

Effects of abdominal, vaginal, and laparoscopic hysterectomies on total oxidant/antioxidant levels

A prospective observational study

Aybuke Tayarar, MD^a, Emre Erdem Tas, MD^{b,*}, Almila Senat, MD^c

Abstract

This prospective observational study aimed to compare abdominal hysterectomy (AH), vaginal hysterectomy (VH), and total laparoscopic hysterectomy (TLH) in terms of oxidative stress (OS) by measuring serum levels of total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI). Of the 3 groups, namely, AH, VH, and TLH, 22 patients were enrolled in each to investigate the aim of the study mentioned above. Patient demographics, clinical and surgical characteristics, and preoperative and postoperative (0th and 24th hours) serum TAS, TOS, and OSI levels were investigated. The groups differed significantly based on surgical indications ($P < .001$). While abnormal uterine bleeding was more prevalent in the AH (95.5%) and TLH (77.3%) groups, pelvic organ prolapse (POP) was more prevalent in the VH group (90.1%). The mean age and menopausal patient rates were significantly higher in the VH group than in the AH and TLH groups ($P < .001$). The groups did not differ significantly in terms of simultaneous bilateral salpingo-oophorectomy rates ($P = .10$). However, additional POP surgery was performed in 14 patients in the VH group. The mean operative time was significantly shorter in the AH group than in the VH and TLH groups ($P = .001$). The groups did not differ significantly based on either the preoperative or postoperative serum TAS levels ($P > .05$). Furthermore, the change in serum TAS levels over time was not significant in any of the groups ($P > .05$). In contrast, preoperative serum TOS and OSI levels were significantly higher in the VH group than in the AH and TLH groups ($P < .05$). The groups did not differ significantly in terms of serum TOS and OSI levels at 0th and 24th hours postoperatively ($P > .05$). Serum TOS and OSI levels increased dramatically over time in the AH and TLH groups ($P < .05$), but not in the VH group ($P > .05$). post hoc analysis showed that the changes in serum TOS and OSI values in the AH and TLH groups were between the preoperative and postoperative 0th hour levels ($P < .001$). Our results indicated that the total antioxidant capacity was preserved in all 3 techniques. However, VH causes less OS than the other hysterectomy techniques.

Abbreviations: AH = abdominal hysterectomy, AUB = abnormal uterine bleeding, BMI = body mass index, BSO = bilateral salpingo-oophorectomy, CBCs = complete blood counts, Hb = hemoglobin, OS = oxidative stress, OSI = oxidative stress index, Plt = platelet, POP = pelvic organ prolapse, TAS = total antioxidant status, TLH = total laparoscopic hysterectomy, TOS = total oxidant status, VH = vaginal hysterectomy, WBC = white blood cell.

Keywords: hysterectomy, laparoscopy, laparotomy, oxidative stress

1. Introduction

Hysterectomy refers to the removal of the uterus and is 1 of the most common gynecological operations. It is indicated for the treatment of various benign and malignant gynecological pathologies. Hysterectomy can be performed using multiple approaches, such as abdominal, vaginal, laparoscopic, robot-assisted, and vaginal natural orifice.^[1] Among these, the first 3 are the most widely used worldwide.^[2,3] Previous analyses have evaluated the advantages and disadvantages of different hysterectomy techniques from the perspective of patients,

surgeons, healthcare institutions, and insurance.^[1] However, our knowledge of the molecular effects of these techniques, such as the oxidative stress (OS) status, is still lacking.

Under normal circumstances, a specific quantity of reactive oxygen species is generated during cellular processes, typically counterbalanced by the body's antioxidant defense mechanisms.^[2] Nevertheless, in the event that excessive amounts of these reactive species are produced, they can exceed antioxidant defenses, resulting in a condition known as OS, which is associated with both acute and chronic adverse conditions.^[2,3] Surgery,

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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like other tissue traumas, initiates the accumulation of free oxygen radicals, which may shift this balance toward OS.^[3,4] However, the effects of different surgical approaches (e.g., laparoscopy and laparotomy) on OS may vary.^[4,5]

Many molecules can be used to detect oxidant and antioxidant status. However, measuring their levels separately is complex and costly.^[5] In the 2000s, a novel automated colorimetric method for measuring the serum levels of total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) was developed by Erel, which provides an overall evaluation.^[6,7] No studies have been conducted to determine the OS caused by hysterectomies. Thus, this study aimed to determine OS caused by hysterectomies performed using different surgical techniques, including abdominal hysterectomy (AH), vaginal hysterectomy (VH), and total laparoscopic hysterectomy (TLH), by measuring serum TAS, TOS, and OSI levels.

