

Original Research Article

Effect of a combination of dexmedetomidine and either isoflurane or sevoflurane on elderly patients undergoing radical resection for gallbladder cancer

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Abstract

Purpose: To determine the efficacy of dexmedetomidine (DEX) plus either isoflurane or sevoflurane, in elderly gallbladder cancer patients given radical resection.

Methods: A total of 278 elderly patients assessed for eligibility and scheduled for radical gallbladder cancer resection in Hunan Cancer Hospital, Changsha, China were recruited. They were randomly assigned at a ratio of 1:1 to receive either DEX plus isoflurane or DEX plus sevoflurane. These two groups were compared with respect to immune functions (CD3+, CD 4+, CD 8+, and CD4+/CD8+ T cells); inflammatory factors, and cognitive function scores.

Results: The sevoflurane cohort had higher immune function indices, lower levels of inflammatory cytokines, and better oxidative stress indices, than the isoflurane cohort ($p < 0.05$). Postoperatively, cognitive function scores in both cohorts were reduced. At postoperative 12 and 24 h, sevoflurane cohort had higher scores than the isoflurane group. Sevoflurane was more effective in stabilizing hemodynamic indices than isoflurane.

Conclusion: DEX plus sevoflurane produces more significant improvements in the cognitive function of elderly patients undergoing radical resection for gallbladder cancer, with milder immune function impairment, milder inflammatory response, and lower degree of oxidative stress, than isoflurane.

Keywords: Dexmedetomidine, Sevoflurane, Isoflurane, Radical resection, Gallbladder carcinoma, Cytokines, Cognition

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INTRODUCTION

Gallbladder carcinoma is a prevalent malignant tumor in the biliary tract, with poor prognosis. The survival period of patients with gallbladder cancer is approximately six months, while in general, less than 5 % of patients survive in 5 years [1,2]. Radical resection is primary treatment for gallbladder cancer [2]. Survival

from the illness has been linked to immunity [3,4]. Impaired cellular immunity is manifested primarily by interactions of nervous, endocrine, immune systems. Surgical anesthesia is considered the culprit in impaired cellular immunity [5,6]. Cognitive dysfunction is a general central nervous system defect after an abdominal operation. In addition, elderly patients are usually comorbid with other basic diseases, for example,

diabetic mellitus and hypertension. During anaesthesia, hemodynamics fluctuate more and postoperative complications occur more frequently, thereby affecting the living standard of the patient [7-9]. Surgical trauma and the pressure of anaesthesia could cause inflammatory reactions. The related cytokines, for example, IL-6 and CRP, are involved in the etiology of cognitive dysfunction [10-12].

It is believed that appropriate anaesthesia could cut down hemodynamic changes in patients with gallbladder cancer during operation, and enhance postoperative cellular immunity [5]. Thus, there is a need to develop appropriate and effective anaesthesia protocols.

It is known that DEX is a potent alternative central α_2 agonist with pain-relieving and tranquilizing properties [13]. Medical research has indicated that it reduces perioperative inflammatory reaction in elder patients [14]. At present, the most frequently used anaesthetic drugs in clinical trials are sevoflurane and isoflurane. Isoflurane is a volatile anaesthesia used in operation for bronchial disease subjects; it controls neuronal stimulation, decreases brain oxygen demand, and regulates oxygen supply [16-18]. Sevoflurane is an anaesthesia which has the advantages of being relatively fast-acting with mild stimulation, which results in shorter postoperative recovery times [19]. Research has shown that combined use of DEX with either isoflurane or sevoflurane is effective in surgery [20, 21]. However, not much is known about the influence of DEX plus either isoflurane or sevoflurane on immunity status, inflammation status and cognitive function of aged patients during radical resection for gallbladder carcinoma.

This research was aimed at investigating the effects of DEX plus either isoflurane or sevoflurane, on immunity indexes, concentrations of pro-inflammatory cytokines, and MMSE scores in aged patients given surgical resection for gall bladder carcinoma.

