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Original Article

Neuroprotective effects of lidocaine on early postoperative cognitive dysfunction and the possible mechanism

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Abstract: Background: Postoperative cognitive dysfunction (POCD) is induced by general anesthesia and surgery. Advancing age is associated with POCD. To make matters worse, elderly people are also at a higher risk of undergoing surgery than younger people. In this paper, the neuroprotective effects of lidocaine on early POCD in elderly patients undergoing orthopedic surgery were investigated and the possible mechanism was explored. Methods: A total of 116 patients scheduled for orthopedic surgery were randomly allocated to lidocaine group and control group (n = 58). Lidocaine group received a bolus of 1 mg/Kg of lidocaine in 5 minutes after induction of anesthesia, and then a continuous infusion at 1.5 mg/Kg/h until the end of surgery. Control group received normal saline as a bolus. Mini-Mental State Examination (MMSE) scores, cerebral oxygen and energy metabolism metrics were compared between lidocaine group and control group. Results: The MMSE scores were significantly decreased on the 3rd day after the end of surgery (T3) compared with before induction of anesthesia (T1) in control group, but were not significantly different between T3 and T1 in lidocaine group. Moreover, the decreased level of control group was greater than lidocaine group. Concentration of cerebral vein oxygen ($CjvO_2$) was lower at the end of surgery (T2) than at T1 in both lidocaine group and control group, but the decreased level was significantly attenuated by lidocaine. Cerebral oxygen extraction rate ($CERO_2$) was lower at T2 than at T1 in lidocaine group, but higher at T2 than at T1 in control group, which indicated that lidocaine could inhibit the elevation of $CERO_2$. Djv-aLac was not significantly different between T2 and T1 in lidocaine group, but higher at T2 than at T1 in control group, which indicated that lidocaine could inhibit the elevation of Djv-aLac. Conclusions: Lidocaine had neuroprotective effects on early POCD in elderly patients undergoing orthopedic surgery, and the possible mechanism was associated with decreased cerebral oxygen and anaerobic metabolism.

Keywords: Postoperative cognitive dysfunction, lidocaine, neuroprotective effects, cerebral oxygen metabolism, cerebral anaerobic metabolism

Introduction

Lidocaine is a local anesthetic which can readily cross the blood-brain barrier [1]. It can decrease required concentrations of general anesthetics during anesthesia [2] and protect neurons [3], which is possibly associated with its neuroprotective effects. Many studies have demonstrated its neuroprotective effects when it is given systemically [4-8].

As a frequent complication following general anesthesia and surgery [9], especially in elderly individuals, postoperative cognitive dysfunction (POCD) is characterized with impaired consciousness and disordered thinking [10, 11]. POCD is associated with the degeneration of the central nervous system [12] and increased surgical morbidity and mortality, decreased postoperative quality of life, prolonged hospital stay, and elevated perioperative medical cost [13, 14]. The precise mechanism of POCD is not yet very clear. Several possible causes are suggested, including an exaggerated systemic inflammation, hypoxemia, cerebral hypoperfusion, endothelial dysfunction, and microembolism [15, 16].

In this study, the neuroprotective effects of lidocaine on early POCD in elderly patients under-

