The Potential Role of Hydrocortisone in Acute Phosphide Poisoning: A Randomized Clinical Trial

Ghada A. Abd El- Hamid, Mona M. Abo El-Noor, Abdel Moty M. Kabbash, Mona S. Elgohary

Department of Forensic Medicine and Clinical Toxicology, Faculty of Medicine, Tanta University, Tanta, Egypt
gh_attia@hotmail.com

Abstract: Metal phosphide poisoning is a worldwide health problem due to its high mortality and no evident specific antidote. Phosphide poisoning is one of these stress conditions that affects adrenal cortex. Hydrocortisone has been proved to have an evident role in treating critical illness- related corticosteroid insufficiency (CIRCI). Reference wise and according to the best of our recent knowledge, this is the first clinical trialevaluating the role of hydrocortisone as an adjuvant therapy in the management of patients with acute phosphide poisoning. This was a single blinded randomized clinical trial conducted on 30 patients with acute aluminium phosphide poisoning (ALP) who were admitted to the Poison Control Unit in Tanta University Emergency Hospital, Egypt with acute phosphide poisoning from September 2016 to September 2017. Interventions included intravenous hydrocortisone (200mg/day) as an adjuvant to the standard treatment versus the standard treatment plus placebo. Outcome measures were assessed regarding mortality, need for mechanical ventilation, and amount of vasopressors needed for normalization of blood pressure, arterial blood pressure at time of discharge and duration of hospital stay. Sociodemo graphic, toxicological and baseline clinical data as well as serum cortisol and plasma ACTH levels measured at time of admission were of no significant difference between both groups. Mortality and need for mechanical ventilation were insignificantly decreased in hydrocortisone treated group. Survivors on hydrocortisone therapy required significantly less norepinephrine doses and less hospitalization period than those who received standard treatment. It was concluded that hydrocortisone administration to AlP poisoned patients could improve hemodynamic state with significant decrease in the dose of norepinephrine required and the length of hospital stay.

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1. Introduction:

Metal phosphides are used worldwide as pesticides for protection of stored grains from rodents & pests **(Farzaneh et al., 2018).** Phosphide poisoning is considered one of the major health problems which could occur accidental, intentialor even occupational **(Ahmadi et al., 2018).**

Metal phosphide poisoning in Egypt is common due to its wide accessibility and low price. They are available in many forms as zinc phosphide powder and aluminium phosphide pellets **(Sagah et al.,2015 and Gouda et al., 2018).**

Phosphide poisoning is considered as an emergency situation due to its high mortality that ranges from 37% to 100% **(Agrawal et al., 2015).** This could be attributed to lack of specific antidote and treatment is only restricted to symptomatic and supportive measures **(Halvaei et al., 2017).**

The most common and serious presentation of acute phosphide poisoning is severe hypotension often resistant to vasopressors. Hypotension is due to volume depletion, adrenal insufficiency and myocardial depression **(Oghabian and Mehrpour, 2016).** Peripheral circulatory failure is one of the poor prognostic factors in acute phosphide poisoning **(Mehrpour et al.,2012)**.

Critical illness is one of the stressful conditions in which activation of hypothalamic-pituitary-adrenal axis (HPA) occurs with increase in cortisol level **(Herman et al.,2016).** Cortisol is a glucocorticoid hormone that is secreted by adrenal cortex. Its importance in stressful conditions is due to its role in maintaining the integrity of endothelial blood vessels, anti-inflammatory effect and reduction of vasodilatation mediated by nitric oxide **(Burford et al., 2017).**

Critical illness-related corticosteroid insufficiency (CIRCI) is a condition that occurs when cortisol level is not sufficiently increased in stress conditions **(Pisano et al., 2017).** Phosphide poisoning is one of these stress conditions that affects adrenal cortex due to phosphine inducing shock and its direct toxic effect on adrenal cortex **(Farnaghi et al.,2013).**

Corticosteroid therapy has an important role in shock by enhancing sensitivity of smooth muscle of blood vessel to vasopressors and also by treating the critical illness-related corticosteroid insufficiency **(Minneci et al.,2009 and Annane,2011).**

So, the aim of this study was to evaluate the role of hydrocortisone as an adjuvant therapy in the management of patients with acute phosphide poisoning.

