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ORIGINAL ARTICLE

Nociceptive and stress hormonal state during abdominal, laparoscopic, and vaginal hysterectomy as predictors of postoperative pain perception

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Abstract The primary objective of this study is to compare pain perception during and after surgery between abdominal hysterectomy (AH), laparoscopic hysterectomy (LH), and vaginal hysterectomy (VH). The secondary objective of this study is to investigate whether pain indicators during surgery predict pain perception and demand for analgesics postoperatively. Prospective observational analysis of intraoperative nociceptive state (by means of pulse transit time; PTT), heart rate, and stress hormone levels (adrenalin and noradrenalin) were correlated with postoperative pain scores and stress hormone levels and demand for postoperative analgesics such as morphine. Intraoperative PTT levels and perioperative and postoperative stress hormone levels did not differ significantly between AH, LH, and VH. During the first hours postoperatively, LH patients showed insignificant lower pain scores, compared to AH and VH. One day postoperatively, LH patients reported significantly lower pain scores. High intraoperative stress hormone levels predicted a significant higher demand for morphine postoperatively, accompanied with significant higher pain scores. No differences were found with respect to intraoperative pain indicators well as pain perception during the first hours after surgery between AH, LH, and VH. If VH is not applicable, LH proves to be advantageous over AH with respect to a faster decline in pain scores.

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Background

Almost without exception, surgery is associated with postoperative pain. Also in hysterectomy, women experience postoperative pain to some degree, despite adequate general and or locoregional anesthesia [1].

Among other superior characteristics, vaginal hysterectomy (VH) is particularly known for its short period of postoperative pain and quick recovery, and also therefore considered the *gold standard* in hysterectomy [2]. Over the recent years, some studies stated that laparoscopic hysterectomy (LH) is preferred over VH with respect to lower postoperative pain scores. However, these studies are underpowered [3–5]. When VH is not applicable, LH shows several advantages over abdominal hysterectomy (AH). Firstly, it is generally known that, compared to the abdominal approach, LH is characterized by less intraoperative blood loss, shorter duration of hospital stay, speedier return to normal activities, and fewer wound or abdominal wall infections [2, 6–8]. Secondly, relatively elevated interleukin-6 and C-reactive protein serum levels found in AH suggests that this approach is associated with inclined tissue damage, compared to LH [9–13]. Thirdly, patients claim to prefer LH over AH probably because of the aforementioned findings, combined with esthetical considerations [14]. Lastly, LH patients report to become pain free in a significantly shorter period of time compared to women operated by laparotomy [1, 2, 8, 15].

Surprisingly, a recent study observed that laparoscopic surgery is associated with higher pain scores in the first hours postoperatively [16]. Others described higher nociceptive pain scores during laparoscopic procedures compared to conventional open surgery [17]. These findings are in contrast with the rationale that minimally invasive surgery (MIS), with accompanying less tissue damage, would result in declined perceived pain. Hypothetically, the observed higher pain perception when applying the laparoscopic approach could be the result of peritoneal absorption of insufflated carbon dioxide in laparoscopy, which can cause referred shoulder pain. Another explanation to the reported higher pain scores could be due to a suboptimal analgesic regimen because anesthesiologists assume MIS to be minimally painful as well. Consequently, because of applying thrifty amounts of analgesics, patients could experience more physical stress during and after laparoscopic surgery. However, previous research indicated that MIS is connected with lower intraoperative stress hormone levels [18, 19].

In conclusion, recent research found conventional surgery not superior to MIS with respect to pain perception during surgery and during the first hours postoperatively. These findings cannot be satisfactorily explained yet.

The objective of this study is to compare pain perception during and after surgery between LH, AH, and VH, and whether pain indicators during surgery (nociceptive state, stress hormones) predict pain perception as well as demand for analgesics (e.g., morphine) postoperatively.

Materials and methods

Each consecutive patient scheduled for either AH, LH, or VH at our department was requested to participate in the study. Informed consent was required as several blood samples were to be collected and participation of the patient was needed with respect to completing the questionnaires and assessing pain intensities postoperatively. Exclusion criteria included disturbances of the central nervous system or psychiatric diseases, chemical substance abuse, chronic use of analgesics, chronic pain, cardiovascular, hepatic or renal insufficiency, pregnancy, extended accompanying prolapse or oncologic surgery, and age less than 18 years. In addition, supracervical hysterectomies were excluded from the study as well. The protocol was approved by the local Human Ethics Committee (protocol number P08.100).

