

Patients with Increased Levels of the Oxidative Stress Biomarker SOD1 Appear to Have Diminished Postoperative Pain After Midline Laparotomy: A Randomised Trial with Special Reference to Postoperative Pain Score (NRS)

JARI KÄRKKÄINEN^{1,2}, TUOMAS SELANDER³, MARTIN PURDY^{1,2},
PETRI JUVONEN¹ and MATTI ESKELINEN^{1,2}

¹Department of Surgery, and ³Science Service Center, Kuopio University Hospital, Kuopio, Finland;

²School of Medicine, University of Eastern Finland, Kuopio, Finland

Abstract. *Background/Aim:* The levels of the oxidative stress biomarker superoxide dismutase (SOD1) in plasma in relation to pain at rest 24 hours after (NRS₂₄) midline laparotomy in patients with rectus sheath block (RSB) analgesia is unknown. *Patients and Methods:* Initially, 56 patients (39 with cancer), each with an intravenous oxycodone pump as patient-controlled analgesia, were randomized to four groups: control group, no RSB (n=12), single-dose (n=16), repeated-dose (n=12) and continuous infusion (n=16) of RSB analgesia. The plasma levels of SOD1 were measured directly before, immediately after and 24 hours after surgery. Pain at rest was scored on an 11-point numeric rating scale 24 hours postoperatively (NRS₂₄: 0=no pain to 10=worst pain). *Results:* The median plasma level of SOD1 increased immediately after operation and this was statistically highly significant (p=0.007). The median plasma level of SOD1 then decreased 24 hours postoperatively and this postoperative decrease was also statistically highly significant (p<0.001). The median plasma levels of SOD1 did not differ significantly between patients with benign disease and those with cancer, preoperatively and after surgery. There was highly significant positive correlation between SOD1 and glutathione peroxidase (GPX1) values postoperatively (r=0.67, p<0.001) and a trend for an inverse correlation between the individual values of the NRS₂₄ and plasma SOD1 values postoperatively in patients with benign disease and those

with cancer (r=-0.30, p=0.09). *Conclusion:* Midline laparotomy significantly alters the level of oxidative stress marker SOD1 immediately after surgery, but the level normalizes 24 hours following surgery. Interestingly, patients with increased levels of SOD1 appeared to have diminished postoperative pain after midline laparotomy.

Superoxide dismutase (SOD) enzymes catalyze the reaction where superoxide is dismutated into hydrogen peroxide, and the correct balance between superoxide and hydrogen peroxide is vital for any organism (1). Cu/Zn superoxide dismutase (SOD1) is a 32-kDa enzyme that in humans is encoded by the SOD1 gene, located on chromosome 21. The first identified SOD enzyme was cytoplasmic copper/zinc SOD1; later, mitochondrial iron/manganese SOD (SOD2) and the extracellular SOD SOD3 were discovered (1). SOD1 has an intramolecular disulfide bond and a Cu/Zn site in each subunit, which is responsible for dismutation of two O₂⁻ anions to H₂O₂ and molecular oxygen (2, 3).

Yiannakopoulou *et al.* reviewed the clinical trials that investigated the oxidative stress in open surgery *versus* laparoscopic surgery (4). They found four trials (5-8) on plasma SOD level and oxidative stress response to surgery and this systematic review aimed to investigate the impact of surgical trauma on oxidative stress. However, there was a great heterogeneity in the measured oxidative markers, methods, time periods and on the types of operation investigated and final conclusions were therefore difficult to draw. The assessment of the SOD1 response, as a biomarker of oxidative stress, to midline laparotomy with rectus sheath block (RSB) analgesia is unknown. Therefore, the aim of this study was to determine the correlation between the plasma level of SOD1 and the pain score at rest 24 hours after midline laparotomy (NRS₂₄) under RSB analgesia in patients with benign disease and those with cancer.