2. Patients and methods:

Patients:

This study was a single blinded randomized clinical trial conducted on patients admitted to the Poison Control Unit in Emergency Hospital of Tanta University with acute phosphide poisoning between the first of September 2016 to the end of September 2017 after obtaining approval from the Research Ethics Committee of Faculty of Medicine, Tanta University. An informed written consent was obtained from each patient or his / her guardian after receiving detailed information about the study. Confidentiality of the results of investigations was considered by making code numbers for every patient. (Research ethics committee approval number: 31081/08/16, Trial ID on Pan African Clinical Trial Registry: PACTR201811766698931). Adult patients with severe acute aluminium phosphide poisoning manifested by systolic blood pressure (SBP)≤80 mmHg, pH ≤7.2, or HCO3 ≤15 meq/L with no history of medical diseases as cardiovascular, renal and hepatic diseases or steroid therapy were included **(Mashayekhian et al., 2016)**. Asymptomatic patients or those with combined ingestion or exposure to other substances including phosphide poisoning were excluded.

Methods:

Thirty adult patients with severe acute phosphide poisoning were randomly allocated into two equal groups (Group I and Group II) using the sequentially numbered, opaque sealed envelopes method **(Doig and Simpson, 2005).** The study was single blind i.e. the patient was blinded to the treatment. All patients received the standard treatment which included either all or some of the following: patient resuscitation, gastric decontamination with 2 ampoules sodium bicarbonate (each ampoule 25 ml containing 2.1 gm sodium bicarbonate) followed by activated charcoal in dose of 1 g/Kg orally, adequate hydration, vasopressors IV infusions, inhalation of 100% oxygen, ranitidine IV, magnesium sulfate IV infusion and other supportive treatment. Patients of group I received hydrocortisone (SOLU-CORTEF), manufactured by Egyptian International Pharmaceutical Industrial Company (E.I.P.I.Co.), 10th of Ramadan city, Industrial Area B1-P.O. Box: 149 Tenth, Egypt. Under license of Pfizer, eachvial containing 100 mg of hydrocortisone sodium succinate powder with ampoule containing 2 ml of sterile water diluents in a dose of200 mg /day intravenously until normalization of blood pressure **(Marik, 2007)**. Group II received placebo in the same manner. Placebo consisted of 0.9% Sodium Chloride IVin a similar order. Patients were carefully monitored for detection of any adverse effects of the study drug.

All the study patients were subjected to full history taking (Age, gender, residence, mode of poisoning, amount and route of exposure, pre-hospitalization period and presence or absence of medical diseases and clinical examination including assessment of level of consciousness by Glasgow Coma Scale (GCS), vital signs, chest, cardiovascular and abdominal examination.

ECG was done for every patient. Laboratory investigations were carried on patients' blood and gastric lavage samples.

Arterial blood sample was drawn in a heparinized tube and used for analysis of arterial blood gases (ABG). Venous blood sample was collected for biochemical and hormonal assay including complete blood count (CBC, liver enzymes, kidney function tests, random blood sugar and serum electrolytes (sodium, potassium and magnesium).

Serum cortisol level was measured using an electrochemiluminescence immunoassay (ECLIA) according to **Manguso et al., 2014**. The recorded level less than 15 µg/dl, 15-33 µg/dl and more than 34 µg/dl were regarded as adrenal insufficiency, critical illness-related corticosteroid insufficiency and adequate adrenal response, respectively **(Kronenberg, 2008).**

Plasma ACTH was measured using an electrochemiluminescence immunoassay (ECLIA) according to **Talbot et al., 2003**. Silver Nitrate test was used for gastric aspirate for detection of phosphine gas (**Chugh et al., 1989$_b$ and Wahab et al, 2008).** It turns black in positive results.

Outcome measures:

This study was a pilot clinical trial (phase II) to test the safety and efficacy of IV hydrocortisone as an adjuvant therapy in acute phosphide poisoning. The primary outcome was mortality; while secondary outcome included the need for mechanical ventilation, amount of vasopressors required for normalization of blood pressure, arterial blood pressure at time of discharge and duration of hospital stay.

