Original Article

Lidocaine administration before tracheal extubation cannot reduce post-operative cognition disorders in elderly patients

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Abstract

Background: Cognitive dysfunction after surgery is common in elderly patients. Many factors such as anesthetic drugs can cause complication in this surgery. Lidocaine is one of the drugs commonly used during anesthesia. So, we designed this study to find out cognitive effect of lidocaine in elderly patients undergoing non-cardiac surgeries.

Materials and Methods: In this double-blinded clinical trial, we enrolled 70 patients older than 65 years age undergoing urologic or orthopedic surgeries, were divided in two groups. Patients randomly received intravenous lidocaine (1.5 mg/kg) or normal saline in the same volume immediately before extubation. Mini mental state examination (MMSE) test was used to evaluate cognitive state at discharge time, 6 and 24 h after surgery.

Results: Mean MMSE scores at the time of discharge from recovery room in lidocaine and saline groups were 22.4 ± 4.5 vs. 22.1 ± 4.4, $P = 0.755$, respectively. It was significantly lower than MMSE before surgery, 6 and 24 h after the operation. The mean MMSE scores and frequency distribution of intensity of cognitive impairments were not significantly different between two groups at different times.

Conclusion: Bolus intravenous lidocaine before extubation, did not affect cognitive states in elders undergoing non-cardiac surgery. Effect of lidocaine on cardiac surgeries is clear, but in non-cardiac surgeries, lidocaine has no clinical effects. So, more studies with different doses of lidocaine and different assessment methods are recommended.

Key Words: Cognitive dysfunction, elderly patients, lidocaine, post-operative

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INTRODUCTION

Cognitive dysfunction is one of the major post-operative problems, especially in the elderly patients. The prevalence varies up to 50% in patients older than 65 years age in different surgeries.[1] Post-operative cognitive dysfunction is affected by several factors such as age, underlying disease, basic cognitive state, metabolic disorders, brain hypoxia, hypotension and type of surgery.[1,2] Cognitive dysfunction may increase mortality, morbidity,

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hospitalization and prolong recovery time.[3-5] On the other hand, the prevalence of cognitive dysfunction is depended on kind of anesthesia and anesthetic drugs. Anticholinergics and benzodiazepines increase post-operative delirium risk, but some anesthetics or short acting analgesics, decrease cognitive impairments.[6-9] Lidocaine, as a local anesthetic and antiarrhythmic drug, is widely used for different therapeutic goals in anesthesia. It has been used as cardiovascular response modifier in extubation.[10] Treatment of intraoperative arrhythmia,[11] reducing post-extubation laryngospasm,[12] and decrease post-operative pain.[13] Some studies were established to find lidocaine cognitive effects: A study which was conducted by Lin *et al*. showed that intravenous administration of lidocaine during general anesthesia with isoflurane reduced cognitive dysfunctions in rats.[14]

Also, Wang *et al*. assayed the effects of bolus and then infusion of lidocaine on patients undergoing CABG (coronary artery bypass graft), the results of this study showed that lidocaine reduces post-operative cognitive dysfunction effectively.[15]

According to increasing use of lidocaine in anesthesia, especially at the time of intubation or extubation, and according to insufficient studies on evaluation of effect of bolus administration of lidocaine on post-operative cognitive impairment, this study is designed to determine the effect of bolus intravenous lidocaine (1.5 mg/kg) without infusion at the end of surgery, on post-operative cognitive function of elders undergoing urologic and orthopedic surgeries with general anesthesia.

MATERIALS AND METHODS

After study approval by the Ethics committee of Isfahan University of Medical Sciences, a double-blinded clinical trial study was performed in elderly patients undergoing urologic and orthopedic surgery with general anesthesia. Seventy patients older than 65 years of age were divided randomly in two equal groups using random-number table.

Patients with ASA I, II, III, (American society of Anesthesiologists), lack of any past history about neurologic, psychologic disorder renal and hepatic dysfunction, no history of alcohol, opium intake, sedative and anticholinergic drug abusing, premedication, and no allergy to lidocaine. Diseases such as hypertension, cardiac diseases, diabetes and also cigarette smoking were recorded in the questionnaires.

Blood pressure variation beyond 20% of basal value, severe bleeding and need to transfusion.

Anesthesia induced in two groups with sodium thiopental 5 mg/kg, atracurium (0.5 mg/kg) and fentanyl (0.1 μ/kg). Then maintenance of anesthesia achieved with isoflurane (0.8% to 1.2%) with N_2o, O_2 (50%) and morphine (0.1 mg/kg). Mechanical ventilation was done with tidal volume 10 ml/kg and respiratory rate 10 per min. Patients were monitored by NIBP (non-invasive blood pressure), electrocardiography, pulse oximetry and capnography during surgery.

