<Original Article>

Intraoperative Slow Train-of-four Monitoring Mode of the Orbicularis Oculi Muscle Prevents Postoperative Nausea and Vomiting

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ABSTRACT

Stimulation of the stomach meridian, which consists of several stomach acupoints around the orbit, restores gastrointestinal peristalsis. We tested the hypothesis that postoperative nausea and vomiting (PONV) occur less in patients who receive intraoperative neuromuscular monitoring of orbicularis oculi muscles by facial nerve stimulation (NOF). We retrospectively analysed patients who underwent elective gynaecological laparoscopic surgery under total intravenous anaesthesia. Predictors included age, body mass index, smoking history, history of PONV/motion sickness, duration of anaesthesia, existence of hysterectomy, analgesic adjuvants, and NOF using slow train-of-four (TOF) throughout anaesthesia. The outcome was the occurrence of PONV within 24 h. Binomial logistic regression analysis was performed to investigate the potential associations between PONV and predictors. The incidence of PONV was 32.7 % (122/373). The occurrence of PONV was significantly positively associated with age (coefficient: 0.0382, p = .0071) and with hysterectomy (coefficient: 0.708, p = .0211), and significantly negatively associated with the presence of TOF (coefficient: −1.6506, p = .0077). Additionally, we assessed the influence of TOF on the occurrence of PONV in the non-hysterectomy group. The occurrence of PONV was significantly negatively associated with the presence of TOF (coefficient: −2.1546, p = .011). Our results support the hypothesis that repetitive NOF ameliorates PONV in patients undergoing gynaecological surgery.

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INTRODUCTION

Postoperative nausea and vomiting (PONV) is an unfavourable postoperative outcome associated with anaesthesia, and anaesthesiologists must minimise its occurrence. The prevalence of PONV is 20–30 % in normal populations [1, 2] and 70–80 % in high-risk populations [3].

Gan and colleagues emphasised the importance of making the best use of strategies from the portfolio of prophylaxis and treatment for PONV. This portfolio comprises not only pharmacological strategies but also non-pharmacological strategies, such as acupoint stimulation [2].

It has been shown that 1-Hz single-twitch and train-of-four (TOF) stimulations at a point located 2–3 cm proximal to the distal crease of the wrist and between the palmaris longus flexor and carpi radialis muscles, namely the P6 acupoint, not only allows the reliable monitoring of neuromuscular testing, but also decreases the incidence of PONV in gynaecological laparoscopic surgery and laparoscopic cholecystectomy [4–6]. In laparoscopic hysterectomy, tetanus stimulation at the P6 acupoint has been reported to reduce the incidence of PONV, whereas other electrical stimulations of neuromuscular testing, such as single-twitch, TOF, and double-burst stimulation, have failed to show effectiveness [7]. Accordingly, several reported neuromuscular monitoring modes applied at the P6 acupoint differ in their effects on PONV. Application of multiple strategies during and after anaesthesia is recommended to minimise the occurrence of PONV in high-risk surgeries such as gynaecological surgery and laparoscopic cholecystectomy [8, 9]. Therefore, it may be difficult to determine whether several modes of neuromuscular testing at a single acupoint, such as P6, restore PONV when sufficient prevention strategies have not been applied to patients who undergo a surgical procedure associated with a high risk of PONV.

In contrast, weakened or reversed peristalsis of the gastrointestinal tract contributes to the mechanisms underlying nausea and vomiting [10]. The stomach meridian (ST: Yang Ming), which consists of 45 stomach points (ST_1–ST_{45}), was used for the normalisation of gastrointestinal tract motility. The stomach channel starts directly below the pupil between the eyeball and the infraorbital ridge (ST_1), and then runs downward along the lateral side of the nose ($ST_{2,3}$), passing to the lateral corner of the mouth (ST_4), curving posterior to the anterior angle of the mandible ($ST_{5,6}$), traveling to the posterior aspect of the mandible ascending in front of the ear (ST_7), followed by the anterior hairline, reaching the forehead (ST_8), running along the throat, and traveling downward to the foot while providing a number of additional points (ST_9–ST_{45}) [11]. ST_2 is one of the most surveyed stomach points in animals in terms of its effects on gastric motility and brainstem circuits, and acustimulation at ST_2 reportedly enhances gastric motility [12].