METHODS

General information

A total of 278 eligible old patients scheduled for radical operation due to gallbladder cancer in Hunan Cancer Hospital, Changsha, China were selected. They were randomly allocated in a 1:1 ratio to DEX plus isoflurane group ($n = 136$) and DEX plus sevoflurane (group $n = 142$). The isoflurane cohort comprised 72 females and 64 males with mean age of 70.23 ± 3.21 years, and

mean educational exposure period of 8.59 ± 4.72 years. The sevoflurane cohort comprised 76 females and 66 males of mean age 70.41 ± 3.57 years, and mean educational exposure period of 8.87 ± 4.57 years. The research was inspected and authorized by Hunan Cancer Hospital, Changsha ethics committee, and followed international guidelines for human studies. Each patient, as well as his/her families were well informed about the procedures involved, and they signed informed consent to accept the medications and surgery.

Inclusion criteria

The included patients were those with confirmed pathological diagnosis of gallbladder cancer, patients with complete clinical data, those expected to survive for > 3 months, those who did not smoke or drink, and patients who had a positive attitude to their health status.

Exclusion criteria

Patients in the following categories were excluded: patients who had epilepsy or mental diseases that prevented communication; those with cardiovascular and cerebrovascular diseases, patients on long-term use of analgesic drugs, those who had a history of abdominal surgery, as well as patients with serious hepatic/renal dysfunction, and those who could not tolerate surgery.

Anaesthesia scheme

All eligible patients in both teams underwent routine examinations which involved monitoring electrocardiogram, blood pressure, and blood oxygen saturation.

Anaesthesia induction procedures involved intravenous remifentanyl ($1 \mu\text{g}/\text{kg}$), rocuronium ($0.5 \text{ mg}/\text{kg}$), dexmedetomidine ($0.5 \mu\text{g}/\text{kg}$), and propofol ($1.5 - 2.0 \text{ mg}/\text{kg}$).

Tracheal intubation was performed after muscle relaxation, and mechanical ventilation was performed with an intelligent anaesthesia machine. The respiration rate was between 18 and 22 per minute; with equal ratio of inspiration to expiration, and tidal volume of $8 - 10 \text{ mL}/\text{kg}$. The P_{CO_2} at the final-tidal tide was kept at $35 - 40 \text{ mmHg}$.

Anaesthesia maintenance procedures

The sevoflurane cohort continuously breathed in sevoflurane (about 2.0%), while the isoflurane cohort continuously breathed in about 1.0%

isoflurane. All patients received remifentanyl for continuous anaesthesia maintenance. Inhalation isoflurane or sevoflurane, and infusion of remifentanyl infusion were discontinued at the last step of the operation. Tracheal intubation was withdrawn after recovery of spontaneous breathing, dysphagia cough reflex, and hemodynamic stability. Then, the patients were awoken and taken to the recovery room.

Determination of indices

Peripheral venous blood (5 mL) was collected before anaesthesia reaction (T0), and at 12 h (T4), 24 h (T5), and three days after operation (T6). The serum samples were obtained through centrifugation at 3000 g for 10 min. The expression levels of interleukins 6 and 8, CRP, A β 40 and A β 42 in serum were determined using ELISA kits, in compliance with the ELISA kit protocols.

Flow cytometry

After surgery, the standard beneficial indices of immunity were determined using flow cytometry. Serum was added to red blood cell lysis buffer (8 mL), kept at laboratory temperature for 10 min, followed by centrifugation. After discarding the upper liquid layer, following addition of 1 mL of PBS, the mixture was transferred to a 1.5-mL Eppendorf tube and centrifuged. Thereafter, red blood cell lysis buffer was added, and after centrifugation, the supernatant was discarded, and 500 μ L of PBS buffer was added to the sediment.

After mixing, the lysed cells were transferred to new tubes and stained. Then, the levels of CD3+, CD4+, CD8+ and CD4+/CD8+ were measured using automatic flow cytometer. Catalase (CAT) activity was determined by spectrophotometry, while SOD and MDA were determined using ELISA kits.

Clinical indicators (eye-opening time, extubation time, surgery time, blood loss, and spontaneous breathing recovery time) were monitored. The hemodynamic indices (heart rate (HR), SBP, DBP) were assessed at T0, at onset of anaesthesia (T1), and during intubation (T2), and extubation (T3). These indexes of unusual intraoperative times were compared.