At the end of surgery, patients were reversed by atropine and neostigmine (0.02 and 0.04 mg/kg retrospectively). In case group, intravenous lidocaine (1.5 mg/kg) and in control group, normal saline as placebo was administered 1 to 2 min before extubation, syringes containing lidocaine or normal saline, were similar in shape and volume and were prepared by one of the research co-workers, but the person who was responsible for injection of lidocaine and evaluation of patients responses was unaware of the contents. Cognitive function of patients was evaluated by MMSE (Mini Mental State Examination)[16] by the person who was unaware of groups of the patients, at 4 stages: Before surgery, at the time of discharge from recovery room, 6 h and 24 h after surgery in surgery ward. Before surgery, patients were educated for MMSE for evaluating cognitive function. Evaluation of patients before surgery in waiting room and then in recovery room was done, if the recovery score based on Aldrete score[17] was 9 or 10.

Systolic and diastolic blood pressure was maintained at the range of ±30% of the basic values. Blood pressure less or higher than 30% of basic values considered as hypotension and hypertensive, respectively and necessary treatment was done, but patients were excluded from the study.

Also, end tidal co_2 was monitored in the range of 30-40 mmHg. MMSE is a cognition measurement system scored from 0 to 30. This scoring system was designed by Folstein *et al*. in 1975 that consists of orientation (10 scores), registration (3 scores), calculation and attention (5 scores), recall (3 scores), and paraxis and language (9 scores). This test is done within 10 to 15 min. Validity and reliability of this test is confirmed in several studies and it is used widely in researches to evaluate cognitive function.[18,19] MMSE score of 24 to 30 is considered normal, 18 to 23 as mild dysfunction and 0 to 17 as severe cognition dysfunction. The time of surgery was defined as the time from skin incision till end of dressing of the wound. Recovery time was defined as the time from extubation till discharge from it based on Aldrete scores.

Data was analyzed statistically by SPSS version 19.

Repeated measure ANOVA was used for comparing MMSE score in different times and independent *t*-test was used for comparing the mean of age, weight, time of surgery and time of staying in recovery room. Mann-Whitney test was applied for comparing frequency distribution of intensity of cognition impairments and ASA class between two groups.

Also, for comparing frequency of sex distribution between two groups, chi-square test was used. And $P < 0.05$ was considered statistically significant.

RESULTS

In this study, a total of 76 patients were evaluated, but finally 70 patients with inclusion criteria ended the study. Patients' characteristics and operating conditions in the two groups are shown in Table 1.

Mean MMSE scores in two groups at different times, are shown in Table 2. Based on the information contained in this table, the mean MMSE score was not similar in lidocaine group at different times. Time of discharge from recovery room was significantly lower than before surgery, 6 and 24 h after the operation. Over the time, at 24 h after surgery, it increased and reached again to the level before the operation. Such a situation is evident in the normal saline group too. The mean MMSE scores were not significantly different between two groups observed at different times.

Frequency distribution of intensity of cognitive impairments in different times between two groups showed no significant difference Table 3.

Table 1: Patients' characteristics and operation variables

Variables	Lidocaine group (*n*=35)	Saline group (*n*=35)	*P* value
Age (year)	66±1	67±2	0.449
Weight (kg)	60±2	61±2	0.221
Gender (male/female)	27/8	28/7	0.849
ASA (I, II, III)	23/8/4	18/12/5	0.108
Operation time (min)	112±51	113±48	0.955
Recovery time (min)	76±29	72±23	0.507
Hypertension	12 (36)	7 (20)	0.133
Diabetes	5 (10)	4 (11)	0.461
Cardiac disease	6 (18)	1 (3)	0.038
Cigarette smoking	6 (18)	5 (14)	0.663

Data is mean±SD or *n* (%)

Table 2: Mini mental state examination scores at different times

Times of evaluation	Lidocaine group (*n*=35)	Salinegroup (*n*=35)	*P* value**
Before operation	25.9±4.4	25.7±3.9	0.850
Discharge from recovery	22.4±4.5	22.1±4.4	0.755
6 h after operation	24.2±4.6	23.1±4.7	0.341
24 h after operation	25.9±4.2	25.2±3.4	0.467
	0.001	0.000	
P value*	0.000	0.000	-
	0.005	0.003	

Data is mean±SD, *Discharge time compared with before operation, 6 h and 24 h after operation respectively within groups, **Comparison between groups