Statistics: For quantitative data, the Shapiro-Wilk test for normality was performed. In case of not normally distributed data, median and interquartile range (expressed as 25th-75th percentiles) and mean ranks were calculated and Mann-Whitney U test was used for comparison between groups. While for normally distributed data, values were expressed as mean ± standard deviation and Independent samples T test was performed for comparison between groups. For qualitative data, they were expressed as numbers and percentages and Pearson's Chi square test was

used to examine association between two variables. When more than 20% of cells have expected count less than 5, Fisher's exact test was used. Significance was adopted at $p < 0.05$ for interpretation of results of tests. All analyses were done using SPSS version 20 **(Knapp, 2017).**

3. Results:

During the period of the current study, patients with zinc phosphide toxicity were presented with mild manifestations not consistent with the inclusion criteria, so, AlP poisoned patients were only included. All AlP poisoned patients showed positive for silver nitrate test as shown in **figure (1)**.

Both studied groups of acute aluminium phosphide poisoning were homogenous as regards gender, age and residence as shown in table (1). All patients in this study were presented with suicidal attempt by oral ingestion of AlP with no homicidal or accidental cases**.** No significant difference was detected between both groups as regard quantity of ingested AlP, delay time before admission and clinical data **(Table 1).**

Serum cortisol and plasma ACTH levels measured at time of admission show no significant difference between both studied groups as shown in **table (2).**

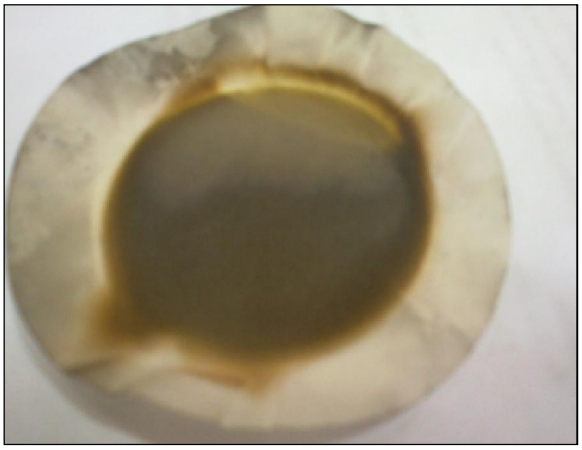

Figure (1): Positive result of silver nitrate test for phosphide showing black discolouration.

Table (1): Sociodemographic, toxicological and clinical data in the studied groups with acute aluminium phosphide toxicity at admission.

	Group I N=15	**Group II N=15**	**Test statistic**	**P value**
Age (years)	19 (18-23)	19 (18-30)	**Z_{mw}=0.088**	**0.930**
Gender Female Male	 8(53.3%) 7(46.7%)	 8(53.3%) 7(46.7%)	**X^2chi-square=0.00**	**1**
Residence Rural Urban	 13(86.7%) 2(13.3%)	 13(86.7%) 2(13.3%)	**X^2chi-square=0.00**	1
Amount (tablet)	0.5(0.5-1)	1(1-1)	**Z_{mw}**=1.646	0.1
Delay time (hours)	2(1-4)	2(1.5-3)	**Z_{mw}**=0.401	0.713
Systolic Blood Pressure	80(70-80)	80(70-80)	**Z_{mw}**=-0.436	0.663
Diastolic Blood Pressure	40(40-50)	40(40-50)	**Z_{mw}**=-0.662	0.508
Heart rate	106(99-114)	102(96-110)	**Z_{mw}**=-0.831	0.406
Respiratory rate	25(21-29)	28(23-30)	**Z_{mw}**=1.228	0.22
Temperature	37(36.5-37.2)	36.8 (36.5-37)	**Z_{mw}**=-0.693	0.489
GCS	15(100%)	14(93.3%)	**X^2exact=0.0**	1
Tachypnea	(53.3%)	(73.3%)	**X^2chi-square=1.292**	0.256
Abdominal pain	(33.3%)	(26.7%)	**X^2exact=0.433**	1

Data are medians (interquartile range), or numbers (%).

- **N=** number
- **Group I:** Patients received both standard treatment & IV hydrocortisone.
- **Group II:** Patients received both standard treatment & placebo.
- **Zmw:** Mann-Whitney U test.
- **X^2exact:** Fisher's Exact test**.**
- **X^2chi-square:** Chi-Square test.