Immune response

The levels of immunity indexes, serum inflammatory factors, oxidative stress indexes,

A β 40 and A β 42 were compared between both cohorts at different times. The simple Mini-mental State Examination (MMSE) scores of the cohorts were monitored and recorded at T0, T4, T5, and T6. Incidences of unwanted responses were compared between the two groups.

Statistical analysis

Statistical analysis was carried out using SPSS 19.0 (Asia Analytics Formerly SPSS, China). Counting data are presented as [n (%)], and were compared between the two groups using chi square test. Measurement data are shown as mean \pm standard deviation ($\bar{x} \pm SD$). The two groups were compared with *t*-test; ANOVA of recurrent measures was utilized to compare between different times, while LSD test was used for post-test. Statistical significance was assumed at $p < 0.05$.

RESULTS

General information on patients

Table 1 shows that there were no marked differences between both teams in age, sex, body mass index (BMI), years of education, ASA grade, tumor size, and lymph node metastasis ($p > 0.05$).

Pertinent clinical indicators

The values of related clinical indicators are presented in Table 2. There were no marked differences in surgery time, blood loss and recovery time for spontaneous respiration between the two cohorts ($p > 0.05$), while eye-opening time and extubation time were markedly shorter in sevoflurane cohort.

Hemodynamic indices

A comparison of the two cohorts with respect to hemodynamic indexes at different times during surgery revealed that at T0, there were no marked differences in heart rate, systolic blood pressure and diastolic blood pressure. The levels of these indexes were reduced in both groups at onset of anaesthesia and intubation, with lower values at onset; their levels during intubation and after extubation were higher than those at T1. From onset of anaesthesia to extubation, levels of SBP and DBP were markedly higher in sevoflurane cohort than in isoflurane cohort. At onset of anaesthesia, HR was markedly higher in sevoflurane cohort than in isoflurane cohort.

Table 1: Basic information on patients [(mean \pm SD, or n [%])]

Parameter	Isoflurane team (n=136)	Sevoflurane team (n=142)	χ^2/t	P-value
Sex			0.009	0.923
Male	64(47.06)	66(46.48)		
Female	72(52.94)	76(53.52)		
Age (years)	70.23 \pm 3.21	70.41 \pm 3.57	0.441	0.659
BMI (kg/m ²)	24.68 \pm 2.57	24.56 \pm 2.31	0.410	0.682
Educational exposure (years)	8.59 \pm 4.72	8.87 \pm 4.54	0.504	0.615
Smoking			0.062	0.803
Yes	45(33.09)	49(34.51)		
No	91(66.91)	93(65.49)		
ASA grade			1.088	0.580
I	38(27.94)	34(23.94)		
II	73(53.68)	85(59.86)		
III	25(18.38)	23(16.20)		
Tumor size			0.023	0.879
≥ 5 cm	41(30.15)	44(30.99)		
< 5 cm	95(69.85)	98(69.01)		
Lymph node metastasis			0.000	0.989
Yes	48(35.29)	50(35.21)		
No	88(64.71)	92(64.79)		

Table 2: Values of clinically relevant indicators (mean \pm SD)

Cohort	Eye opening time (min)	Extubation time (min)	Surgery time (min)	Bleeding volume (mL)	Time of recovery of spontaneous breathing (min)
Isoflurane (n=136)	16.02 \pm 2.14	21.89 \pm 2.31	78.37 \pm 14.28	181.87 \pm 28.49	15.23 \pm 3.43
Sevoflurane (n=142)	14.33 \pm 2.35	20.11 \pm 2.09	76.32 \pm 15.02	180.28 \pm 34.11	15.17 \pm 3.31
<i>t</i>	6.261	6.742	1.165	0.421	0.148
<i>P</i> -value	<0.001	<0.001	0.245	0.674	0.882