Monitoring the responses of the adductor polis muscle to electrical stimulation of the ulnar nerve is a common method of intraoperative neuromuscular monitoring. It is generally accepted that monitoring the responses of the orbicularis oculi muscle to facial nerve stimulation is a reasonable method for this purpose [13, 14]. Compared with stimulation at a single acupoint, such as P6, a line of this manoeuvre effectively stimulates several ST points, particularly from ST_1 to ST_7. Thus, we hypothesised that the incidence of PONV is lower in patients who receive neuromuscular monitoring of the orbicularis oculi muscle via facial nerve stimulation. There are no similar studies. This study aimed to evaluate this hypothesis in gynaecological laparoscopic surgery using a retrospective cohort method.

MATERIALS and METHODS

This study was approved by the Institutional Review Board of the Japanese Red Cross Society Wakayama Medical Center (approval no. 294) and was conducted in accordance with the STROBE statement checklist Ver. 4. We obtained oral informed consent from all patients before anaesthesia for postoperative interviews and the possible use of the data for the clinical study. The postoperative interview included questions related to wound pain intensity level (using a visual analogue scale), as well as the presence or absence of symptoms such as pruritus, PONV, new occurrence of neurological deficits, intraoperative awareness, and memory of dreaming during anaesthesia. All nursing staff (including ward and operating room staff) recorded the issue of PONV based on its definition as an episode in which a patient suffers from nausea that lasts over 15 min or vomiting. The staff anaesthesiologists read the ward records to check for the occurrence of PONV and other issues before visiting the patients for the interview. The staff anaesthesiologists asked every patient about PONV; for example, "Have you experienced nausea that lasted more than 15 minutes or vomiting after surgery?" Irrespective of whether the occurrence of PONV in the ward record coincided with that in the interview, the staff anaesthesiologists indicated "PONV: Yes" on the postoperative interview sheet when either the ward record or the postoperative interview could confirm this. Every postoperative interview sheet was uploaded to the medical records program.

We retrospectively analysed the medical records of patients who underwent elective gynaecological laparoscopic surgery under total intravenous anaesthesia with propofol and remifentanil between April 2008 and June 2013. During anaesthesia, tracheal intubation with intravenous rocuronium was performed and none of the patients received postoperative opioids. We excluded patients aged < 16 years, those with decreased consciousness, and those with dementia. Predictors included age, body mass index (BMI), smoking history, history of PONV and motion sickness, duration of anaesthesia, hysterectomy, analgesic adjuvants, and neuromuscular monitoring of the orbicularis oculi muscle by facial nerve stimulation using slow TOF mode with an interval of 5–10 min by means of the TOF WATCH® SX (Nihon Kohden, Tokyo, Japan) throughout the anaesthesia period.

The outcome was the occurrence of PONV within 24 h postoperatively. Since patients often resume oral intake the next day after gynaecological laparoscopic surgery in our hospital, we focused on the occurrence of PONV within 24 hours after surgery, during which PONV could affect their oral intake from the next day. Each clinical variable was retrieved from a database of anaesthetic charts, postoperative interview sheets, and medical records. A post hoc power test was used to determine the power of our analysis. To determine the type of test required, we used the Shapiro–Wilk normality test to investigate whether the numerical variables (age, BMI, and duration of anaesthesia) followed a normal distribution.

We used summary statistics to explore the data. We reported the measure of variability of the numerical variables as mean ± standard deviation (SD). Categorical variables are reported as counts (% frequency). Considering the results of the Shapiro–Wilk normality test, we used the non-parametric Wilcoxon rank sum test for numerical variables. Chi square test and Fisher's exact test for categorical variables to investigate potential differences between the two groups of PONV (Yes and No). In addition, we used binomial logistic regression analysis to investigate the potential associations of PONV with other variables. Further, to determine the best model for each of these variables, we used a stepwise algorithm to choose the best model according to the Akaike inclusion criterion from the package "step" [15]. We set the significance level of our test to $p < 0.05$. For all statistical analyses, we used R (version 4.2.3; R Foundation, Vienna, Austria).