Patients who had adequate adrenal response whose serum cortisol level was more than 34 µg/dl was found among 11 patients (36.7%) of all patients; four of them were in group I (26.7%) while the remaining seven were in group II (46.7%). However, Critical illness related corticosteroid insufficiency

patients (CIRCI) whose serum cortisol level from 15 to 33µg/dl was observed in 14 patients (46.7%) of all patients; eight patients were in group I (53.3%) and six patients were in group II (40%). Meanwhile, adrenal insufficiency was diagnosed in 5 patients (16.6%) whose serum cortisol level less than 15µg/dl [3 patients (20%) in group I and 2 patients (13.3%) in group II]. No significant difference between both groups regarding serum cortisol level was found as illustrated in **figure (2)**.

Mortality and need of mechanical ventilation were insignificantly decreased in hydrocortisone treated group as demonstrated in **table (3).**

Survivors on hydrocortisone therapy required significantly less norepinephrine doses than those who received standard treatment. Moreover, the length of hospital stay showed significant decrease in hydrocortisone treated group when compared to the other group who received standard treatment. No significant difference between both studied groups as regards blood pressure at time of discharge **(Table 4).**

Table (2): Median values of serum cortisol and plasma ACTH levels in the studied groups with acute AlP toxicity at admission.

	Groups		Tests of significance	
	Group I N=15	Group II N=15	Z_{mw} test	P value
Serum cortisol (µg/dl	26.1(20.66-51.2)	32(25.88-59.1)	1.141	0.254
Plasma ACTH pg/ml	343(204 -521)	433(217 – 618)	0.684	0.512

- Data are medians (interquartile range).
- **N=** number
- **Group I:** Patients received both standard treatment & IV hydrocortisone.
- **Group II:** Patients received both standard treatment & placebo.
- **Zmw:** Mann-Whitney U test.

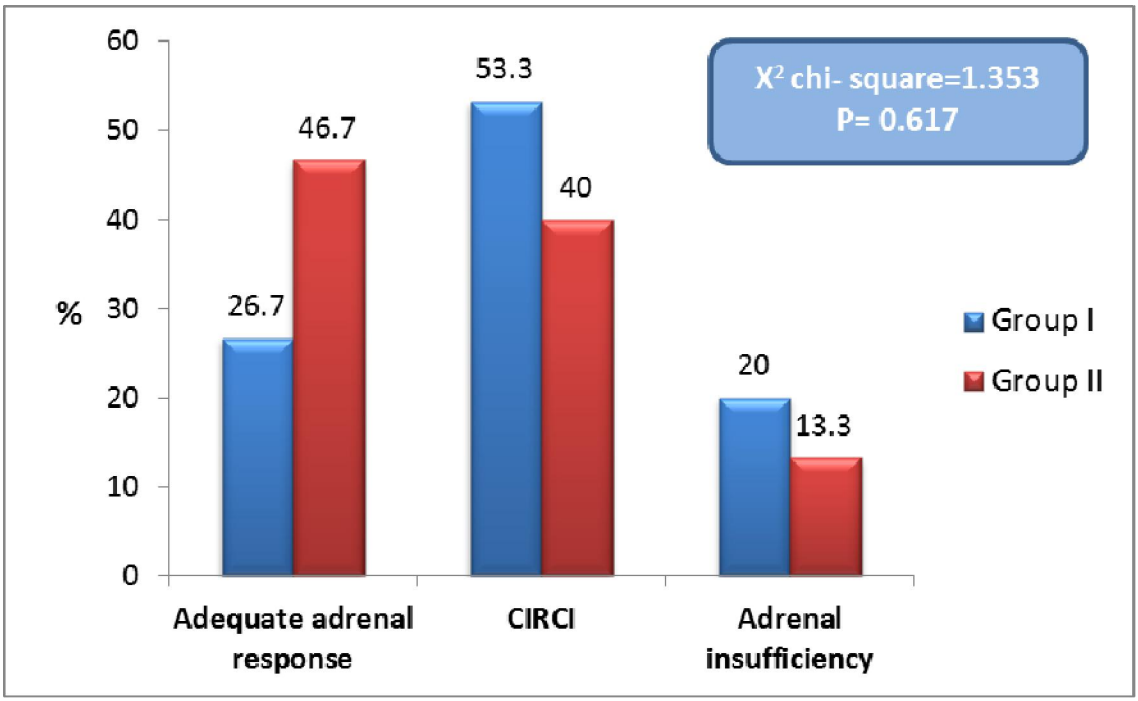

Figure (2): Classification of the studied groups with acute aluminium phosphide toxicity according to serum cortisol levels at admission.