2. Methods

This study had a prospective clinical design. After obtaining approval from the Ankara Yıldırım Beyazıt University Clinical Research and Ethics Committee (decision number 124 on December 11, 2019), the study was conducted between December 12, 2019 and June 31, 2020 at the Department of Gynecology of the Ankara City Hospital, Ministry of Health, where abdominal, vaginal, or total laparoscopic hysterectomies were performed in patients for benign gynecological reasons. Using G*Power Ver.3.0 Software (Germany), the study determined a total sample size of 66 cases, with 22 women in each group. This calculation was based on a 1-way ANOVA test employing a power of 80% and an alpha level of .05. Before the study commenced, explicit permission was obtained from all individuals who willingly agreed to participate in the research by signing a “consent form for informed voluntary participation.”

Patients who were pregnant or lactating, smoking, had a history of any additional medical illnesses, currently undergoing medical treatment, with a history of chemotherapy or radiotherapy, used hormonal contraceptives or intrauterine devices, had a >4-cm uterine myoma, acute inflammatory disease, or a premalignant/malignant lesion detected by Pap smear or endometrial sampling were excluded from the study. None of the volunteers experienced any intraoperative or postoperative complications.

We recorded patients' demographic data, including age, gravidity, body mass index (BMI) (kg/m²), menopausal status, and personal and family medical histories. The clinical characteristics of patients, including results from pre- and postoperative laboratory testing, imaging, and histopathological examinations, were assessed using the hospital's computer automation system. Surgical methods and operative times (minute) were obtained from the medical records.

3. Details about surgeries

All patients received general anesthesia. For general anesthesia induction, 1 mg/kg lidocaine (Aritmal 2.5% mL, Osel Pharmaceutical Industry, Istanbul, Türkiye), 2.5 mg/kg propofol (Propofol-Lipuro, 1.10% mg/mL, B Braun Medical Foreign Trade Joint Stock Company, Istanbul, Türkiye), 1 mcg/kg fentanyl (Talinat 0.5 mg/10 mL, Vem Pharmaceutical Industry, Istanbul, Türkiye), and 0.6 mg/kg rocuronium (Muscuron 50 mg/5 mL, Koçak Farma Pharmaceuticals and Chemical Industries, Istanbul, Türkiye) were administered. Maintenance was achieved with a 50% air + 50% oxygen mixture with 2% sevoflurane (Sevorane 100% inhalation solution, AbbVie Medical Pharmaceuticals, Istanbul, Türkiye). Before surgery, all patients were administered 1 g cefazolin (Cezol 1g, Deva Holding Company, Istanbul, Türkiye) as an IV prophylactic antibiotic.

Patients who underwent AH were placed on a flat table in the horizontal supine position. In contrast, those who underwent VH or TLH were placed in the dorsolithotomy position. After sterilization, all patients underwent bladder catheterization.

For AH and VH, pedicles were held, cut conventionally, and tied with No. 1 polyglactin 910 sutures (Vicryl, Ethicon, New Jersey). Reconstructive pelvic organ prolapse (POP) surgeries, such as anterior colporrhaphy, posterior colporrhaphy, or sacrospinous ligament fixation, were performed, if required, along with VH. The vaginal vault was then closed with a single-layer no. 1 polyglactin 910 suture (Vicryl, Ethicon).

For TLH, the operation was performed under an intra-abdominal pressure of 12 mm Hg using a bipolar electrocautery system (LigaSure Maryland Jaw 5 mm laparoscopic sealer/divider instrument, Valleylab, Tyco Healthcare Group, Galway, Ireland). The vaginal vault was then closed intracorporeally with a single-layer no. 2 polyglactin 910 suture (Vicryl, Ethicon, New Jersey).