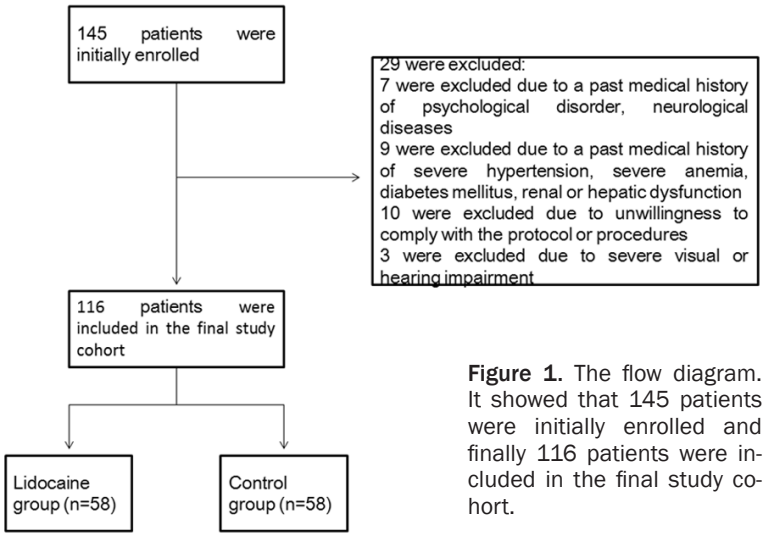

Figure 1. The flow diagram. It showed that 145 patients were initially enrolled and finally 116 patients were included in the final study cohort.

going orthopedic surgery were investigated and the possible mechanism was explored. The aim was to provide the basis for application of lidocaine in orthopedic surgery.

Materials and methods

Participants

A total of 145 patients scheduled for orthopedic surgery were enrolled in Gansu Provincial Hospital from January 2016 to June 2017. Twenty-nine patients were excluded according to exclusion criteria, and 116 patients were included in the final study cohort (**Figure 1**).

Inclusion criteria included: (1) American Society of Anesthesiologists (ASA) physical status I or II; (2) Ranging from 64 to 80 years old; (3) Preoperative Mini-Mental State Examination (MMSE) scores ≥23. Exclusion criteria included: (1) A past medical history of psychological disorder, neurological diseases (including Alzheimer's disease and stroke history), and drug or alcohol abuse; (2) A past medical history of severe hypertension, severe anemia, diabetes mellitus, renal or hepatic dysfunction; (3) Unwillingness to comply with the protocol or procedures; (4) Severe visual or hearing impairment. This study received the approval of the ethic committee of Gansu Provincial Hospital (201528116), and all patients provided written informed consents.

Grouping and general anesthesia

The 116 participants included in the final study cohort were randomly allocated to lidocaine group (n = 58) and control group (n = 58). Randomization was performed using random number table and was concealed until after consent was obtained. Participants in lidocaine group received a bolus of 1 mg/kg of lidocaine in 5 minutes after induction of anesthesia, and then a continuous infusion at 1.5 mg/kg/h until the end of the surgery. Participants in control group received normal saline as a bolus and a continuous infusion with the same volume and rate as lidocaine group.

General anesthesia was performed using standard protocols. Pulse oximetry, electrocardiography, capnography, invasive arterial pressure and central venous pressure (CVP) were continuously monitored during anesthesia. Anesthesia was induced with 0.05-0.1 mg/Kg of midazolam, 0.5-1 μg/Kg of sufentanil, 1.5-2.5 mg/Kg of propofol, and 0.8-1.0 mg/Kg of rocuronium. It was then maintained with 4 mg/Kg/h of propofol, 0.2 μg/Kg/min of remifentanil, 2.0 μg/Kg/min of cisatracurium, 0.5 μg/Kg/h of dexmedetomidine, and inhaled 0-4% of sevoflurane. Bispectral Index Score was maintained at 40-60.

Evaluation of cognitive function

An experienced psychometrician, who received standard training in MMSE [17], evaluated individual cognitive function of participants preoperatively and three days post-operatively in a quiet room using the MMSE. The psychometrician completed all interpretation and data scoring. Both the psychometrician and participants were blinded to grouping. MMSE scores consisted of digit symbol test, accumulative test, digit span-forward test, digit span-reverse test and trace connection test A. The same version of the MMSE was administered at the 2 time points. POCD was determined using the criteria recommended by Moller JT et al [18].