Correspondence to: Matti Eskelinen, MD, Ph.D., School of Medicine, University of Eastern Finland, P.O. Box 100, FI-70029 KYS, Finland. Tel: +358 17173311, Fax: +358 17172611, Mobile: +358 400969444, e-mail: matti.eskelinen@kuh.fi

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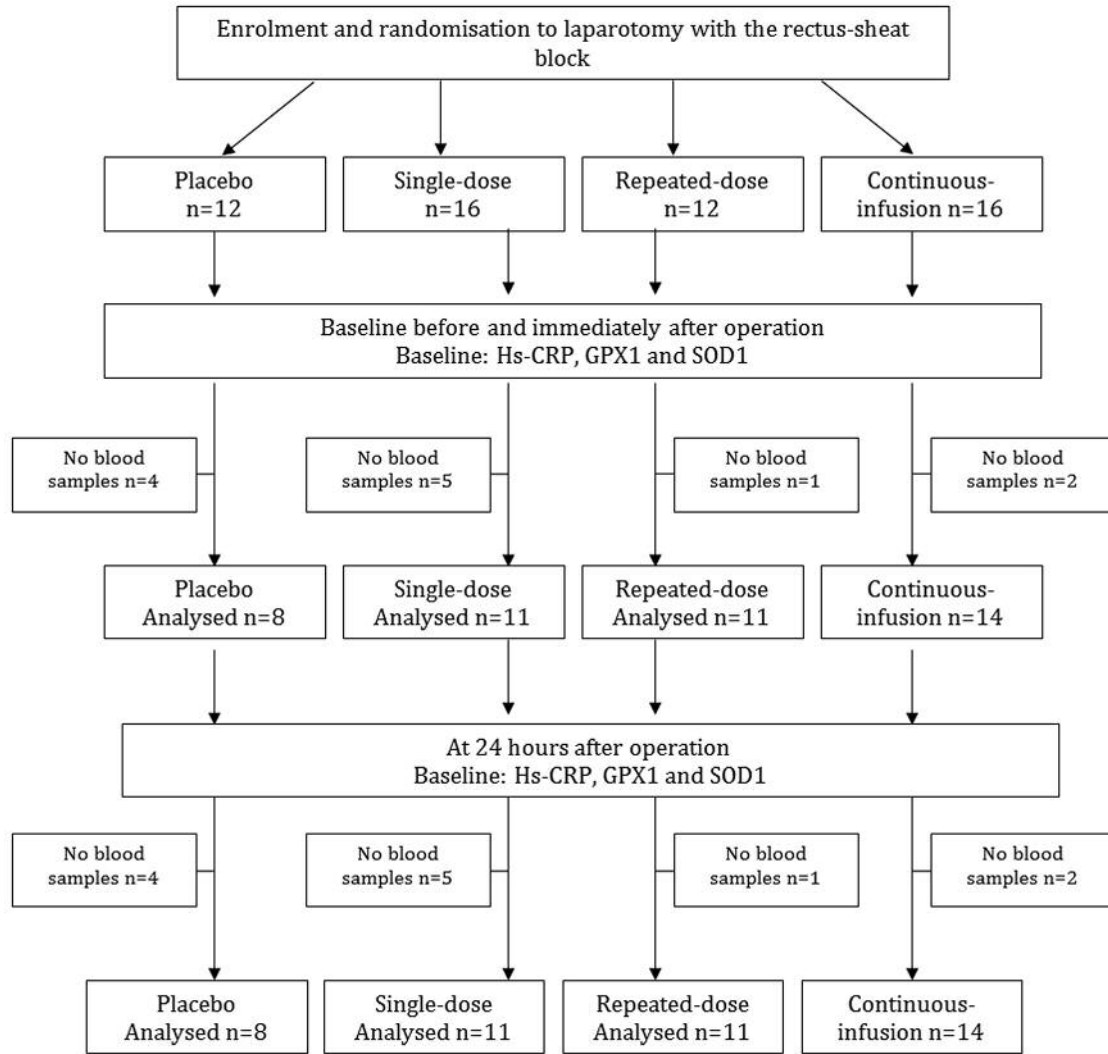


Figure 1. Consort figure of the study design.