After inclusion, plasma catecholamine concentrations (CAMI; norepinephrine and epinephrine levels in nanomoles per liter) were measured at our outpatient department in order to obtain baseline levels. Three more CAMI samples were obtained during surgery (i.e., instantly after intubation, after ligation of the second uterine artery, and after closing the vaginal cuff) and two more samples 4 and 8 h postoperatively, respectively. Each obtained sample consisted of 4 ml venous blood in an EDTA-fuse, instantly stored in a −20 °C environment and analyzed according to protocol within 60 min.

Each patient was asked to assess her pain level using a visual analog scale (VAS) meter (ranging from zero for no pain at all to 10 for intolerable pain) preoperatively (before premedication had been administered) and 4, 8, and 24 h postoperatively, provided she self-rated herself awake (>4 VAS).

In order to correct for catastrophization of pain (exaggerated or extreme negative conception of pain), each patient was provided with a concise validated questionnaire, which was to be filled out on the day prior to surgery [20, 21]. This baseline questionnaire aimed to assess actual pain experience, possible fear of the upcoming surgery, as well as expectations about pain during the first hours after surgery.

A validated mode to assess nociceptive state in patients was by means of measuring the pulse transit time (PTT). Pulse transit time was defined as the interval from the ECG R-wave to the upstroke of the waveform of the pulse oximeter of the same cardiac cycle. Elevation in PTT levels were associated with a low nociceptive stress response, while lowering of PTT indicated elevation in nociceptive stress state.

Pain perception during surgery was measured by continuously assessing nociceptive state as well as by determining stress hormonal levels (i.e., catecholamines, also known as “fight or flight” stress hormones). Perceived pain was assessed during the first 24 h postoperatively.

During surgery, continuous 3-lead ECG and infrared pulse oximeter waveforms were obtained from Cardiocap II and Capnomac Ultima devices (Datex, Helsinki, Finland). These signals were linked to a custom made analog computer (Marc Geerts, Leiden University Medical Center, The Netherlands), which calculated the PTT for each heart beat. The pulse oximeter was attached to the index fingertip of the left arm. PTT and heart rate (HR) values were measured continuously. General anesthesia was induced according to the following guideline: remifentanil at 10 $\mu g kg^{-1} h^{-1}$, followed by an induction dose of propofol (2 mg/kg) and atracurium (0.5 mg/kg). The trachea of all patients was subsequently intubated (tube sizes, 8–9) and propofol was continued at an infusion rate of 6–10 $\mu g kg^{-1} h^{-1}$. Since this was an observational study, the attending anesthesiologist was allowed to change the drug doses and infusion rates according to his or her own discretion. His or her decisions were based on the routine parameters used to guide anesthesia (heart rate, blood pressure, patient movement, and sudomotor responses).

If patients received general anesthesia combined with epidural anesthesia, epidural anesthesia was continued up to the second day after surgery. Postoperatively, every patient was provided with patient-controlled analgesia (an electronically controlled infusion pump, delivering a prescribed amount of intravenous analgesic when activating the button). The amount of peri- and postoperatively provided analgesics were recorded.

Provided patients undergoing LH experienced more pain during surgery and during the first 8 h postoperatively, compared to AH, we aimed to assess a 30 % mean difference (alpha=0.05) in PTT during surgery, with SD 0.2. Based on results from former research with PTT comparing laparoscopy with laparotomy, 15 patients in each group were needed to achieve a power of 0.90. The VH group primarily acted as a control group as no adequate comparable research on pain perception in vaginal surgery was available.

Data was analyzed using SPSS 17.0 statistical software (Chicago, IL, USA). Variables were tested for normal distribution using the Kolmogorov–Smirnov test. If variables lacked a normal distribution, Spearman's rank correlation coefficients where calculated. Differences between groups were assessed with the chi-square test for proportions and, if normally distributed, Student-independent samples *t* test for continuous variables. One-way analysis of variance (ANOVA) was used to assess differences between the three groups. 95 % Confidence intervals (95 % CI) and standard deviations were calculated; *P* values <0.05 were considered statistically significant.