- **Group I:** Patients received both standard treatment & IV hydrocortisone.
- **Group II:** Patients received both standard treatment & placebo.
- **CIRCI:** Critical illness related corticosteroid insufficiency.
- **X^2chi-square:** Chi-Square test.

Table (3): Comparison between the studied groups with acute AlP poisoning regarding mortality and need of mechanical ventilation.

		Groups				X^2chi-square Test	P value
		Group I N= 15		Group II N= 15			
		N	%	N	%		
Mortality	Yes	6	40	11	73.3	**3.394**	**0.065**
	No	9	60	4	26.7		
Need of mechanical ventilation	Yes	6	40	10	66.7	**2.134**	**0.143**
	No	9	60	5	33.3		

- **N=** number
- **Group I:** Patients received both standard treatment & IV hydrocortisone.
- **Group II:** Patients received both standard treatment & placebo.
- **X^2chi-square:** Chi-Square test.

Table (4): Comparison between the survivors regarding dose of vasopressors, duration of hospital stay and blood pressure before discharge.

	Survivors		Tests of significance	
	Group I N=	Group II N=	Test statistic	P value
Dose of vasopressors (norepinephrine) (mg)	24 (16-32)	52 (36-68)	Z_{mw}= 2.256	0.024*
Duration of hospital stay (hours)	58 (54-64)	90 (72-108)	Z_{mw}=2.089	0.034*
SBP before discharge	107.78±8.33	110.0±8.16	t= 0.466	0.664
DBP before discharge	72.22±4.41	675±9.57	t= 0.943	0.405

- Data are medians (interquartile range), or mean ± SD
- **N=** number
- **Group I:** Patients received both standard treatment & IV hydrocortisone.
- **Group II:** Patients received only standard treatment.
- **X2exact:** Fisher's Exact test**.**
- **Zmw:** Mann-Whitney U test.
- **IQR**: Interquartile range**.**
- **SD:** Standard deviation.
- **t**: independent T test**.**

4. Discussion:

The current study was a randomized clinical trial which was held to evaluate the role of hydrocortisone as an adjuvant therapy in the management of patients with acute phosphide poisoning.

As patients included in this study were randomly allocated, no significant difference was found between both groups regarding socio-demographic data, toxicological data, and clinical examination and laboratory investigations of AlP poisoned patients at admission including serum cortisol and plasma ACTH.

According to the serum cortisol level of AlP poisoned patients on admission, it was found that the majority of AlP patients fell within the critical illness related corticosteroid insufficiency (CIRCI) category (46.7%), patients with adrenal insufficiency represented 16.6%, while 36.7% of patients were of the adequate adrenal response category. This was partially in line with the study of **Farnaghi et al. (2013)** and **Masoud & Barghash (2013)** who reported that the majority of AlP poisoned patients matched with CIRCI category (80% and 64.3% respectively). Despite patients with CIRCI show normal serum cortisol level, yet such level does not show the expected rise during the shock and stress state induced by AlP poisoning **(Farnaghi et al., 2013).**

It was suggested that The adrenal cortex changes induced by AlP poisoning are either due to shock or due to the direct toxic effect of phosphine on adrenal cortex cells **(Masoud & Barghash, 2013).** The latter was proved by the histopathological study of adrenal cortex in AlP poisoned patients with inadequate adrenal response that showed complete lipid depletion, haemorrhage and necrosis **(Chugh et al., 1989_a).**

Regarding the plasma adrenocorticotropic hormone (ACTH) level in the present study on admission, all patients in both groups had high plasma ACTH level with median values of 343 pg/mL and 433pg/mLin group I and II respectively**.** The high plasma ACTH levels observed in AlP poisoned

patients could be attributed to the activation of hypothalamic-pituitary-adrenal (HPA) axis upon exposure to stressful conditions or critical illness with rapid increase in hypothalamic corticotropin releasing hormone (CRH) production which leads to a corresponding increase in ACTH levels from pituitary gland with subsequent increase in cortisol levels secreted from the adrenal glands **(Herman et al., 2016).** Furthermore, loss of diurnal variation in cortisol secretion and reduction in negative feedback mechanism on pituitary gland by cortisol during stressful condition could explain the high plasma ACTH in those patients **(Cooper & Stewart, 2007).**

