponement to re-sequencing, and unexpected lengthy operation were some of the examples. Third, oral dose of aescin yields unpredictable bioavailability due to individual absorption variability. Unfortunately, there were no commercial injectable forms at the time of the study. Given the injectable form, the comparison between groups would have been more accurate. And fourth, patients who were not fully awakened at 30 minutes could give inaccurate verbal numerical pain score.

Conclusion

Single oral dose of 40 mg aescin extract could not reduce the incidence of POST in patients undergoing general anesthesia with ETT in the first postoperative 24 hours. It also did not reduce the severity of POST as compared to placebo. However, it could hasten the recovery from POST almost 2-fold within the first 24 hours with statistical significance.

What is already known on this topic?

Research studies on POST prevention and treatment have reported inconsistent results with various measures and drugs. The horse chestnut *(Aesculus hippocastanum)* extract or aescin has anti-inflammatory and anti-edematous property. Its efficacy in preventing or relieving POST is unprecedented.

What this study adds?

Aescin neither reduced the incidence nor the severity of POST in patients undergoing general anesthesia with endotracheal tube in the first 24 postoperative hours. However, it hastened the speed of recovery from POST, if any, in the first 24 postoperative hours as compared to placebo.

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Potential conflicts of interest

The authors declare no conflict of interest.

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