Table 1 **Shapiro–Wilk normality test results for age, body mass index, and duration of anaesthesia**

Variable	**W**	***p*-value**
Age	0.98	< 0.0001
BMI	0.92	< 0.0001
Duration of anaesthesia	0.83	< 0.0001

A *p*-value lower than 0.05 ($p < 0.05$) indicates that this variable does not follow a normal distribution. BMI: body mass index.

RESULTS

We determined that the power of our analysis was very good (power = 97.1 %) for the sample size ($n = 373$) and small effect size (Cohen's d = 0.2).

The results of the Shapiro–Wilk normality tests showed that all the numerical variables followed a non-normal distribution (**Table 1**; $p < .0001$); hence, we decided to use the non-parametric Wilcoxon rank-sum test. In total, we examined 373 cases in our study, of which 122 presented with PONV and 251 did not. Intravenous adjuvants included butorphanol, tramadol, scopolamine, and lidocaine. The only postoperative antiemetic was prochlorperazine (5 mg intramuscular) when requested. The mean age of the patients who presented with PONV (41.90 ± 10.66 years) was significantly higher ($p < .0001$) than that of the patients who did not present with PONV (35.89 ± 9.10 years) (**Table 2**; **Figure 1**). The mean anaesthesia duration of the patients who presented with PONV (107.87 ± 43.44 min) was significantly higher ($p = .0002$) than that of the patients who did not present with PONV (92.34 ± 39.56 min) (**Table 2**; **Figure 2**). Fisher's exact tests showed a significant relationship between PONV and hysterectomy ($p < 0.0001$) (**Table 2**; **Figure 3**). The binomial logistic regression model selected by stepwise regression showed that the occurrence of PONV was significantly and positively associated with age (coefficient 0.0382, $p = .0071$; **Table 3**) and with the presence of hysterectomy (coefficient 0.708, $p = .0211$; **Table 3**) and negatively associated with the presence of TOF (coefficient −1.6506, $p = .0077$; **Table 3**) after adjusting for cofounders in the multivariate analyses. According to these odds ratios, age and hysterectomy contributed to an increase in the incidence of PONV, and the presence of TOF contributed to a decline in the incidence of PONV. We next evaluated the contributions of hysterectomy and age to the effect of TOF on the occurrence of PONV. **Table 4** shows the types of laparoscopic surgery with or without hysterectomy, and **Table 5** shows the number of patients with or without hysterectomy together with the analysis of the distributions of TOF on age and hysterectomy using Mann–Whitney U and chi-square analyses, respectively. The two analyses revealed that the predictors of age and hysterectomy did not significantly contribute to the effect of TOF on the occurrence of PONV.

After these analyses, we subset the data included only in the non-hysterectomy group to exclude the influence of hysterectomy on PONV occurrence. We then assessed the influence of TOF on the occurrence of PONV in the non-hysterectomy group. In this analysis, we used Fisher's exact test to investigate potential differences in TOF between non-hysterectomy patients with or without PONV. The results showed that there were no significant differences in TOF between the PONV groups ($p = .2019$) (**Table 6**). We then excluded hysterectomy from the best model defined by "step" to subset the dataset. The results showed that the occurrence of PONV was negatively associated with TOF (coefficient −2.1546, $p = .011$; **Table 7**).