During the first 12 postoperative hours, 50 mg of IV pethidine hydrochloride was administered in 4-hour intervals, followed by IM or IV administration of 75 mg diclofenac sodium or 100 mg oral tablets of diclofenac sodium, depending on the patient's needs. Fluid intake was permitted 6 hours after surgery, and solid food was allowed after the initial bowel movements. Bladder catheters were removed after adequate mobilization. If necessary, vaginal packing was placed during the operation and removed 24 hours later.

4. Blood samples

Serum samples were collected from all patients at the admission of hospital, 1 day before surgery (preoperative), at the end of surgery (postoperative 0th hour), and 1 day after surgery (postoperative 24th hour). EDTA tubes were used to collect blood samples for complete blood counts (CBCs), whereas uncoated tubes were used to measure the serum TAS and TOS levels. CBCs were performed preoperatively and at the 24th hour postoperatively. In contrast, the other samples were centrifuged at 3200 rpm for 10 minutes to obtain the serum fraction for further evaluation of TAS and TOS levels. Serum samples were stored at -80°C for future biochemical analyses.

Serum TAS and TOS levels (expressed as mmol/L trolox equiv/L and $\mu\text{mol H}_2\text{O}_2$ equiv/L, respectively) were measured using commercially available kits (Rel Assay, Gaziantep, Türkiye) at the end of the study. The OSI was determined using the ratio of TOS to TAS. For its calculation, the TAS value was converted to $\mu\text{mol/L}$ and the OSI value was determined using the following formula: $\text{OSI (arbitrary unit)} = \text{TOS } (\mu\text{mol H}_2\text{O}_2 \text{ equivalent/L}) / \text{TAS } (\mu\text{mol trolox equivalent/L})$.

5. Statistical analysis

Statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk). The Kolmogorov-Smirnov test was used to assess data normality. Normally distributed data are expressed as the mean \pm standard deviation. In contrast, non-parametric data are expressed as the median and interquartile range. One-way analysis of variance (ANOVA) and Kruskal-Wallis tests were used for intergroup data comparisons. The paired-sample *t*-test and repeated-measures ANOVA were used to examine changes in data over time. The chi-square test was used to compare categorical data. Statistical tests were considered significant at a *P* value < .05, while post hoc correction tests were considered significant at a *P* value < .017 (.05/3).

6. Results

The mean age of all patients was 55.2 ± 9.1 years, and half (*n* = 33) were in menopause. Regarding surgical indications, 40

of 66 patients (60.6%) underwent surgery for abnormal uterine bleeding (AUB), and the remaining patients (26/66, 39.4%) underwent surgery for POP. Simultaneous bilateral salpingo-oophorectomy (BSO) was performed in 47 out of 66 patients (71.2%). Additional reconstructive POP surgeries were performed on 14 patients in the VH group (21.2%).

The mean age was significantly higher in the VH group than in the AH and TLH groups (61.9 years vs 51.2 and 52.4 years, respectively; $P < .001$). Similarly, the proportion of menopausal patients was significantly higher in the VH group than in the AH and TLH groups (90.4% vs 22.7% and 36.4%, respectively; $P < .001$). However, the groups did not differ significantly based on parity and BMI (P values were .58 and .50, respectively). The AH, VH, and TLH groups exhibited significant differences in terms of surgical indications ($P < .001$). AUB was more prevalent in the AH (95.5%) and TLH (77.3%) groups, whereas POP was more prevalent in the VH group (90.1%). Fewer simultaneous BSO was performed in the VH group than in the AH and TLH groups (54.5% vs 77.2% and 81.8%, respectively), with no significant difference between the groups ($P = .10$). The mean operative time was significantly shorter in the AH group than in the VH and TLH groups (61.9 minutes vs 116.8 minutes and 122.0 minutes, respectively; $P = .001$). The demographic and surgical characteristics of the AH, VH, and TLH groups are given in Table 1.