Table 3: Indexes of hemodynamics at various intraoperative periods

Variable	T0	T1	T2	T3	F	P
Isoflurane						
DBP (mmHg)	82.08 \pm 5.23	72.31 \pm 6.12	74.13 \pm 4.08	76.02 \pm 7.13	74.028	<0.001
SBP (mmHg)	134.06 \pm 13.27	110.37 \pm 10.38	116.78 \pm 13.28	121.56 \pm 12.74	87.770	<0.001
HR (times /min)	75.23 \pm 10.31	63.31 \pm 8.27	68.89 \pm 9.03	74.81 \pm 8.79	51.776	0.273
Sevoflurane						
DBP (mmHg)	82.37 \pm 5.38	78.37 \pm 5.11*	80.27 \pm 4.58*	82.28 \pm 5.03*	20.250	<0.001
SBP (mmHg)	134.28 \pm 13.22	119.34 \pm 12.37*	123.67 \pm 12.02*	133.31 \pm 11.32*	50.735	<0.001
HR (times /min)	75.02 \pm 10.23	68.31 \pm 8.36*	70.98 \pm 8.75	74.48 \pm 9.12	16.86	0.294

* the isoflurane team compared, $P < 0.05$.

Immune functions

The immune function indexes of both teams were compared. At onset of anesthesia, the levels of beneficial immunity indexes in the two cohorts were comparable.

However, post-anaesthesia, these indexes were markedly reduced in both groups, reaching the lowest values at T4, and increasing at the last two time points. Figure 1 depicts details of the changes in levels of these immunity indexes at the various intraoperative periods in the two cohorts.

Inflammatory cytokine levels

Figure 2 shows comparison of the levels of inflammatory cytokine between the 2 cohorts. At T0, serum inflammatory cytokine levels were comparable in both groups. However, the levels of inflammatory cytokines were enhanced postoperatively, peaking at T5, and reducing 3 days post-surgery. From 12 h to 3 days after operation, the levels of inflammatory cytokines and CRP were markedly lower in sevoflurane group than in isoflurane group. At 12 h and 24 h,

there were lower serum IL-8 level in sevoflurane cohort than in isoflurane cohort.

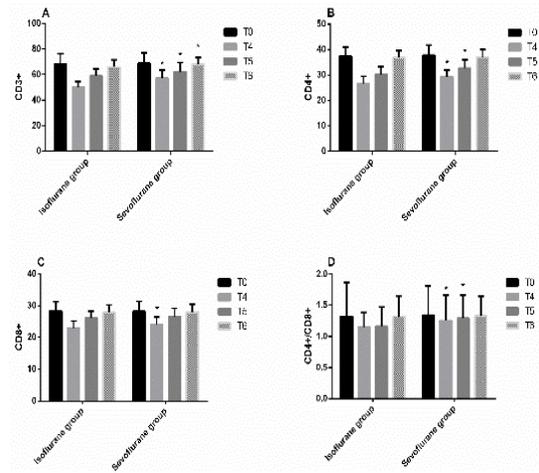


Figure 1: Changes in levels of immunity indexes. A: CD3+ level at every period of time in both teams. B: Changes in CD4+ value in every time period in both groups. C: CD8+ levels in both cohorts at different periods. D: Ratio of CD4+/CD8+ in both cohorts at each time point. * $P < 0.05$, compared with isoflurane group at the same period

Oxidative stress indices

Figure 3 shows comparison of oxidative stress marker levels in both cohorts. Before anesthesia, oxidative stress indexes were comparable in both teams ($p > 0.05$). The mean values of SOD and CAT from 12 h to 3 days after operation, were markedly decreased in both cohorts, relative to values at T0, reaching the lowest levels 3 days after operation, but they were higher in sevoflurane cohort than isoflurane cohort. Within the same period, the contents of MDA were increased, relative to values before anesthesia, and MDA content peaked at T5, but was reduced at T6. The MDA level was markedly lower in sevoflurane cohort than in isoflurane cohort.

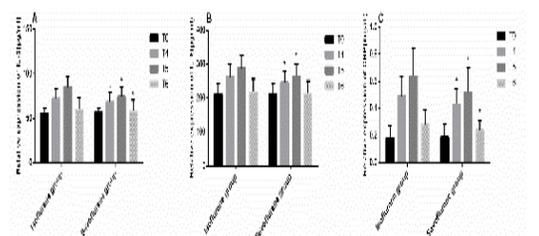


Figure 2: Comparison of levels of inflammatory cytokines. A: Values of IL-6 in both groups at different times. B: Levels of IL-8 in both cohorts at each time point. C: CRP levels in both cohorts at each time point. * $P < 0.05$, compared with isoflurane group