Table 2 Summary statistics stratified by postoperative nausea and vomiting

Variables	Postoperative nausea and vomiting			
	No (*n* = 251)	Yes (*n* = 122)	*p*-value	Significance
Age (years)	35.89 ± 9.10 36 (30–41.5)	41.90 ± 10.66 43 (34–50)	< 0.0001	***
BMI (kg/m^2)	21.21 ± 3.02 20.4 (19.17–22.67)	21.85 ± 3.41 21.26 (19.47–23.62)	0.0896	
Smoking history, *n* (%)			0.0757	
- No	209 (83.27 %)	110 (90.16 %)		
- Yes	42 (16.73 %)	12 (9.84 %)		
History of PONV and motion sickness, *n* (%)			0.9156	
- No	215 (85.66 %)	104 (85.25 %)		
- Yes	36 (14.34 %)	18 (14.75 %)		
Duration of anaesthesia (min)	92.34 ± 39.56 85 (68–105)	107.87 ± 43.44 100 (78–132)	0.0002	***
Hysterectomy, *n* (%)			< 0.0001	***
- No	202 (80.48 %)	67 (54.92 %)		
- Yes	49 (19.52 %)	55 (45.08 %)		
Butorphanol, *n* (%)			0.8649	
- No	181 (72.11 %)	89 (72.95 %)		
- Yes	70 (27.89 %)	33 (27.05 %)		
Tramadol, *n* (%)			0.9943	
- No	111 (44.22 %)	54 (44.26 %)		
- Yes	140 (55.78 %)	68 (55.74 %)		
Scopolamine, *n* (%)			0.5999	
- No	143 (56.97 %)	66 (54.10 %)		
- Yes	108 (43.03 %)	56 (45.90 %)		
Lidocaine, *n* (%)			0.7588	
- No	146 (58.17 %)	73 (59.84 %)		
- Yes	105 (41.83 %)	49 (40.16 %)		
TOF, *n* (%)			0.054	
- No	217 (86.45 %)	114 (93.44 %)		
- Yes	34 (13.55 %)	8 (6.56 %)		

BMI: body mass index; TOF: train-of-four; PONV: postoperative nausea and vomiting. ***Significant variables

DISCUSSION

The key finding in this retrospective cohort study is that slow TOF monitoring of the orbicularis oculi muscle by electrical stimulation of the facial nerve with an interval of 5–10 min significantly reduces the odds ratio for the occurrence of PONV in gynaecological laparoscopic surgery, suggesting that this manoeuvre has great potential to ameliorate PONV.

Risk factors for PONV include younger age, female sex, non-smoking status, a history of PONV or motion sickness, use of volatile anaesthetics and nitrous oxide, postoperative opioids, and prolonged duration of anaesthesia [16, 17]. Moreover, Apfel and colleagues reported that abdominal surgeries, especially laparoscopic, bariatric, and gynaecological surgeries, were also associated with an increased

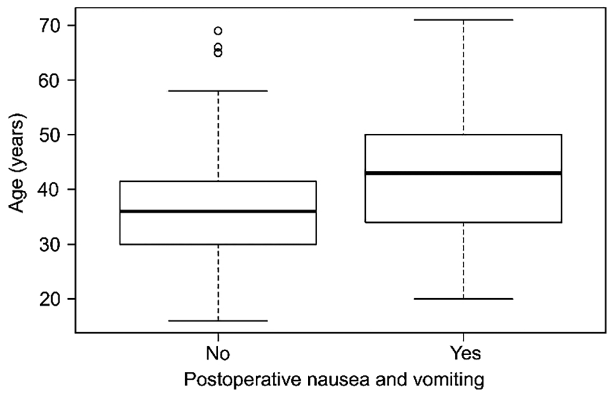

Figure 1 **Mean age of patients with and without postoperative nausea and vomiting**

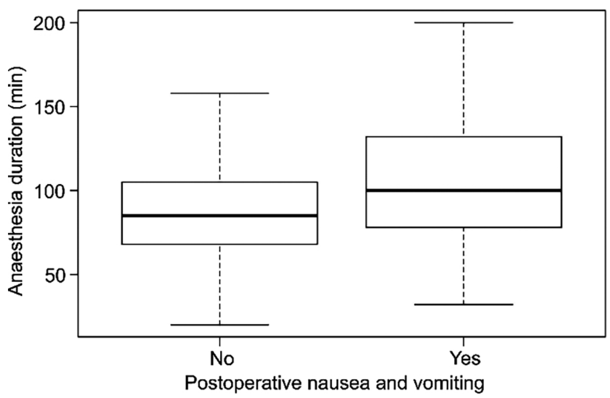

Figure 2 **Mean anaesthesia duration of patients with and without postoperative nausea and vomiting**

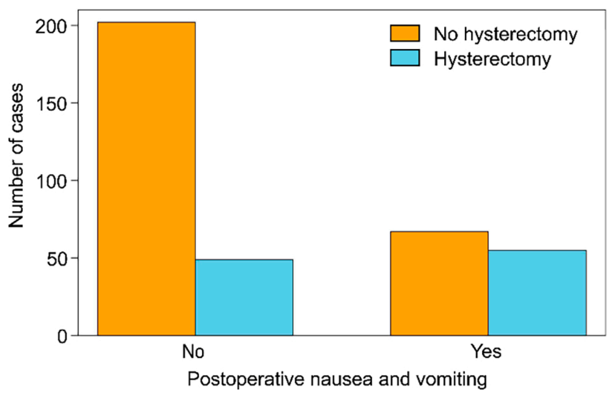

Figure 3 **Association of hysterectomy with postoperative nausea and vomiting**

prevalence of PONV [16, 18].