Table 3: Frequency distribution of intensity of cognitive dysfunction

Time of evaluation	Intensity	Lidocaine group (*n*=35)	Saline group (*n*=35)	*P* value*
Before operation	Normal	24 (69)	26 (34)	0.720
	Mild	8 (23)	9 (26)	
	Severe	3 (8)	0	
Discharge from recovery	Normal	16 (46)	13 (37)	0.435
	Mild	13 (37)	15 (43)	
	Severe	6 (17)	7 (20)	
6 h after operation	Normal	18 (51)	20 (57)	0.918
	Mild	14 (40)	9 (26)	
	Severe	3 (9)	6 (17)	
24 h after operation	Normal	25 (71)	26 (74)	0.955
	Mild	8 (23)	8 (23)	
	Severe	2 (6)	1 (3)	

Data is *n* (%), *Comparison between groups

DISCUSSION

Bolus intravenous lidocaine before extubation did not affect cognitive states in elders undergoing non-cardiac surgery. Mean MMSE scores at the time of discharge from recovery room in lidocaine and saline groups were 22.4 ± 4.5 vs. 22.1 ± 4.4, $P = 0.755$, respectively. It was significantly lower than MMSE before surgery, 6 and 24 h after the operation. The mean MMSE scores and frequency distribution of intensity of cognitive impairments were not significantly different between two groups at different times.

In several studies, some factors are known as risk factors for cognition impairments, such as cardiovascular and psychologic disorders,[20-23] ASA III and IV,[24] intraoperative brain hypoxia and hypotension,[25,26] CABG,[27] diabetes, old age,[5] alcohol and cigarette abusing.[28] In this study, only cardiac disorders was the sole risk factor, which had a significant difference between two groups, but because post-operative cognition impairments did not have significant difference between two groups. It seems that presence of cardiac disorders is not a strong risk factor in patients undergoing surgery.

On the other hand, patients who had hemodynamic variability beyond defined range were removed from study. Thus, hemodynamic instability could not affect

the results of our study. Also, hypertension, diabetes, and smoking which are known as post-operative cognition dysfunction risk factors, were similar between two groups and could not affect the result of our study.

According to Table 3, incidence of post-operative cognition impairments in this study was reported 26% to 30% in different hours after surgery. Most part of these cognition impairments was mild.

In a study conducted by Pan *et al.*, incidence of early post-operative cognition dysfunction (after a week) in elders undergoing laparotomy with general anesthesia was reported 44%.[29] However, in study performed by Pan, they used neuropsychological tests instead of MMSE. In another study conducted by Williams-Russo *et al.*, incidence of cognitive dysfunction after orthopedic surgery in elderly patients was 4%.[30] This survey was long term and performed at the 6 months of post-surgery. The result of Williams study showed that cognition impairments can continue for several months after surgery. Fortunately, its incidence has decreased by time. Cognition dysfunction after cardiac surgeries is common (50% to 80%). The high incidence is attributed to brain damages after cardiopulmonary bypass.[31]

There were no significant statistical differences in Mean of MMSE score and also frequency distribution of intensity of cognition dysfunction in two groups at different hours after surgery. Protective effects of lidocaine on brain cells have been confirmed in many studies. This effect of lidocaine is probably due to reduced ionic shift from ischemic cell membranes,[32] brain metabolism reduction[33] and inhibition of exotoxins release in brain ischemic cells.[34] Unlike the results of Wang *et al.*, our study did not confirm the same effects of lidocaine. This can be due to higher incidence of post-operative cognition dysfunction after cardiac surgeries. So, lidocaine had been effective in surgeries with higher prevalence and intensity of cognition dysfunctions, but not prominently effective in non-cardiac surgeries (because of lower prevalence and intensity of cognition dysfunction), also in Wang *et al.* study, lidocaine infused 4 mg/kg/mint and then added (4 mg/kg) in prime solution of cardiopulmonary pump, in addition to bolus dose of lidocaine, but in our study, we used only bolus dose of lidocaine before extubation. It seems that bolus dose of lidocaine has not been enough for protective effect on brain cells.

Some studies showed that lidocaine brain protective effects are correlated with its plasma level. So, that needed plasma level of lidocaine for manifesting this neuroprotective effect was in range of therapeutic antiarrhythmic level or a slightly more.[32,34]

Another limitation of our study was lack of long-term post-operation evaluation, which was because of rapid discharge of patients. So, because of lack of communication with patients out of hospital, evaluation of cognition dysfunction was limited only to 24 h after surgery.

Finally, the results showed that intravenous lidocaine administration at the end of surgery and before extubation had no prominent effect on improvement of cognition impairments in elderly undergoing non cardiac surgery with general anesthesia. So, more studies with higher doses of lidocaine and other cognition assessment methods are recommended.

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