Patients and Methods

The study was approved by the Ethics Committee of Kuopio University Hospital District, Finland (DNRO 120/2011, November 11, 2011), registered in the EudraCT database (EudraCT number 2011-005136-25, Consort diagram, Figure 1) and the ClinicalTrials.gov database (ClinicalTrials.gov Identifier: NCT02869841), and was conducted in accordance with the Declaration of Helsinki. Participants gave written consent after receiving verbal and written information on the study. Operations were carried out at Kuopio University Hospital, Kuopio between 2012 and 2015. The CONSORT flowchart of the study is presented in Figure 1. The study design was a prospective, randomized, clinical trial with four parallel groups. Patients undergoing midline laparotomy each had an intravenous oxycodone pump as patient-controlled analgesia, and were then randomized into a control group (no RSB) or into one of three active RSB analgesia groups: single-dose, repeated-dose or continuous infusion of

levobupivacaine. The study patients had intravenous oxycodone pumps as patient-controlled analgesia (PCA). The randomization list was generated by computer (www.randomization.com) and a sealed-envelope method was used for blinding and randomization was done preoperatively.

The primary outcome measures were the plasma levels of high-sensitivity C-reactive protein (hs-CRP), glutathione peroxidase (GPX1) and SOD1 measured at three time points with high-sensitivity assays: before, immediately after, and 24 hours after operation surgery in the control *versus* those in the three active groups, and the overall pain at rest surveyed and filed on an 11-point numeric rating scale at 24 hours following surgery (NRS₂₄: 0=no pain to 10=worst pain).

All RSB procedures were performed by an experienced surgeon in the operating room before wound closure. The study protocol with exclusion criteria and informed consent were fully described in our earlier original work (9-11).

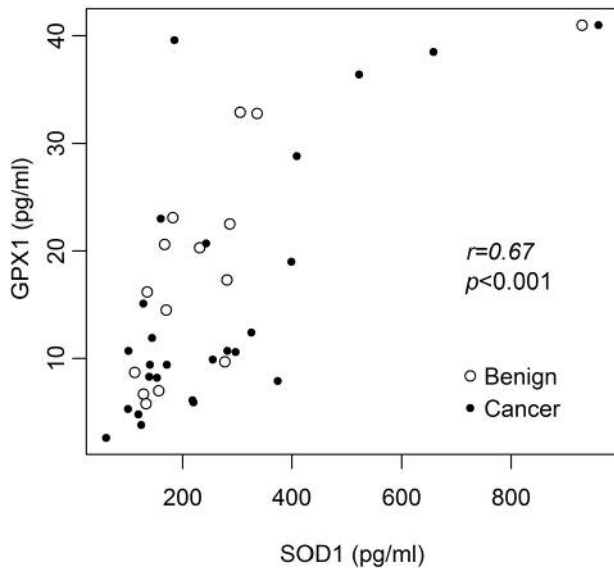


Figure 2. Scatter plots of the postoperative (POP1) plasma values of superoxide dismutase (SOD1) versus glutathione peroxidase (GPX1) in patients with benign disease and those with cancer ($r=0.670$, $p<0.001$).

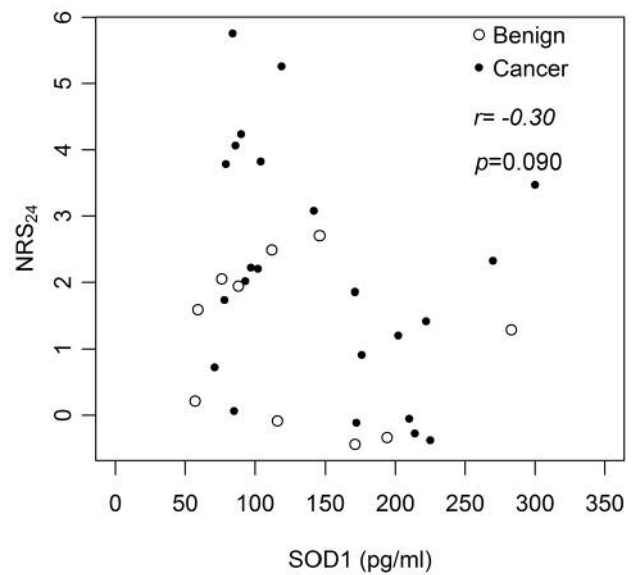


Figure 3. Scatter plots of the individual postoperative numeric rating scale at rest 24 hours postoperatively (NRS_{24}) values versus postoperative (POP2) plasma values of superoxide dismutase (SOD1) in patients with benign disease and those with cancer ($r=-0.30$, $p=0.09$).