Except for the preoperative serum hemoglobin (Hb) levels, which were significantly higher in the VH group than in the AH and TLH groups (13.3 g/dL vs 11.9 g/dL and 12.5 g/dL, respectively; $P = .01$), the AH, VH, and TLH groups did not differ significantly based on preoperative and postoperative 24th hour serum CBCs levels. The change in CBC levels over time revealed that the serum white blood cell (WBC) count levels increased significantly at the 24th hour postoperatively in all groups (P values = .001). In contrast, serum Hb levels decreased significantly at the 24th hour postoperatively in all the groups (P values < .05). When the groups were compared in terms of mean in serum Hb level decrease, it was significantly lower in the AH group than in the VH and TLH groups (.40 g/dL vs .95 g/dL and 1.0 g/dL, respectively. $P = .01$). Serum platelet (Plt) count levels decreased at 24th hour postoperatively in all groups but were significant in the VH and TLH groups, except for the AH group (P values were .001, .001, and .49, respectively). The preoperative and postoperative serum CBC levels in the AH, VH, and TLH groups are shown in Table 2.

The AH, VH, and TLH groups did not differ significantly based on either preoperative or postoperative serum TAS levels ($P > .05$). Although preoperative serum TOS and OSI levels

were significantly higher in the VH group than in the AH and TLH groups (P values were .01 and .02, respectively), the groups did not differ significantly in terms of serum TOS and OSI levels at the 0th and 24th hours postoperatively ($P > .05$). On the other hand, the change in serum TAS levels over time was not significant in any of the groups ($P > .05$). However, the changes in serum TOS and OSI levels over time were significant in the AH and TLH groups ($P < .05$), but not in the VH group ($P > .05$). post hoc analysis showed that the changes in serum TOS and OSI values in the AH and TLH groups were between the preoperative and postoperative 0th hour levels ($P < .001$). The preoperative and postoperative (0th and 24th hours) serum TAS, TOS, and OSI levels in the AH, VH, and TLH groups are shown in Table 3.

7. Discussion

Among the surgical techniques, VH seems to be the most advantageous and is recommended as the first choice.^[1] However, the adopted surgical approach varies according to the indication for surgery, uterine mobility, BMI, preoperative medical and surgical history, surgeon and surgical team experience, and patient preference.^[8,9] In the present study, the VH group differed from the AH and TLH groups regarding age, menopausal status, and surgical indications. However, these parameters were interrelated. For instance, the mean age and menopausal women ratio were significantly higher in the VH group, and POP, the incidence of which increases with age and menopause,^[10] was the major indication for the VH group. In contrast, the mean age of the AH and TLH groups was in their early 50s, less than half of whom were menopausal. AUB, whose incidence is more prevalent in perimenopause,^[11] was the major indication for these groups.

Simultaneous BSO with hysterectomy is influenced by various factors, including race, age, parity, indication, and surgical route.^[12] In our study, the rate of simultaneous BSO with hysterectomy was 71.2%, consistent with the rates reported in similar age groups.^[12] However, the rate of simultaneous BSO was affected by the surgical route. Although there was no significant difference between the groups, fewer simultaneous BSOs were performed in the VH group. This finding aligns with previous reports.^[12,13]

Minimally invasive surgeries are associated with a quickest return to normal activities and early discharge from the hospital. Two hysterectomy techniques, VH and TLH, are considered minimally invasive surgeries.^[1] However, in contrast to VH, TLH has a learning curve, requires expertise, and is

Table 1
Demographic and surgical characteristics of the abdominal hysterectomy, vaginal hysterectomy, and total laparoscopic hysterectomy groups.

Characteristics	AH group (n = 22)	VH group (n = 22)	TLH group (n = 22)	P^*
Age (yr)	51.2 ± 7.9	61.9 ± 9.1	52.4 ± 6.3	<.001
Parity	3 (3)	3 (2)	3 (2)	.58
BMI (kg/m ²)	29.7 ± 5.2	27.3 ± 4.1	26.5 ± 3.7	.05
Menopause				
No	17 (25.8)	2 (3.0)	14 (21.2)	<.001
Yes	5 (7.6)	20 (30.3)	8 (12.1)	
Surgical indication				
AUB	21 (31.8)	2 (3.0)	17 (25.8)	<.001
POP	1 (1.5)	20 (30.3)	5 (7.6)	
Uni- or bilateral salpingo-oophorectomy				
Yes	17 (77.3)	12 (54.5)	18 (81.8)	.10
No	5 (22.7)	10 (45.5)	4 (18.2)	
Operative time (min)	61.9 ± 16.9	116.8 ± 20.6	122.0 ± 32.0	.001

Data are presented as the mean ± standard deviation, median (interquartile range), or n (%).

