Neuroprotective Effects of Lidocaine on Early Postoperative Cognitive Dysfunction in Patients Undergoing Shoulder Arthroscopy with Beach Chair Position: A Randomized Trial

Seham M. Moeen, Golnar M.fathy, Mostafa AT, Islam M. Abdelhamid*, Ahmed Abdelhafez.
Department of Anesthesia and Intensive Care, Faculty of Medicine, Assiut University, Assiut, Egypt.
Corresponding Author: Islam M. Abdelhamid, M.Sc.
E-mail address: drislamelmelegy110@gmail.com

Abstract

Background: Surgery and general anaesthesia both cause postoperative cognitive dysfunction (POCD). The beach chair position (BCP) is the most often used posture in shoulder arthroscopy. One of the disadvantages of BCP is increasing the risk of cerebral hypoperfusion, hypoxia, hypotension, and bradycardia, which can trigger POCD. This paper investigated the neuroprotective effects of Lidocaine on early POCD in patients undergoing shoulder arthroscopy in the beach chair position.

Patients and Methods: A total of 80 patients scheduled for arthroscopic rotator cuff repair (ARCR) under general anesthesia in a beach chair position (BCP) were randomly allocated to the lidocaine group and control group (n = 40). The Lidocaine group received a loading dose of 1 mg/ kg diluted in 10 ml of normal saline that was infused over 5 minutes after induction of anesthesia then, followed by a continuous infusion at 1.5 mg/ kg/ h diluted in normal saline to a volume of 50 ml until the end of surgery. The control group received normal saline after induction of anesthesia with the same volume and rate changes as the lidocaine group until the end of surgery. Mini-Mental State Examination (MMSE) scores, Serum lactate levels, and Hemodynamic variables (mean arterial pressure and heart rate) were compared between the lidocaine and control groups.

Results: The MMSE scores were significantly decreased 24 hours after surgery in the control group compared with the lidocaine group. On the other hand, serum lactate levels 30 min after extubation were not significantly different between the two groups.

Conclusion: IV lidocaine is safe and effective and has a neuroprotective effect on early POCD in patients who underwent ARCR under general anesthesia in BCP.

Keywords: Post operative cognitive dysfunction (POCD) – Mini mental state examination (MMSE) - Beach chair position (BCP) - Lidocaine - Shoulder arthroscopy

Introduction:

Arthroscopic diagnosis and treatment of shoulder disorders have replaced open procedure as the primary treatment method[(1)]. Both the beach chair position (BCP) and the lateral decubitus position (LDP) are generally considered reliable and efficient techniques for carrying out successful arthroscopic shoulder procedures[(2)]. The benefits of BCP include no brachial plexus strain, adequate intra-articular visualization, and the ability to convert to an open technique if needed[(3,4)]. The BCP has been used in combination with deliberate hypotension to reduce intraoperative blood loss and allow for a substantially blood-free surgical area[(5)]. This combination, however, has the potential risk of decreasing cerebral perfusion pressure and oxygenation during surgery, resulting in cerebral ischemia[(6)].

Lidocaine is a widely used local anesthetic and antiarrhythmic medication of

class IB that easily passes the blood-brain barrier[7]. Evans et al. first documented lidocaine's cerebral protection in a feline model of cerebral arterial gas embolism[8]. Lidocaine's effects on perioperative neuroprotection were later discovered. However, the mechanisms underpinning Lidocaine treatment-induced neuroprotection are still unknown[9].
Lidocaine may protect the brain, reduce cerebral metabolic rate, slow ischemic transmembrane ion shift, and decrease ischemic excitotoxin production[10].

This study investigated the neuroprotective effects of Lidocaine on early POCD in patients undergoing elective arthroscopic rotator cuff repair (ARCR) under general anesthesia in beach chair position (BCP). The aim was to assess the neuroprotective effects of intraoperative intravenous (IV) lidocaine infusion compared to placebo (normal saline) and provide the basis for applying Lidocaine in shoulder arthroscopic surgery.

Patients and Methods

Participants

The Institutional Medical Ethics Committee, Faculty of Medicine, Assiut University (IRB no. 17101280) obtained the study. It was recorded on the Egyptian Universities Libraries Consortium (http://www.eulc.edu.eg). It was prospectively registered at www.clinicaltrial.gov, number NCT04634656.