EDTA-blood samples were taken at the prespecified time-points and centrifuged at $1000 \times g$ for 15 min. Plasma was separated and stored frozen at -70°C until analyzed. The plasma GPX1 assays were performed using sandwich-type enzyme-linked immunoassay (ELISA) with BioVendor GPX1 ELISA Kit (Brno, Czech Republic). Plasma hs-CRP was analyzed with a Cobas 6000-analyzer (Hitachi, Tokyo, Japan) using the method by Roche Diagnostics (Mannheim, Germany). The plasma SOD1 assays were performed using sandwich-type ELISA with BioVendor Cu/Zn SOD ELISA Kit.

The data were entered and analyzed with a statistical software program (IBM SPSS Statistics 22.0; IBM Corp., Armonk, NY, USA). Baseline characteristics between groups were tested by Fisher exact test and then analysis of continuous variables was performed by analysis of variance (ANOVA). Group differences at the three time points were tested by Kruskal–Wallis test and Mann–Whitney U -test or Wilcoxon signed-rank test. The results of the laboratory measurements are presented as the median with interquartile range as distributions were right skewed. A two-sided p -value of less than 0.05 was considered statistically significant. The results of the individual GPX1 and SOD1 values immediately postoperatively for patients are shown as scatter plots with Spearman's correlation coefficients in Figure 2. The results of the individual SOD1 values 24 hours postoperatively *versus* the postoperative NRS_{24} values for patients are shown as scatterplots with Spearman's correlation coefficients in Figure 3.

Results

The patients' clinical data were similar in the four study groups, but body mass index and body weight were significantly higher in patients in the single dose and control

group than in the other two study groups (Table I). The study group consisted of 15 patients with benign disease, nine patients with gastrointestinal cancer, 17 patients with gynecological cancer and three patients with other malignancy (Table I).

The median plasma levels of SOD1 increased by $\sim 13\%$ immediately after surgery and this increase was statistically highly significant ($p=0.007$, Table II). The median SOD1 level then decreased by $\sim 45\%$ at 24 hours postoperatively ($p<0.001$, Table II). However, no differences were detected in the SOD1 values between the control and the three active groups preoperatively and after operation. The patients in the single-dose group had a trend for a lower median SOD1 value 24 hours after surgery compared to each of the other three groups (Table III). The median plasma SOD1 level preoperatively or after operation did not differ significantly between patients with cancer and those with benign disease however (Table IV). There was significant correlation between the SOD1 and GPX1 values immediately after operation and 24 hours postoperatively ($r=0.67$ and $r=0.63$, respectively, Figure 2, $p<0.001$) and a trend for inverse correlation between the individual values of the NRS_{24} and plasma SOD1 values 24 hours postoperatively in patients with cancer and those with benign disease ($r=-0.30$, $p=0.09$, Figure 3). The median plasma level of hs-CRP increased only slightly immediately after surgery and this increase was not statistically significant ($p=0.274$, Table II). The median hs-CRP level then increased by 57 fold at 24 hours postoperatively ($p<0.001$, Table II).

Table I. Clinical data in the four study groups of patients undergoing midline laparotomy. Data are mean (standard deviation) or number of cases*.

Variable	RSB method				p-Value
	Control n=8	Single n=11	Repeated n=11	Continuous n=14	
Age (years)	62.6 (14.3)	60.8 (12.6)	63.3 (10.8)	58.0 (10.1)	0.74
Sex: male/female*	4/4	4/7	2/9	2/12	0.22
Height (cm)	166.6 (8.6)	168.4 (7.9)	165.7 (7.2)	164.3 (6.6)	0.62
Weight (kg)	78.6 (11.8)	83.7 (12.8)	67.8 (13.7)	68.8 (10.6)	0.007
BMI (kg/m ²)	28.3 (3.8)	29.6 (4.4)	24.6 (4.3)	25.7 (4.9)	0.03
Time in the operative room (min)	229.4 (113.4)	274.9 (148.4)	235.7 (112.0)	279.7 (178.5)	0.85
Operative time (min)	209.6 (141.2)	221.8 (156.4)	154.4 (95.0)	253.3 (168.9)	0.55
Perioperative bleed (ml)	696 (741)	822(906)	697 (967)	1340(928)	0.31
ASA 1/2/3/4*	0/6/2/0	0/7/3/1	0/5/6/0	2/7/5/0	0.43
Length of skin incision(s) (mm)	27.2 (6.6)	24.4 (7.8)	24.2 (7.9)	29.7 (7.3)	0.31
Type of disease*†					
Benign disease	1	3	5	6	0.32
GI-cancer	3	2	2	2	
Gyn-cancer	3	4	4	6	
Other cancer	1	2	0	0	

BMI: Body mass index; ASA: American Society of Anesthesiologists physical status score. †Benign disease, n=15; GI: gastrointestinal tract cancer, n=9; Gyn: gynecological cancer, n=17; other malignancy, n=3.