Evaluation of cerebral oxygen and energy metabolism

Blood samples from the jugular vein bulb and peripheral artery were collected before induction of anesthesia (T1), at the end of surgery

Table 1. Baseline data of lidocaine group and control group

	Lidocaine group (n = 58)	Control group (n = 58)	χ^2/t	*P*
Sex (male/female)	21/37	28/30	1.731	0.188
Age (year)	70.96±2.49	71.12±2.68	0.333	0.736
BMI	20.89±3.67	21.05±3.95	0.226	0.834
ASA classification (I/II)	36/22	31/27	0.883	0.347
Operation time (min)	128.59±8.24	129.23±8.62	0.409	0.685

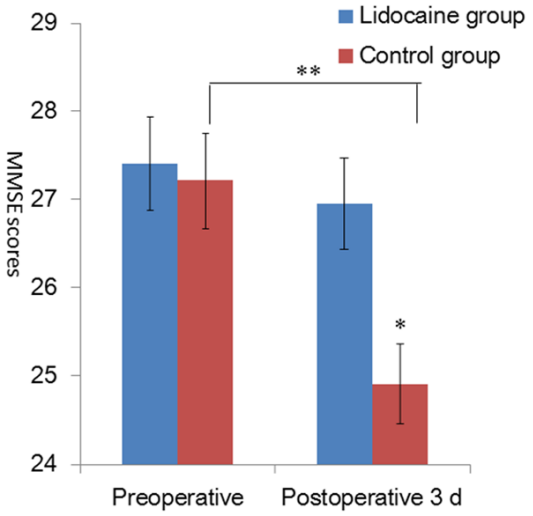

Figure 2. MMSE scores of lidocaine group and control group at preoperation and postoperative 3 days. *P<0.05, *vs* preoperative; **P<0.05, *vs* lidocaine group.

(T2) and on the 3rd day after the end of surgery (T3). Blood gas analysis was performed, and concentrations of blood glucose and plasma lactic acid were measured. Cerebral oxygen extraction rate ($CERO_2$), cerebral extraction rate of glucose (CER_{Glu}) and difference between cerebral vein and artery for plasma lactic acid (Djv-aLac) were calculated using Fick equation. The calculation formula was given out in detail, as follows.

(1) Concentration of arterial oxygen (CaO_2) = 1.34 × Hb × saturation of arterial oxygen (SaO_2) + 0.0031 × pressure of arterial oxygen (PaO_2). (2) Concentration of cerebral vein oxygen ($CjvO_2$) = 1.34 × Hb × saturation of jugular vein bulb oxygen ($SjvO_2$) + 0.0031 × pressure of jugular vein bulb oxygen ($PjvO_2$). (3) Difference between cerebral artery and vein for oxygen ($Da\text{-}jvO_2$) = CaO_2 - $CjvO_2$. (4) $CERO_2$ = ($Da\text{-}jvO_2$/CaO_2) × 100%. (5) Difference between cerebral artery and vein for blood glucose (Da-jvGlu) = arterial glucose (Glua) - jugular vein bulb glucose (Glujv). (6) CERGlu = (Djv-aLac/Glua) × 100%. (7) Djv-aLac = jugular vein bulb lactic acid (Lacjv) - arterial lactic acid (Laca).

Statistical analysis

The sample size was computed with the formula: $N = [(Z_{\alpha/2} + Z_{\beta})\sigma/\delta]^2(Q1^{-1} + Q2^{-1})$. Quantitative data were expressed as mean ± SD and qualitative data as percentage (%). Quantitative data at baseline were analyzed with Student's *t* test and qualitative data with chi-square test. MMSE scores, cerebral oxygen ($SjvO_2$, CaO_2, $CjvO_2$ and $CERO_2$) and energy metabolism metrics (CER_{Glu}, Laca, Lacjv, Glua, Glujv and Djv-aLac) were analyzed with repeated measures ANOVA. All data were analyzed with the SPSS version 19.0 for Windows (SPSS Inc., USA). Significance was set at P<0.05.

Results

Baseline data

The final study cohort (116 patients) included 49 males and 67 females with a mean age of 71.04±2.59 years. Baseline data of lidocaine group and control group were shown in **Table 1**. The differences in sex, age, body mass index (BMI), ASA classification and operation time were not statistically significant (P>0.05).