Abbreviations: AH = abdominal hysterectomy, AUB = abnormal uterine bleeding, BMI = body mass index, POP = pelvic organ prolapse, TLH = total laparoscopic hysterectomy, VH = vaginal hysterectomy.

* One-way ANOVA, Kruskal-Wallis, and chi-square tests were used for intergroup data comparisons.

Table 2

Preoperative and postoperative serum complete blood count parameters in the abdominal hysterectomy, vaginal hysterectomy, and total laparoscopic hysterectomy groups.

Parameters		AH (n = 22)	VH (n = 22)	TLH (n = 22)	P*
White blood cell count ($\times 10^3/\mu\text{L}$)	Preoperatively	7.0 \pm 2.9	6.8 \pm 1.6	7.2 \pm 1.4	.85
	24th hour postoperatively	13.4 \pm 4.8	12.3 \pm 3.6	11.7 \pm 2.8	.35
	P†	.001	.001	.001	
Hemoglobin (g/dL)	Preoperatively	11.9 \pm 1.7	13.3 \pm 1.1	12.5 \pm 1.4	.01
	24th hour postoperatively	11.5 \pm 1.4	12.3 \pm 1.1	11.5 \pm 1.3	.07
	P†	.02	.01	.01	
Platelet count ($\times 10^3/\mu\text{L}$)	Preoperatively	280.0 \pm 89.0	288.7 \pm 78.7	310.3 \pm 92.9	.49
	24th hour postoperatively	269.7 \pm 70.7	247.1 \pm 74.5	258.8 \pm 54.2	.50
	P†	.49	.001	.001	

Data are presented as the mean \pm standard deviation.

Abbreviations: AH = abdominal hysterectomy; CBC = complete blood count; TLH = total laparoscopic hysterectomy; VH = vaginal hysterectomy.

* One-way ANOVA variance was used to compare the AH, VH, and TLH groups.

† The paired-sample T-test was used to examine changes in complete blood counts level over time.

Table 3

Preoperative and postoperative serum total antioxidant status, total oxidant status and oxidative stress index levels in the abdominal hysterectomy, vaginal hysterectomy, and total laparoscopic hysterectomy groups.

Parameters		AH (n = 22)	VH (n = 22)	TLH (n = 22)	P*
Serum TAS level (mmol/L trolox equiv/L)	Preoperatively	.96 \pm .25	1.11 \pm .22	.99 \pm .23	.09
	0th hour postoperatively	.96 \pm .22	1.04 \pm .22	1.11 \pm .32	.18
	24th hour postoperatively	.89 \pm .25	1.05 \pm .13	1.0 \pm .26	.08
	P†	.25	.39	.10	
Serum TOS level ($\mu\text{mol H}_2\text{O}_2$ equiv/L)	Preoperatively	7.6 \pm 4.77	13.8 \pm 10.2	8.6 \pm 4.8	.01
	0th hour postoperatively	13.8 \pm 8.1	15.4 \pm 13.3	16.0 \pm 13.3	.78
	24th hour postoperatively	11.9 \pm 8.1	12.0 \pm 6.7	15.3 \pm 20.1	.61
	P†	.006	.48	.009	
Serum OSI level (AU)	Preoperatively	8.1 \pm 5.2	14.4 \pm 13.5	8.4 \pm 3.2	.02
	0th hour postoperatively	14.5 \pm 7.9	15.9 \pm 15.6	15.2 \pm 11.5	.90
	24th hour postoperatively	13.1 \pm 8.0	11.8 \pm 7.5	16.2 \pm 24.2	.61
	P†	.003	.47	.02	

Data are presented as the mean \pm standard deviation.

Abbreviations: AH = abdominal hysterectomy, AU = arbitrary unit, OSI = oxidative stress index, TAS = total antioxidant status, TOS = total oxidant status, TLH = total laparoscopic hysterectomy, VH = vaginal hysterectomy.

* One-way ANOVA variance was used to compare the AH, VH, and TLH groups.