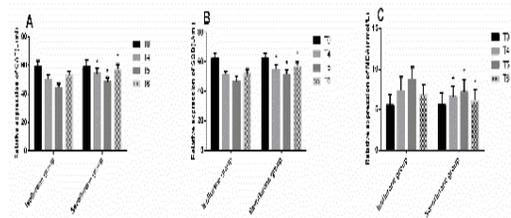


Figure 3: Levels of oxidative stress indicators. A: CAT values. B: SOD activities in both cohorts at each period. C: MDA levels in the two cohorts at each time points. * $P < 0.05$, compared with isoflurane cohort at the same time point

Changes in serum Aβ levels

There were markedly higher values of Aβ42 and Aβ40 after extubation than at pre-anesthesia ($p > .05$). The pattern of changes in these parameters are shown in Figure 4.

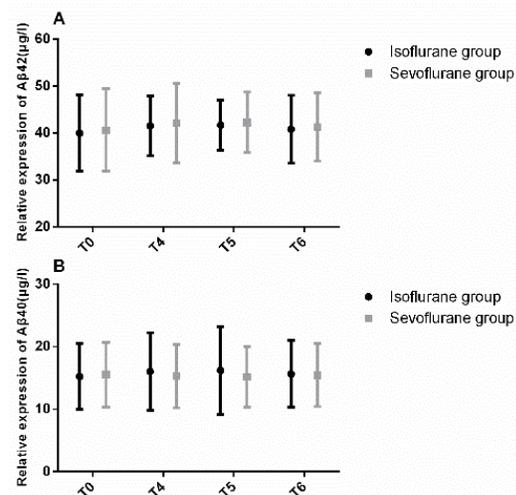


Figure 4: Serum levels of Aβ factors. A: serum Aβ42 levels in both cohorts. B: Serum Aβ40 levels in both cohorts

Changes in cognitive function

The MMSE scores of the isoflurane and sevoflurane cohorts were compared, as shown in Figure 5. At T0, MMSE score were comparable in both cohorts ($p > 0.05$). Scores at T4 and T5 in both groups were lower, when compared with scores at T0. At 12 h and 24 h post-operation, MMSE scores were markedly higher in sevoflurane cohort than in isoflurane cohort.

Incidence of adverse reactions

Table 4 shows the incidence of adverse reactions in each cohort. The total incidence of adverse reactions was 22.80 % in isoflurane cohort, and 19.73% in the sevoflurane cohort.

There was no statistical difference between the 2 cohorts.

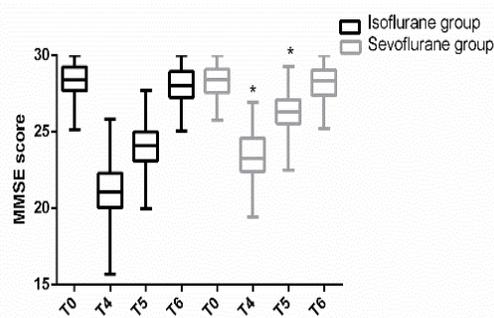


Figure 5: Comparison of MMSE scores. Before anesthesia, MMSE scores in both cohorts were comparable. However, at T4 and T5, scores in both units were lower than that at T0 ($p < 0.05$). At 12 h and 24 h post-operation, MMSE scores were markedly higher in sevoflurane cohort than in isoflurane cohort. * $P < 0.05$, vs isoflurane cohort

DISCUSSION

At present, the pathogenesis of gallbladder cancer is not well understood. However, the risk factors for this disease are chronic cholecystitis, obesity, female sex, gallstones, and prolonged bacterial infection of the gallbladder [22]. Some researchers have demonstrated that postoperative adverse reactions are increased because of wrong choice and dosage of anaesthetic drugs [23,24]. The use of DEX could decrease the number of narcotic medications, and inhibit sympathetic nerve function, thereby playing an analgesic effect. Moreover, respiratory depression is weakened, cognitive impairment is alleviated, and hemodynamics is stabilized [25]. Isoflurane and sevoflurane are primarily used as anaesthetics in cardiac operations. The latter is believed by many cardiac anesthesiologists to outperform isoflurane [26]. However, there very little research support for this view.

The T-lymphocyte subsets are human immune cells involved in responses, and they are also essential in cellular tissues of the immune system. The T-cell subsets reflect the entire

status of immunity [27-29]. Anaesthetic systems with the most negligible impact on the function of immune cells reduce pain in patients to maximum levels [30].