The dorsal vagal complex (DVC), which consists of the area postrema (AP), nucleus of the solitary tract (NTS), and dorsal motor nucleus of the vagus (DVM), plays a role in the control of emesis by the medulla oblongata. The AP and NTS, both of which receive emetic signals from the afferent vagal nerve and blood, relay signals to the DVM and then send efferent signals to the gastrointestinal tract, thus triggering an emetic response, such as weakened or reversed peristalsis [10, 19]. Liu et al. [12] have shown that stimulation of orofacial acupoints activates motility of the gastrointestinal tract through the inhibition of signals from the NTS to the DMV. The DVC acts not only as a terminal of vagal afferent signals from the thoracic and abdominal organs, but also as a controller of the vagal tone of these organs [19, 20]. Therefore, one of the main targets of acustimulation for the treatment of gastrointestinal disorders and disturbed gastrointestinal motility is the DVC [12]. As impaired gastrointestinal motility is one of the factors underlying emesis [21], slow TOF mode during anaesthesia may act on DVC-like acustimulation at ST points, particularly $ST_{1\text{-}7}$, to ameliorate PONV.

In contrast, both facial nerve stimulation and the resultant contraction of the orbicularis oculi muscle, even if the contraction is not detectable, activate the 1st and 2nd trigeminal nerve terminals, which relay signals via the trigeminal ganglion to the spinal trigeminal nucleus (SpV), which consists of three subnuclei: the oralis (SpVo), interpolaris (SpVi), and caudalis (SpVc) [22, 23]. It has been shown that both excitatory (via α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid [AMPA], and N-methyl-D-aspartate [NMDA] receptors) and inhibitory (via γ-aminobutyric acid A [$GABA_A$] and glycine receptors) modulation play a crucial role in intersubnuclear synaptic transmission [22]. However, to the best of our knowledge, there have been no reports on the functional connections between the subnuclei (SpVo, SpVi, and SpVc) and the DVC. Therefore, we were not able to clarify whether slow TOF during anaesthesia inhibits signals from the NTS to the DMV via the SpV.

Nevertheless, it is generally accepted that $GABA_A$ receptor-mediated control plays a major role in DMV neuronal activity [24]. Dexamethasone, one of the most important drugs for preventing and treating PONV, enhances GABA release to inhibit emesis [19], and propofol acts on both the AP and NTS via $GABA_A$ receptors to inhibit emesis [25, 26]. These facts greatly support the idea that $GABA_A$ receptor mediation in the DVC contributes greatly to antiemesis. Furthermore, a histological investigation of the brainstem of macaque monkeys showed that dendrites of the subnuclei of the SpV that contain GABA connect to various nuclei and subnuclei of the brainstem [27], suggesting the possible existence of GABA mediation between the SpV and DVC. It may be postulated that SpV and its subnuclei activated by slow TOF with an interval of 5–10 min during anaesthesia act on the DVC via a $GABA_A$-mediated mechanism to inhibit emesis, and propofol-based anaesthesia may have an additive effect. Further studies on the mechanism underlying our results are required to clarify this issue.

Given that slow TOF mode at the facial nerve achieves an extremely low odds ratio for PONV, this study might

Table 3 Results of the binomial logistic regression analysis

Variables	Estimate	OR [95 % CI]	*p*-value	Significance
(Intercept)	−2.4313	0.09 [0.03–0.29]	**0.0001**	***
Age	0.0382	1.04 [1.01–1.07]	**0.0071**	***
Smoking history (yes vs. no)	−0.6535	0.52 [0.24–1.05]	0.0783	
Duration of anaesthesia	0.0051	1.01 [1–1.01]	0.104	
Hysterectomy (yes vs. no)	0.708	2.03 [1.11–3.72]	**0.0211**	***
Butorphanol (yes vs. no)	−0.5274	0.59 [0.29–1.19]	0.1423	
Scopolamine (yes vs. no)	−0.8004	0.45 [0.19–1.04]	0.0651	
Lidocaine (yes vs. no)	0.6369	1.89 [0.87–4.27]	0.1151	
TOF (yes vs. no)	−1.6506	0.19 [0.05–0.62]	**0.0077**	***

OR: odds ratio, CI: confidence interval, TOF, train-of-four.
Statistically significant variables are indicated by *** and bold letters.