Cognitive function

As shown in **Figure 2**, there was no significant difference in the MMSE scores between lidocaine group (27.41±3.08) and control group (26.95±2.97) at T1 (P>0.05). The MMSE scores were significantly decreased at T3 (24.91±2.62) compared with T1 in control group (P<0.05). However, the MMSE scores were not significantly different between T3 (27.22±3.14) and T1 (xxx) in lidocaine group (P>0.05). Moreover, the decreased level of MMSE scores was greater in control group than in lidocaine group (2.31, 95% confidence interval: 1.53-3.09 vs 0.46, 95% confidence interval: 0.26-0.65; P<0.05). These results indicated that lidocaine had neuroprotective effects.

Cerebral oxygen metabolism

As shown in **Figure 3**, there was no significant difference between T1 and T2 for $SjvO_2$ in both

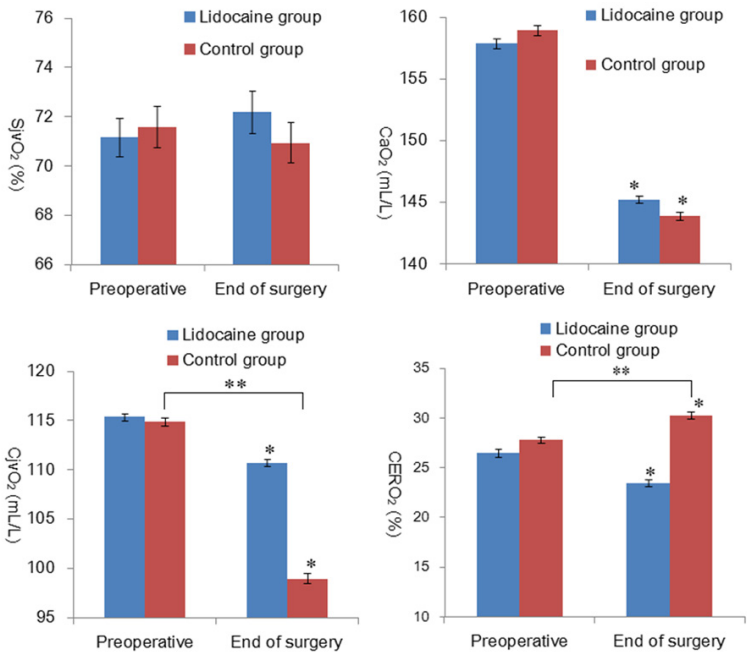

Figure 3. Cerebral oxygen metabolism metrics of lidocaine group and control group at preoperation and end of surgery. *P<0.05, *vs* preoperative; **P<0.05, *vs* lidocaine group.

lidocaine group (71.16±7.52 *vs* 72.17±8.13) and control group (71.58±7.86 *vs* 70.93±7.69), and the intergroup difference for (T2-T1) was also not significant. CaO_2 was lower at T2 than at T1 in both lidocaine group (145.23±9.14 *vs* 157.84±11.38) and control group (143.89±10.57 *vs* 158.92±12.87), but the intergroup difference for (T2-T1) was not significant. $CjvO_2$ was lower at T2 than at T1 in both lidocaine group (110.69±4.85 *vs* 115.32±5.09) and control group (98.94±5.21 *vs* 114.85±5.44), and T1-T2 was greater in control group than in lidocaine group. This indicated that the decreased level of $CjvO_2$ was significantly attenuated by lidocaine. $CERO_2$ was lower at T2 than at T1 in lidocaine group (23.44±2.28 *vs* 26.47±2.49), but higher at T2 than at T1 in control group (30.26±2.13 *vs* 27.78±2.04), which indicated that lidocaine could inhibit the elevation of $CERO_2$.