Findings

Patient characteristics were comparable between groups with respect to indication, age, BMI, American Society of Anesthesiologists classification, and preoperative pain perception (Table 1). Perioperative blood loss and amounts of anesthetics administered did not differ between groups, while length of surgery was significantly higher in LH and uterus weight was significantly higher in AH. Patients receiving general anesthesia combined with epidural analgesics were equally distributed in LH and AH. However, VH significantly more often received general anesthesia exclusively.

During the first 90 min of surgery, PTT and HR levels did not differ significantly between AH, LH, and VH (Fig. 1). Perioperative and postoperative stress hormone levels did not differ significantly between groups (Table 2). However, subgroup analysis in patients receiving general anesthesia exclusively showed significant lower noradrenalin levels in LH patients during the first hours after surgery compared to AH.

Analysis of the preoperatively completed questionnaire yielded no differences with respect to actual pain experience, fear of having surgery, and expectations about pain during the first hours after surgery. Preoperative pain scores were comparable between groups (Fig. 2). During the first hours after surgery, LH patients showed insignificant lower pain scores, compared to AH and VH (VAS_{delta} −1.57 (−3.41 to 0.29) and VAS_{delta} −1.66 (−3.54 to 0.23), respectively). About half of the AH and LH patients opted for general anesthesia combined with regional (epidural) anesthesia. In general, patients with postoperative epidural analgesics showed significantly lower pain scores in the first 4 h postoperatively, compared to patients without epidural analgesics (VAS_{delta} −2.17 (−3.32 to −1.02)). However, subgroup analysis of LH patients yielded no difference in pain scores between LH patients with postoperative epidural analgesics compared to LH patients without epidural analgesics (VAS_{delta} −0.40 (−1.66 to 2.44)). One day postoperatively, LH patients reported significantly lower pain scores, compared to AH patients (VAS_{delta} −1.50 (−3.06 to −0.01)). Observed differences in the general anesthesia group mainly contributed to this finding.

High intraoperative CAMI levels predicted a significant higher demand for morphine postoperatively accompanied

Table 1 Study group characteristics

	Total (*n*=45)	95 % CI	*P* value	AH (*n*=15)	LH (*n*=15)	VH (*n*=15)
Age (years)	48.2	45.9–50.4	0.129	51.4 (8.5)	46.6 (5.6)	46.7 (7.2)
BMI (kg/m^2)	26.9	25.1–28.7	0.165	28.3 (7.1)	24.5 (4.6)	27.8 (4.7)
Preoperative pain score (VAS)	0.9	0.41–1.35	0.964	0.9 (1.4)	0.9 (1.8)	0.8 (1.5)
ASA I (%)	55.6		0.181	73.3	53.3	40.0
General anesthesia and epidural (%)	40.4		0.027	53.3	53.3	6.7
Length of surgery (min)	107.3	94.7–119.9	0.005	98.7 (37.2)	134.3 (44.7)	89.1 (30.8)
Blood loss (ml)	195.9	131.6–260.2	0.308	230.7 (245.9)	126.0 (150.9)	231.0 (229.9)
Uterus weight (grams)	291.2	202.6–379.7	0.017	446.6 (447.0)	279.6 (135.6)	147.3 (81.9)
BIS (mean values)	39.9	37.3–42.5	0.213	40.1 (4.5)	37.8 (4.9)	43.3 (8.3)
Atracurium dose (mg)	46.8	40.6–53.1	0.084	55.7 (25.6)	42.5 (14.0)	40.5 (8.0)
Remifentanil dose (μm/kg/h)	12.1	9.2–15.1	0.736	5.4 (3.1)	7.4 (4.2)	4.7 (3.9)
Propofol dose (mg/kg/h)	5.9	4.6–7.2	0.187	5.4 (3.1)	7.4 (5.3)	4.7 (4.4)

Values between brackets are standard deviations. Differences between groups were calculated using one-way ANOVA for continuous variables and chi-square for proportions

AH abdominal hysterectomy, *LH* laparoscopic hysterectomy, *VH* vaginal hysterectomy