Table 4 Types of laparoscopic surgery with or without hysterectomy

Hysterectomy (Yes): 108 patients	Vaginal hysterectomy
	Vaginal hysterectomy + oophorectomy
Hysterectomy (No): 265 patients	Enucleated myomectomy
	Adnexectomy
	Removal of adnexal tumour
	Removal of ectopic gestation
	Removal of endometriosis lesions
	Division of adnexal adhesion

Table 5 Number of patients with and without hysterectomy and analysis of the distributions of slow TOF (yes) on age and hysterectomy (Mann–Whitney U and chi-squared tests, respectively)

	Age (years)	Hysterectomy (yes/no)
Slow TOF (yes)	36 (27.25–44.25)	8/34
Slow TOF (no)	37 (31–45)	96/235
p-value	0.3067	0.1753

TOF: train-of-four

Table 6 Relationship between TOF and with/without PONV in non-hysterectomy patients

TOF	Postoperative nausea and vomiting		*p*-value
	No (*n* = 202)	Yes (*n* = 67)	
No	173 (85.64 %)	62 (92.54 %)	0.2019
Yes	29 (14.36 %)	5 (7.46 %)	

have several limitations. First, the sample size of this study, which included several types of surgery, was relatively small. Second, the incidence of PONV after gynaecologic laparoscopic surgery is reportedly 70–80 % [28, 29]. However, it can decrease to 17–29 % when appropriate multimodal antiemetic measures are taken [30, 31]. Considering the incidence of PONV in this study (32.7 %), the prevention and treatment of PONV in our sample might have been insufficient, based on the recommendations of Fero et al. [8]. Third, **Table 2** showed no significant relationship between PONV and TOF (p = 0.054). We consider that there is no difference in background between the groups of with and without TOF.

However, this was a retrospective observational study, and the application of TOF monitoring was not randomised. Based on the results obtained in this study, it is difficult to conclude whether neuromuscular monitoring of the orbicularis oculi muscles using facial nerve stimulation reduces the incidence of PONV. However, another important finding in this study was that slow TOF at the facial nerve allowed a low odds ratio, regardless of the presence or absence of hysterectomy, although hysterectomy has been found to be a possible risk factor for PONV in gynaecological laparoscopic surgery. These findings encourage us to

Table 7 Results of the binomial logistic regression analysis results for the non-hysterectomy subset

Variables	Estimate	OR [95 % CI]	*p*-value
(Intercept)	−2.104	0.12 [0.03–0.5]	**0.0041**
Age	0.0336	1.03 [1–1.07]	**0.0353**
Smoking history (yes)	−1.2968	0.27 [0.08–0.74]	**0.021**
Duration of anaesthesia	0.0049	1 [1–1.01]	0.206
Butorphanol (yes)	−0.7756	0.46 [0.19–1.1]	0.0824
Scopolamine (yes)	−1.156	0.31 [0.08–1.04]	0.0721
Lidocaine (yes)	1.0321	2.81 [0.94–10.5]	0.0871
TOF (yes)	−2.1546	0.12 [0.02–0.57]	**0.011**

OR: odds ratio, CI: confidence interval, TOF, train-of-four. Statistical significance indicated in bold text.

explore the possibility of using the stomach meridian for PONV prevention; for example, the effects of commercially available acustimulation devices at ST acupoints and longer duration of use (not only during the anaesthesia period but also afterward).

In summary, the results of this study support the hypothesis that the incidence of PONV is lower in patients who receive neuromuscular monitoring of the orbicularis oculi muscles via facial nerve stimulation.

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CONFLICT OF INTEREST DECLARATION

The authors declare no conflicts of interest associated with this manuscript.

DATA AVAILABILITY STATEMENT

All data generated or analysed during this study are included in this published article.

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