Cerebral energy metabolism

As shown in **Figure 4**, there were no significant differences between T2 and T1 for CER_{Glu} (8.87±2.95 *vs* 9.26±3.14 for lidocaine group, 9.16±3.29 *vs* 9.19±3.31 for control group), Laca (1.88±0.42 *vs* 1.84±0.44 for lidocaine group, 1.89±0.46 *vs* 1.82±0.39 for control group) and Lacjv (1.79±0.28 *vs* 1.77±0.24 for lidocaine group, 1.82±0.33 *vs* 1.68±0.31 for control group) in both lidocaine group and control group, and the intergroup differences for (T2-T1) were also not significant. Both Glua (6.18±1.28 *vs* 4.97±1.31 for lidocaine group, 6.43±1.09 *vs* 5.26±0.97 for control group) and Glujv (5.46±1.47 *vs* 4.18±1.35 for lidocaine group, 5.95±1.53 *vs* 4.76±1.44 for control group) were higher at T2 than at T1 in both lidocaine group and control group, but the intergroup differences for (T2-T1) were not significant. Djv-aLac was not significantly different between T2 and T1 in lidocaine group (-0.16±0.11 *vs* -0.12±0.07), but higher at T2 than at T1 in control group (0.69±0.29 *vs* -0.13±0.10), and the intergroup difference for (T2-T1) was significant. This indicated that lidocaine could inhibit the elevation of Djv-aLac.

Discussion

POCD can be induced by general anesthesia and surgery [9]. Originally, the studies about POCD focused on cardiac surgery. A recent study showed that POCD is also frequent in non-cardiac surgery and even in minor non-invasive procedures, such as coronary angiography [19]. A multi-center study reported that the incidence of POCD was 25% and 10%, respectively at 1 week and 3 months after non-cardiac surgery [18]. Many studies demonstrated that advancing age is associated with POCD [18, 20-22]. To make matters worse, elderly people are also at a higher risk of undergoing surgery than younger people [23]. Therefore, the prevention of POCD in elderly patients undergoing surgery should be paid attention to.

The effects of lidocaine on neuroprotection have been demonstrated by several clinical and animal studies [4-8]. A recent report indicated that lidocaine may improve cognitive function and act as an effective neuroprotec-