Eighty-four patients scheduled for elective arthroscopic rotator cuff repair (ARCR) under general anesthesia in beach chair position (BCP) were enrolled in the Arthroscopy Unit of the Orthopedic Department at Assiut University Hospital from January 2021 to February 2022. four patients were excluded according to exclusion criteria, and 80 patients were included in the final study cohort **(Figure 1).**

Inclusion criteria included: (1) American Society of Anesthesiologists (ASA) physical status I - II; (2) Ranging from 20 to 65 years old; (3) Preoperative Mini-Mental State Examination (MMSE) scores ≥ 23; (4) Both male and female gender; (5) Patients undergoing elective arthroscopic rotator cuff repair (ARCR) under general anesthesia in BCP. Exclusion criteria included: (1) A past medical history of psychological disorder, neurological diseases (including Alzheimer's disease and stroke history), hypertension, severe anemia, diabetes mellitus, renal or hepatic dysfunction, and drug or alcohol abuse; (2) Un-willingness to comply with the protocol or procedures; (3) Mini-Mental State Examination (MMSE) score < 23 before surgery; (4) History of adverse reactions to Lidocaine. This study was approved by the Institutional Medical Ethics Committee, Faculty of Medicine, Assiut University (IRB no. 17101280), and all patients provided written informed consent.

Grouping and General Anesthesia

The 80 participants included in the final study cohort were randomly allocated to the lidocaine group (n = 40) and control group (n = 40). Randomization was performed using computer-generated random numbers in a double-blind manner using numbered sealed envelopes into two equal groups (40 each). Participants in the lidocaine group received Lidocaine in a loading dose of 1 mg/ kg diluted in 10 ml of normal saline that was infused over 5 minutes after induction of anesthesia and then followed by a continuous infusion at 1.5 mg/ kg/ h diluted in normal saline to a volume of 50 ml until the end of surgery. Participants in the control group received normal saline after induction of anesthesia with the same volume and rate changes as the lidocaine group until the end of surgery. In this study, only the researcher knows which treatment or intervention the participant receives until the trial ends.

All patients received a standardized anesthetic protocol. Patients were premedicated with IV midazolam 0.02 mg/ kg one hour before induction of general anesthesia after insertion of a 22 G peripheral IV cannula on the opposite site of surgery. On arrival at the operating theater, standard monitoring, including electrocardiography (ECG), noninvasive

blood pressure, and pulse oximetry, were applied, and patients were continuously monitored. After full preoxygenation, anesthesia was induced with propofol (1.5-2 mg/ kg) and fentanyl (2 ug/ kg), and the trachea was intubated 2-3 min after IV administration of cis-atracurium 0.15 mg/ kg. The lungs were mechanically ventilated with oxygen to maintain the end-tidal carbon dioxide (ETCO2) tension at 30- 35 mmHg. Anesthesia was maintained with cis-atracurium 0.03 mg/ kg, sevoflurane, and oxygen. Patients received IV fluid at 6-8 ml/ kg/ h of lactated ringer solution during surgery. Approximately 10 min after induction of anesthesia, when hemodynamics became stable, the head was secured in a neutral position to ensure cerebral venous drainage was not impaired. The back of the operating room table was then raised to 65-75^{o} above the horizontal plane to place the patients into a beach-chair position (BCP) using a beach-chair table, and then the surgery was started. At the end of surgery, the drug infusion and incremental doses of cis-atracurium were stopped. The residual neuromuscular blocker was antagonized with neostigmine 0.05 mg/ kg and atropine 0.02 mg/ kg. After extubation and full recovery, the patient was transferred to the post-anesthesia care unit (PACU).

Intraoperative Data

Hemodynamic variables [mean arterial pressure (MAP) and heart rate (HR)] and oxygen saturation (SpO2) were recorded before induction of anesthesia, 10 minutes after induction of anesthesia, 10 minutes after changing to beach chair position, 10 minutes after returning to supine position, and 10 minutes after extubation.

Intraoperative hypotension (MAP > 60 mmHg) was recorded and treated with 6 mg ephedrine. Intraoperative hypertension (MAP < 70 mmHg) or tachycardia (increase in the HR > 20% of the baseline) were recorded and treated with 1mcg/kg fentanyl.
Intraoperative bradycardia (HR > 60 beats/ min) was recorded and treated with 0.5 mg atropine.

Duration of anesthesia, duration of surgery, and duration of BCP.

Evaluation of Cognitive Function

An experienced psychometrician who received standard training in MMSE[11] evaluated the individual cognitive function of participants pre-operatively and 24 hours post-operatively in a quiet room using the MMSE. The MMSE test is a brief 30-point questionnaire used to screen for cognitive impairment.