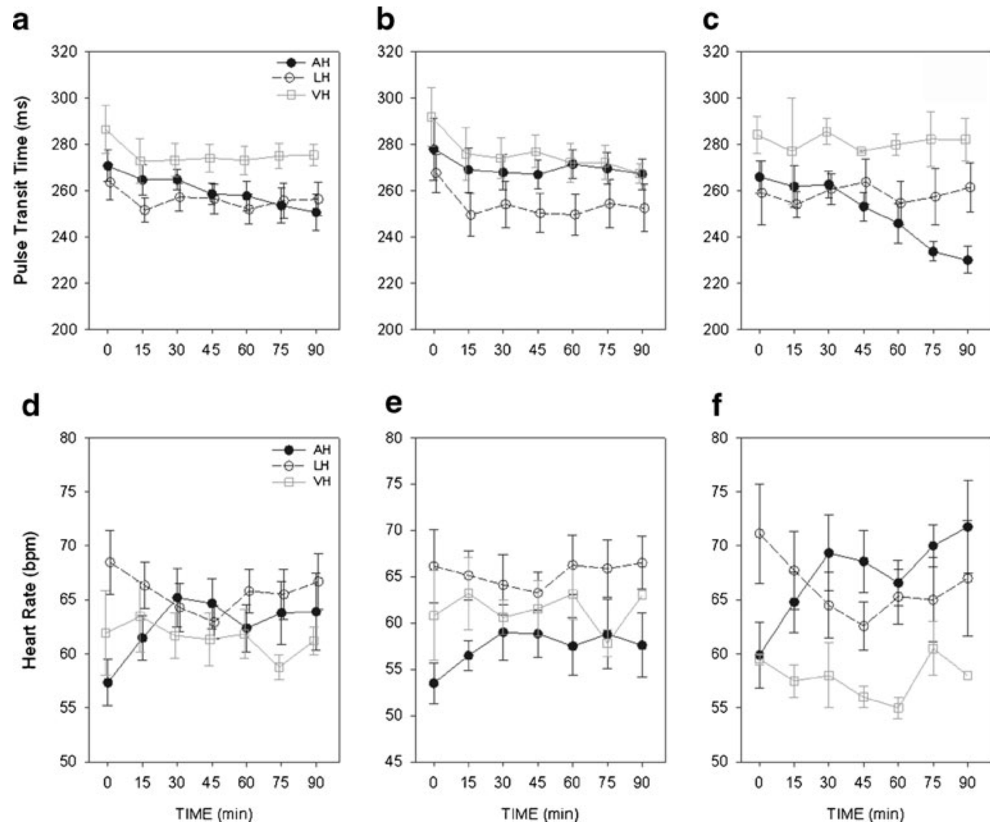

Fig. 1 Intraoperative PTT and HR levels in total (**a** and **d**), in general anesthesia (**b** and **e**), and general and epidural anesthesia combined (**c** and **f**). *PTT* pulse transit time (microsecond), *HR* heart rate (beats per minute), *AH* abdominal hysterectomy, *LH* laparoscopic hysterectomy, *VH* vaginal hysterectomy. Differences between groups were calculated using one-way ANOVA for continuous variables. *Error bars* represent standard errors of the means

with significant higher pain scores (Table 3). Low mean PTT and high HR levels did not predict a higher demand for postoperative analgesics or pain scores. However, high PTT levels were associated with elevated intraoperative propofol use.

Discussion and conclusions

Pain perception during the first hours after surgery and intraoperative pain indicators are comparable between abdominal, laparoscopic, and vaginal hysterectomy. These outcomes