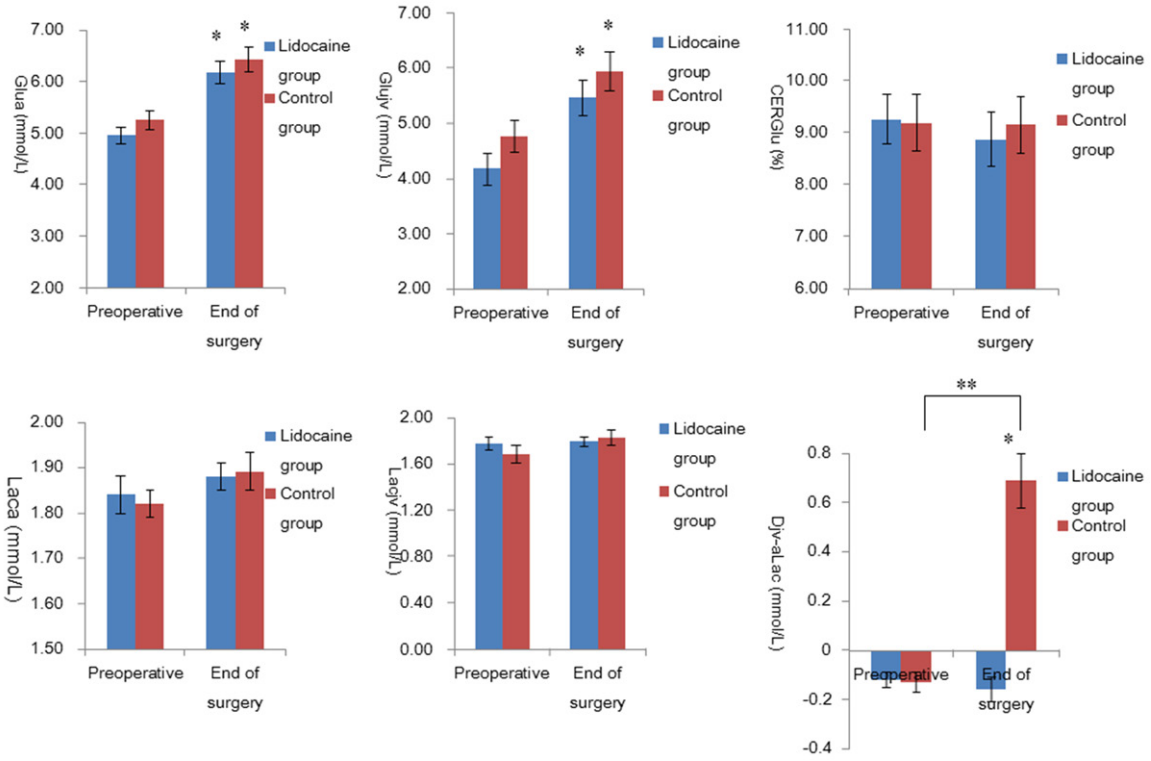

Figure 4. Cerebral energy metabolism metrics of lidocaine group and control group at preoperation and end of surgery. *P<0.05, *vs* preoperative; **P<0.05, *vs* lidocaine group.

tive agent in treating early POCD of elderly patients undergoing spine surgery [24]. However, the underlying mechanism is still not fully elucidated. It is speculated that the neuroprotective effects of lidocaine are possibly correlated with the following mechanisms, including decelerating the ischemic transmembrane ion shift, reducing the cerebral metabolic rate and the ischemic excitotoxin release [16].

In this study, lidocaine could elevate the MMSE scores significantly in elderly patients undergoing orthopedic surgery. This result suggested that lidocaine had neuroprotective effects, which was consistent with previous reports. In addition, our results showed that lidocaine could elevate $CjvO_2$ significantly, and meanwhile decrease $CERO_2$ and Djv-aLac significantly.

In clinical practice, cerebral oxygenation is usually evaluated through measuring $SjvO_2$ of the jugular vein bulb and calculating $Da\text{-}jvO_2$ and $CERO_2$. $SjvO_2$ is an integrated index, which can reflect the balance of cerebral oxygen supply and consumption with a normal value of 55%~75%. Lactate is the endproduct of anaerobic glycolysis, and the brain can release and absorb lactate. For the variation of lactic acid in cells, the concentration of lactic acid in the jugular vein bulb is a better index than the concentration of lactic acid in cerebrospinal fluid. Djv-aLac can reflect the net production of lactate and is usually regarded as the amount of lactic acid produced by anaerobic glycolysis of the brain. A positive value of Djv-aLac means anaerobic glycolysis in the brain. In this paper, lidocaine could decrease $CERO_2$ and Djv-aLac significantly, which suggested that it could decrease cerebral oxygen and anaerobic metabolism.

As a local anesthetic of amide derivatives, lidocaine may block ion channels and does not induce anaerobic metabolism. In addition, lidocaine can inhibit synaptic transmission. Astrup J et al reported that a large dose of lidocaine (100~160 mg/Kg) can preserve cellular energy by reducing cerebral metabolic rate during neuronal ischemia in the whole cerebral ischemia model of dogs [25]. Lei B et al reported that lidocaine can reduce apoptosis in the ischemic penumbra region in the transient focal cerebral ischemia model of rats [26]. Cao H et al found

that lidocaine can decrease the number of dead cells in rat hippocampal slices [27]. Our study showed that the neuroprotective effects of lidocaine might be associated with decreased cerebral oxygen and anaerobic metabolism.

In summary, lidocaine had neuroprotective effects on early POCD in elderly patients undergoing orthopedic surgery, and the possible mechanism was associated with decreased cerebral oxygen and anaerobic metabolism.

Disclosure of conflict of interest

None.

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