However, no differences were detected in the hs-CRP values between the control and the three active groups preoperatively and after operation (Table III).

Discussion

Reactive oxygen species are products containing oxygen molecules that can regulate immune responses and cell signaling. In addition, they have potential to cause harm by damaging both nuclear and mitochondrial DNA, RNA, lipids, and proteins. These reactions lead to mutations and genomic instability (12). These products can also modulate signaling molecules and alter functions of enzymes and proteins involved in carcinogenesis (12). To avoid cell damage, the living cell needs defense mechanisms against free radicals such as oxygen, hydrogen peroxide and superoxide. These protective functions maintain balance between intracellular reactive species and antioxidant activity. All three known SODs are responsible for the reaction where superoxide is dimutated into H₂ and O₂ (2, 3).

In this study, we sought answers to build a bridge between oxidative stress and inflammation in relation to postoperative pain. The primary end-point of our study was to examine postoperative pain (NRS₂₄) and the plasma level of SOD1 in patients undergoing midline laparotomy randomized into the control group or to different RSB analgesia groups. Each study patient had an intravenous oxycodone pump for patient-controlled analgesia.

The main hypothesis of our study was whether the post-surgery placement of the RSB reduced oxidative stress and pain following surgery in patients with benign disease and cancer.

Table II. Postoperative alteration of plasma high-sensitivity C-reactive protein (hs-CRP), glutathione peroxidase (GPX1) and superoxide dismutase (SOD1) levels in all groups combined (all patients). Plasma marker levels were measured before operation (PRE), immediately after operation (POP1), and 24 hours after operation (POP2). Median (interquartile range) values are shown. The Wilcoxon signed-rank test was used.

Marker	Time point	All patients	p-Value
hs-CRP (mg/l)	PRE	3.3 (0.85-12.9)	
	POP1	4.8 (0.8-46.9)	0.274 ^a
	POP2	186.9 (97.2-337)	<0.001 ^b
GPX1 (pg/ml)	PRE	13.2 (7.7-19.7)	
	POP1	11.9 (8.1-22.8)	0.282 ^a
	POP2	8.7 (5.3-15.5)	0.006 ^b
SOD1 (pg/ml)	PRE	164.0 (114-212)	
	POP1	185.0 (137-301)	0.007 ^a
	POP2	105.0 (86-176)	<0.001 ^b

^avs. PRE; ^bvs. POP1.

We earlier reported a statistically significant inverse correlation between the individual plasma values of hs-CRP and 8-OHdG and significant difference in GPX1 value preoperatively in patients with cancer compared to those with benign disease (9-11, 13-15). We reported a significant correlation in the satisfaction for pain treatment (NRS₂₄) and plasma concentrations of anti-inflammatory cytokine interleukin-10 (IL10) and pro-inflammatory cytokine IL1β postoperatively. In this study, we found a trend for an inverse correlation between the individual values of the NRS₂₄ and

Table III. Plasma high-sensitivity C-reactive protein (hs-CRP), glutathione peroxidase (GPX1) and superoxide dismutase (SOD1) levels in the four study groups. Plasma levels were determined before operation (PRE), immediately after operation (POP1) and 24 hours after operation (POP2). Median (interquartile range) values are shown. The Kruskal–Wallis test was used.