Table 2 Mean catecholamine (CAMI) levels during and after surgery

		Total (n=45)	95 % CI	P value	AH (n=15)	LH (n=15)	VH (n=15)
Total	Noradrenalin during surgery (nmol/L)	1.66	1.26–2.07	0.658	1.53 (0.88)	1.52 (1.00)	1.92 (1.95)
	Noradrenalin after surgery (nmol/L)	1.05	0.82–1.28	0.517	1.10 (0.75)	0.86 (0.27)	1.17 (0.28)
	Adrenalin during surgery (nmol/L)	0.18	0.09–0.27	0.413	0.12 (0.16)	0.16 (0.30)	0.26 (0.42)
	Adrenalin after surgery (nmol/L)	0.08	0.06–0.09	0.286	0.07 (0.03)	0.07 (0.05)	0.10 (0.09)
					AH (n=6)	LH (n=7)	
No epidural	Noradrenalin during surgery (nmol/L)	1.75	1.16–2.34	0.392	2.01 (1.09)	1.53 (0.87)	
	Noradrenalin after surgery (nmol/L)	1.11	0.67–1.56	0.013	1.62 (0.82)	0.67 (0.20)	
	Adrenalin during surgery (nmol/L)	0.27	0.07–0.46	0.636	0.22 (0.21)	0.31 (0.40)	
	Adrenalin after surgery (nmol/L)	0.09	0.06–0.12	0.355	0.07 (0.03)	0.10 (0.06)	
					AH (n=9)	LH (n=8)	
With epidural	Noradrenalin during surgery (nmol/L)	1.36	0.90–1.82	0.527	1.22 (0.58)	1.51 (1.17)	
	Noradrenalin after surgery (nmol/L)	0.89	0.68–1.10	0.186	0.76 (0.49)	1.03 (0.21)	
	Adrenalin during surgery (nmol/L)	0.04	0.02–0.06	0.355	0.05 (0.04)	0.03 (0.04)	
	Adrenalin after surgery (nmol/L)	0.06	0.04–0.07	0.690	0.06 (0.02)	0.05 (0.04)	

Values between brackets are standard deviations. Differences between groups were calculated using one-way ANOVA for continuous variables; independent samples T tests were applied to calculate differences between two subgroups

AH abdominal hysterectomy, *LH* laparoscopic hysterectomy, *VH* vaginal hysterectomy

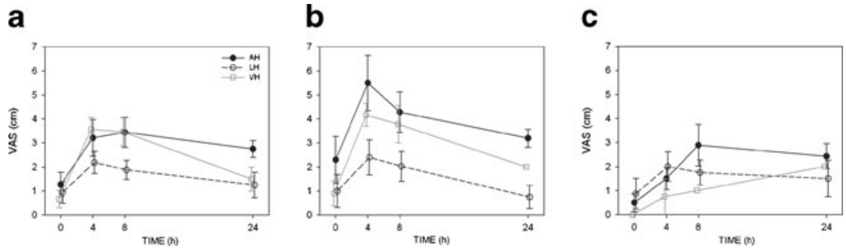

Fig. 2 Baseline and postoperative pain scores in AH, LH, and VH in total (**a**), after general anesthesia (**b**) and general and epidural anesthesia combined (**c**). Preoperative pain scores were comparable between groups. During the first hours after surgery, LH patients showed insignificant lower pain scores, compared to AH and VH (VAS_{delta} −1.57 (−3.41 to 0.29) and VAS_{delta} −1.66 (−3.54 to 0.23), respectively). In general, patients with postoperative epidural analgesics showed significantly lower pain scores in the first 4 h postoperatively, compared to patients without epidural analgesics (VAS_{delta} −2.17 (−3.32 to −1.02)). However, subgroup analysis of LH patients yielded no difference in pain scores between LH patients with postoperative epidural analgesics compared to LH patients without epidural analgesics (VAS_{delta} −0.40 (−1.66 to 2.44)). One day postoperatively, LH patients reported significantly lower pain scores, compared to AH patients (VAS_{delta} −1.50 (−3.06 to −0.01)). *AH* abdominal hysterectomy, *LH* laparoscopic hysterectomy, *VH* vaginal hysterectomy. Differences between groups were calculated using one-way ANOVA for continuous variables. *$P<0.05$, significant differences. *Error bars* represent standard errors of the means

suggest that an unambiguous anesthetic protocol for both conventional as well as laparoscopic surgery is justified. Minimally invasive surgery is not associated with a minimum of pain perception. This is in contrast with the previously observed minimal tissue damage in MIS. Therefore, MIS patients should be offered a "conventional" anesthetic regime. However, addition of epidural analgesics did not significantly lower postoperative pain scores in MIS patients.

On a patient level, we observed that elevated intraoperative noradrenalin levels predicted elevated postoperative pain scores, accompanied with an increased demand for postoperative rescue analgesia. These findings are solely applicable in a research setting and not clinically relevant, as determination of noradrenalin values is time consuming and rather expensive.