Reference wise and according to the best of our recent knowledge, hydrocortisone was studied for its efficacy in the management of patients with different critical illnesses such as septic shock **(Sprung et al., 2008 and Gibbison et al., 2017).** However, no randomized clinical trial was held previously to evaluate the role of hydrocortisone as an adjuvant therapy in the management of patients with acute phosphide poisoning. Therefore, this study is the first one to evaluate the role of hydrocortisone in the management of critical illness induced by acute AlP poisoning.

Regarding the outcome measures of this study, administration of hydrocortisone reduced the mortality rate in group I compared to group II (40% in group I versus 74.3% in group II). Although mortalityrate was improved with hydrocortisone administration, yet the difference is not statistically significant. However, this result seemed a good result when compared to high mortality rates recorded in the previous studies of **Mehrpour et al. (2008_b), Mathai & Bhanu (2010), Khurana et al. (2011) and Masoud & Barghash (2013)** which were 71%, 60%, 76%and 64% of AlP poisoned patients respectively.

In addition, the percentage of patients who required mechanical ventilation was lower in group I than in group II with no statistical difference between both groups (40% in group I versus 66.7% in group II). Despite the insignificant difference between group I and II regarding the need for mechanical ventilation, yet the low percentage in group I (40%) is a favorable result when compared to the high percentage recorded in other studies like those carried out by **Mehrpour et al. (2008_b)** and **Agrawal et al. (2015)** which were100% and 85.7% of AlP poisoned patient respectively.

In favor of the effectiveness of hydrocortisone administration in reducing the mortality rate and lowering the need for mechanical ventilation in AlP poisoned patients, we have some additional data which support the hypothesis that hydrocortisone improves the outcome measures of AlP poisoned patients. First, the dose of norepinephrine administered to survivors was significantly lower in group I than in group II (median value was 24 mg in group I versus 52mgin group II). Second, the duration of hospital stay among survivors in group I was less than that of group II (median value was 58 hours in group I versus 90 hours in group II). This difference was statistically significant.

The significant lowering in the norepinephrine dose and in the duration of hospital stay among survivors in group I could be explained by the role of hydrocortisone in increasing retention of intravascular fluid as it induces sodium retentionvia both mineralocorticoid and glucocorticoid receptors which help in correction of hypovolemia that characterizes AlP poisoning **(Annane, 2011).**

Furthermore, hydrocortisone plays an important role for maintenance of cardiac contractility, vascular tone, endothelial integrity and blood pressure by increasing the sensitivity of vascular smooth muscle to both exogenous and endogenous vasopressors together with enhancement of cardiovascular reactivity to angiotensin II and catecholamines (**Marik et al., 2008** and **Minneci et al., 2009).**

Administration of high dose of norepinephrineis associated with several side effects such as pulmonary edema, bowel ischemia, immunomodulation and hyperglycemia **(Martin et al., 2015 and Yamamura et al., 2018).** Therefore, the significant lowering in the dose of norepinephrine administered to AlP poisoned patients reported in this study may help to avoid these side effects or even minimize their occurrence with subsequent lowering of mortality rate.

Moreover, the significant decrease in the length of hospital stay recorded among AlP poisoned patients may be translated into substantial savings in health care costs and resources as the length of hospital stay is a major cost component of hospital budgets **(Zyoud et al.,2010).**

Conclusion:

The present study revealed that hydrocortisone administration to AlP poisoned patients especially those with failure of elevation of serum cortisol beyond the normal level (CIRCI) or even those who showed low levels (adrenal insufficiency) could improve the hemodynamic state of these patients together with inducing significant decrease in the required norepinephrine dose and the duration of hospital stay.

Limitations:

The present study limitations include small sample size; however, this was a pilot study investigating the safety and efficacy of hydrocortisone in acute phosphide poisoning, and its results will be a beginning for larger trials based on sample size

calculation. The study was a single blinded randomized clinical trial so, masking was lacking because healthcare providers had the information about patients who received hydrocortisone.

Conflict of interest

The author (s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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