† Repeated-measures analysis of variance (ANOVA) was used to examine changes in TAS, TOS, and OSI levels over time.

associated with a longer operation time until experience is gained.^[14] A Cochrane review investigating different hysterectomy techniques concluded that, while TLH typically involves a longer operation time than other hysterectomy methods, the results comparing AH and VH in terms of operation time are inconsistent.^[1] In our study, the mean operation time was significantly longer in the TLH and VH groups than in the AH group. In a study conducted at a clinic where assistant training was provided, as is the case in our clinic, the reported operative times in the AH, VH, and TLH groups were quite similar to those in our study.^[8] As other authors have emphasized, we concluded that the longer operation time in the TLH group was related to assistant training and the surgeons' learning curve.^[1,8,14] However, we believe the prolonged operation time in the VH group was due to additional POP surgeries performed solely in this group.

AUK is a common complaint in perimenopause and may be related to anemia.^[15] As expected, preoperative serum Hb levels were significantly lower in the AH and TLH groups, whose main surgical indication was AUB, than in the VH group. However, the decrease in postoperative serum Hb levels was significantly lower in the AH group than in the other groups. Despite this seemingly counterintuitive finding, prior reports do not suggest that minimally invasive methods, such as VH and TLH, result in a smaller serum Hb drop.^[1,7,15,16] In contrast, serum WBC levels increased significantly in all groups

postoperatively, an expected finding in surgery-related inflammation.^[16] On the other hand, our study revealed that serum Plt levels decreased postoperatively in all groups. However, the results of a few studies that have evaluated the relationship between serum Plt levels and hysterectomy have been inconsistent.^[17–19] For instance, Zhao et al reported that serum Plt levels increased postoperatively in patients who underwent AH and TLH.^[17] In contrast, Toz et al reported decreased serum Plt levels in patients who underwent TLH.^[19] In another study, Millis et al reported that serum Plt levels decreased after hysterectomy in dogs.^[18] These results indicate that further studies are required in this area.

Previous studies have suggested that laparoscopic surgery may serve as an ischemia/reperfusion model, where pneumoperitoneum reduces intestinal perfusion and deflation post-surgery allows for splanchnic reperfusion.^[20,21] In their study, Glantzounis et al found that serum TAS levels decreased significantly in laparoscopic cholecystectomy but not in open cholecystectomy.^[21] Similar findings were obtained by Aktimur et al in patients who underwent open and laparoscopic appendectomy.^[5] However, in an animal study, Lee et al showed that serum TAS levels were affected by intra-abdominal pressure, and serum TAS levels did not differ significantly over time when intra-abdominal pressure was ≤ 12 mm Hg.^[22] Similarly, Aran et al found that serum TAS levels did not differ over time in patients who underwent laparoscopic ovarian cystectomy at an

intra-abdominal pressure of 12 mm Hg.^[23] Our study supports the previous findings of Lee et al and Aran et al, and neither between the groups nor over time the significant differences observed in terms of serum TAS levels.

Reports examining the association between OS, POP, and menopause have shown that oxidative products increase in both POP and menopause.^[20,21] Our study supports this suggestion, and serum TOS and OSI levels were significantly higher in the VH group, in which POP and menopause rates were significantly higher than in the other groups. On the other hand, our results showed that serum TOS and OSI levels in the AH and TLH groups, unlike in the VH group, increased significantly on the 0th hour postoperatively compared with preoperatively. This finding suggests that VH may be less associated with OS. The discrepancy between our results and those of previous studies, which suggested that laparoscopic surgery was less likely to be associated with oxidative products and OS, may result from methodological differences, such as demographics, indications, type of surgery, and operation time.^[4,5]

In conclusion, in terms of OS, this study evaluated the 3 most widely used hysterectomy techniques worldwide: AH, VH, and TLH. Our results showed that the total antioxidant capacity was preserved in all 3 techniques. However, VH causes less OS than the other hysterectomy techniques. Limitations of our study include the small sample size. Furthermore, in some cases, the addition of BSO or reconstructive POP surgery to the hysterectomy procedure may have affected the data. On the other hand, our study's strength is to monitor the systemic OS response caused by different hysterectomy techniques up to 24 hours after surgery in an as-yet-unexplored field. However, larger randomized controlled trials are required to arrive at definitive conclusions.

Author contributions

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