The intraoperative PTT values in our study did not show a significant difference between conventional and MIS procedures, which was observed in other research [17]. Perhaps, minor heterogeneity in indication for surgery in that former study was causing selection bias. Hypothetically, homogeneity of the patient sample in our study reproduces PTT levels more accurately.

Table 3 Correlations between intraoperative and postoperative stress indicators

Principal stress indicators	r_s	*P* value
PTT and mean postoperative pain VAS	0.04	0.776
PTT and postoperative analgesics use	0.29	0.27
PTT and intraoperative Propofol dose	0.44	0.038
HR and mean postoperative pain VAS	−0.21	0.162
HR and call for postoperative analgesics use	0.13	0.62
Intraoperative NOR and postoperative NOR	0.37	0.005
Intraoperative ADR and postoperative ADR	0.42	0.001
Intraoperative NOR and postoperative pain VAS	0.30	0.046
Intraoperative ADR and postoperative pain VAS	0.37	0.012
Postoperative pain VAS and postoperative analgesics use	0.72	0.029

As parameters lacked a normal distribution, the Spearman's rank correlation coefficient (r_s) was applied to provide a measure of association between principal stress indicators

AH abdominal hysterectomy, *LH* laparoscopic hysterectomy, *VH* vaginal hysterectomy, *PTT* pulse transit time, *VAS* visual analog scale, *HR* heart rate, *NOR* noradrenalin, *ADR* adrenalin

From a scientific perspective, a randomized controlled trial would provide optimal reliable outcomes indicating which approach in hysterectomy is associated with the lowest pain perception. However, from both practical as well as ethical perspective, this design is not feasible anymore, due to two reasons. Firstly, former research provided evidence that VH is superior over AH and LH with respect to many aspects and consequently patients should be offered the best available option [2, 3]. Secondly, with respect to applied amounts of analgesics, no ethical committee would allow a protocol that would not take into account patient specific demand for supplementary analgesics. Therefore, we consider an observational cohort study to be the best available option.

Analysis of intraoperatively administered analgesics yielded no statistically significant differences between groups. Besides, postoperative calls for rescue analgesics were recorded and therefore appropriate for analysis. Furthermore, the observational design of this study facilitates instant applicability in daily practice.

Each previous study on pain perception after hysterectomy mainly focused on the time needed to become pain free [1–3, 8, 22]. One recent study concentrated on pain scores during the first hours after surgery and found higher scores in laparoscopic procedures compared to the conventional approach [16]. However, that study did not take into account the intention-to-treat principle with respect to assessment of pain VAS scores, consequently overrating conscious "laparoscopic" patients while excluding uncooperative, drowsy "abdominal" patients. Also, no correction for amount of administered analgesics was made. In our study, both corrections for consciousness as well as administered analgesics were taken into account.

The few articles, that studied stress hormonal values as an outcome in comparisons between minimally invasive and conventional surgery, found lower values in the minimally invasive group [18, 19]. Similar to our study, relatively elevated intraoperative noradrenalin levels were found in the conventional group. The only study researching postoperative hormonal state did determine serum cortisol, a circadian hormone with a long half-life [18]. Our study assessed catecholamines (120 s half-life) at specific time points during and after surgery.

VH and LH, both regarded as true exponents of minimally invasive surgery, are often considered to be minimally painful as well. However, with respect to nociceptive and stress hormonal intraoperative pain indicators, no significant lower values in this study were found, compared to the abdominal approach. These outcomes were confirmed with observed comparable pain scores during the first hours after surgery. As intraoperative and postoperative administered analgesics were corrected, these outcomes are likely to be reliable.

Although not a primary outcome of this study, the added value of epidural analgesics to general anesthesia, with respect to postoperative pain perception in LH patients is questionable. Probably traction on tissue during VH and peritoneal wound healing in AH might explain the differences compared with LH. Also others found lower postoperative pain scores in MIS [3, 4]. This study states that, although LH is preferred over AH with respect to postoperative pain perception, this minimally invasive approach in hysterectomy remains a major surgical procedure. However, perhaps MIS patients are better served in a fast track system without accompanying epidural analgesics, consequently enhancing a quicker recovery [23].

Declaration of interest The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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