Marker	Time point	RSB method				p-Value
		Control	Single	Repeated	Continuous	
hs-CRP (mg/l)	PRE	3.48 (1.2-13.0)	4.65 (0.89-48.23)	1.20 (0.59-4.00)	6.45 (0.62-73.54)	0.591
	POP1	6.6 (1.0-13.2)	9.18 (2.9-83.3)	2.30 (0.59-5.13)	25.9 (1.03-231.8)	0.289
	POP2	246.1 (82.2-469.5)	189.5 (96.2-349.0)	206.5 (81.5-284.4)	159.0 (79.3-478.9)	0.875
GPX1 (pg/ml)	PRE	12.05 (8.8-19.2)	10.70 (5.4-16.7)	19.17 (6.7-22.0)	17.00 (9.5-18.9)	0.503
	POP1	11.90 (8.20-36.4)	9.40 (6.1-23.0)	15.10 (6.5-29.8)	15.10 (10.2-20.6)	0.775
	POP2	10.57 (5.8-16.3)	5.13 (3.2-9.2)	8.63 (5.3-19.2)	12.29 (6.7-19.6)	0.032
SOD1 (pg/ml)	PRE	150 (101-288)	146 (96-287)	171 (113-216)	168 (128-199)	0.922
	POP1	281 (144-522)	160 (101-305)	184 (123-275)	243 (151-292)	0.392
	POP2	119 (93-202)	87 (59-105)	116 (88-171)	167 (94-217)	0.138

plasma SOD1 values postoperatively in patients with benign disease and those with cancer.

The significant enhancement in the level of SOD marker but not in the GPX marker immediately after midline laparotomy may be a new finding, although the rise in the SOD level following surgery is in line with the results of Turker *et al.* in patients undergoing open heart surgery with cardiopulmonary bypass (16). In another study, the SOD marker levels were found to be increased 1 week postsurgery, while the GPX level stayed markedly lower than that before surgery (17).

Postoperatively, the antioxidative SOD1 and GPX1 levels in plasma were lowest in the single-dose group, lower than in the control group. This may be a true sequence of local oxidative stress caused by the local analgesic agent (18). Repeated analgesic blocks, and continuous blocks in particular, may cause a rise in the concentration of analgesic (levobupivacaine) in the plasma following surgery. This in turn has anti-inflammatory properties thus also attenuating oxidative stress, postoperatively. Although the exact mechanism of action remains unclear, it could explain the tendency towards a better anti-oxidative SOD1 level and less pain at rest 24 hours postoperatively. On the other hand, proper treatment of the incisional pain also diminishes oxidative stress.

Although the limitation of this study is the small sample size, the patients in the control group had no levobupivacaine injected and they were blinded using similar wound dressing to that for the patients in the active groups. Therefore, it is unlikely that there is a study bias from the local anesthetic used or placement of the RSB catheters, and it is possible to compare the control group with the active groups. Interestingly, recent studies have demonstrated that lidocaine and levobupivacaine may have anti-inflammatory effects when used perioperatively (19) and they may also modulate the immune system (20).

Table IV. Plasma high-sensitivity C-reactive protein (hs-CRP), glutathione peroxidase (GPX1) and superoxide dismutase (SOD1) levels in patients with benign disease (n=15) and those with cancer (n=29). Plasma levels were measured before operation (PRE), immediately after operation (POP1) and 24 hours after operation (POP2). Median (interquartile range) values are shown. The Mann-Whitney U-test was used.

Marker	Time point	Benign	Cancer	p-Value
hs-CRP (mg/l)	PRE	2.20 (0.6-3.8)	4.7 (0.9-61.6)	0.160
	POP1	2.50 (0.6-6.1)	8.61 (0.8-60.9)	0.255
	POP2	136.0 (62.2-254.5)	192.2 (104.4-372.9)	0.271
GPX1 (pg/ml)	PRE	18.0 (12.5-22.0)	10.0 (5.7-17.9)	0.005
	POP1	17.3 (8.7-23.1)	10.7 (7.5-21.3)	0.253
	POP2	11.9 (6.7-24.7)	8.1 (5.2-12.3)	0.126
SOD1 (pg/ml)	PRE	167 (132-216)	160 (107-211)	0.647
	POP1	182 (135-286)	202 (136-338)	0.989
	POP2	105 (76-171)	112 (86-196)	0.610

In conclusion, the results suggest that midline laparotomy does significantly alter the level of the oxidative stress marker SOD1 immediately after surgery, but the levels normalize 24 hours following surgery.

A new finding is the highly significant correlation between the individual plasma SOD1 and GPX1 values, and a trend for inverse correlation between the individual values of the NRS₂₄ and plasma SOD1 values postoperatively in patients with benign disease and those with cancer.

Conflicts of Interest

The Authors have no conflicts of interest or financial ties to disclose. The Authors alone are responsible for the content and writing of this article.

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