In this study, compared with isoflurane, sevoflurane had less effect on the levels of immune cells post-surgery. In a previous study on patients undergoing abdominal operation, it was found that sevoflurane produced milder disruption in the levels of CD3+, CD4+, and CD4+/CD8+ than propofol [31]. The mechanism of this surgically-induced inflammatory response is complicated. It has been revealed that C-reaction protein and interleukins-6 and 8 exert potent biological impacts which are implicated in modification of immune reactions [32, 33]. Wang *et al* have revealed that sevoflurane anaesthesia causes increased levels of inflammatory cytokines (IL-6, IL-8, and TNF- α), which can be reversed by DEX [34]. In this study, patients given sevoflurane showed lower postoperative levels of IL-6, CRP and IL-8 than those who received isoflurane, suggesting significant mitigation of postoperative inflammatory responses and cognitive impairment by DEX plus sevoflurane. During oxidative stress damage, SOD and CAT are antioxidant enzymes which play antioxidative defense roles [35]. Superoxide dismutase protects cells from damage through removing superoxide anions [36]. An increase in MDA reflects oxidative stress status, and antioxidant enzymes mitigate free radical-induced damage to the cell membrane and macromolecular substances [37]. A prior animal study showed excellent alleviation of oxidative stress by sevoflurane to isoflurane [38].

In this study, sevoflurane showed more benefits of oxidative stress mitigation than isoflurane. However, this result requires more supportive evidence and verification. In a previous research, Gang *et al* found no significant differences in operative time and amount of blood loss between both groups of patients [39]. Rajan and others have shown that sevoflurane resulted in better recovery and greater clinical benefits such as cognitive function, extubation time, and orientation, than isoflurane [40].

Table 4: Incidence of adverse events [n (%)]

Group	Nausea and vomiting	Gastrointestinal tract reaction	Dizziness	Facial oedema	Restless-ness	Total incidence
Isoflurane (n=136)	7(5.15)	8(5.88)	5(3.68)	3(2.21)	8(5.88)	22.80%
Sevoflurane (n=142)	5(3.52)	9(6.34)	6(4.23)	2(1.41)	6(4.23)	19.73%
χ^2						0.267
P-value						0.606

Operation time, blood loss, and time of recovery of spontaneous breathing were similar for all patients. However, the eye-opening time and extubation time were markedly shorter in sevoflurane cohort than in the isoflurane group. A previous study showed better stability with sevoflurane than with other inhalant drugs [41]. In the present study, sevoflurane plus DEX resulted in better hemodynamics than DEX plus isoflurane. This result could be attributed to increase in local cerebral blood flow, regulation of intracranial pressure, and protection of functional neurons by sevoflurane, all of which facilitated the recovery of cognitive function.

Research has demonstrated an association between blood A β 42/A β 40 ratio and severity of Alzheimer's illness: aggregation of A β 42 in neurons affects cognition [42,43]. In this research, the serum A β levels of the patients remained unchanged. It has been speculated that decreased cognition in patients could lead to cerebral hypometabolism, hypoperfusion, or vascular lesions, rather than A β fluctuations [39].

Research has shown that DEX reduced the rate of cognitive impairment after sevoflurane anaesthesia, and improved the MMSE scores in the patients [44]. From the analysis, the higher MMSE scores in the sevoflurane group indicate better improvements in cognitive function by DEX plus sevoflurane, relative to the isoflurane group. Moreover, there were no differences in incidence of adverse reactions between the two cohorts. This showed the safety profiles of sevoflurane and isoflurane, which is consistent with previous research [45].

Limitations of the study

The use of small sample size, and the short observation time are limitations in this study. Therefore, there is need for a long-term study and longer period of observation in order to further elucidate the impacts of inhalant anaesthetics on human A β . This will facilitate the identification of influencing factors during the perioperative period.

CONCLUSION

This study has demonstrated that DEX plus sevoflurane results in more significant improvements in the cognitive function of elderly patients undergoing radical resection for gallbladder cancer, with more minor immune function impairment, milder inflammatory response and milder oxidative stress, than DEX plus isoflurane.

DECLARATIONS

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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