It includes simple questions and problems in some areas: "the time and place of the test, repeating lists of words, arithmetic, language use comprehension, and basic motor skills[12]". Postoperative cognitive dysfunction (POCD) was considered when there was a decrease in the MMSE score of 2 points or more from the preoperative value[13].

Statistical Analysis

Our primary outcome variable was the cognitive function of the patients assessed by the Mini-Mental State Examination (MMSE) test. Based on previous research[3], a power analysis showed that we needed to include 35 patients in each group to show a true difference of 2.0 points in mean MMSE score 24 hours after surgery between both groups with a type I error of 0.05 and a power of 80%. We included 40 patients in each group to account for patients' dropouts. The sample size was calculated using the G*power software version 3.1.9.2.

Data entry and analysis were done using SPSS version 22 (Statistical Package for Social Science). Data were presented as a number, percentage, mean, standard deviation, median, and range. The chi-square test was used to compare between Categorical variables. Independent samples t-test and Paired Samples t-test were done to compare continuous variables between both groups.

Results

The final study cohort (80 patients) included 58 males and 22 females.

Univariate analysis of Demographic and perioperative data of both groups, including age, sex, body mass index (BMI), education, smoking, and American Society of Anesthesiologists (ASA) classification, were shown in **Table 1**. The differences in sex, age, body mass index (BMI), ASA classification, education, and smoking were not statistically significant (P > 0.05).

Univariate analysis of intraoperative data, including duration of anesthesia, surgery, and BCP, were shown in **Table 1**. The differences between the two groups were not statistically significant (P > 0.05).

Intraoperative Complications

Univariate analysis of intraoperative complications: hypertension was significantly higher in Group C than in Group L. Also, bradycardia was significantly higher in Group L than in Group C (P < 0.05). On the other hand, there were no significant differences between the groups in terms of tachycardia or hypotension (P > 0.05) (**Table 2)**.

Cognitive Function

Univariate analysis of changes in MMSE between both groups postoperative. The MMSE scores were significantly decreased in Group C (26.67 ± 2.31) 24 h postoperative compared with the Lidocaine (28.08 ± 2.20) group (P < 0.05) **(Table 3)**. Moreover, the decreased MMSE scores in Group C 24 h postoperative were in attention and recall. The greater incidence of postoperative cognitive dysfunction (POCD) was in Group C, as 21 (52.5 %) patients in Group C suffered from POCD, while no patient experienced POCD in Group L (**Figure 2)**. These results indicated that Lidocaine had neuroprotective effects.

Serum Lactate Level

There were no significant differences in serum lactate levels between both groups 30 min after extubation (2.09 ± 0.27) (2.15 ± 0.27) with (P > 0.05) (**Table 4).**

Tables

Table (1): Demographic Data

	Group L (n= 40)	Group C (n= 40)	P-value
Sex (male/female)	(30/10)	(28/12)	0.617
Age (years)	40.50 ± 10.93	44.70 ± 13.56	0.131
BMI	25.73 ± 3.58	26.03 ± 3.41	0.699
ASA (I/II)	(32/8)	(30/10)	0.592
Education (Yes/No)	(28/12)	(30/10)	0.617
Smoking (Yes/No)	(12/28)	(14/26)	0.633
Duration of anesthesia (min)	129.50 ± 26.60	129.12 ± 33.28	0.956
Duration of surgery (min)	98.00 ± 26.04	99.13 ± 33.59	0.867
BCP (min)	109.75 ± 26.07	109.63 ± 34.35	0.985

Data expressed as mean ± SD and frequency (percentage). P value considered significant if < 0.05

Table (2): Intraoperative Complications

	Group L (n= 40) No.	%	Group C (n= 40) No.	%	P-value
Hypertension	3	7.5%	14	35.0%	0.003
Hypotension	2	5.0%	3	7.5%	1.000
Bradycardia	7	17.5%	1	2.5%	0.057
Tachycardia	0	0.0%	0	0.0%	--

Data expressed as mean ± SD and frequency (percentage). The p-value is considered significant if < 0.05.

Table (3): Changes in Mini-mental State Examination (MMSE) Score Values

	Group L (n= 40)	**Group C (n= 40)**	**P-value[1]**
Orientation:			
Preoperative	10.00 ± 0.00	9.98 ± 0.16	0.320
24h Postoperative	10.00 ± 0.00	9.95 ± 0.22	0.156
P-value[2]	--	0.323	
Registration:			
Preoperative	3.00 ± 0.00	3.00 ± 0.00	--
24h Postoperative	3.00 ± 0.00	3.00 ± 0.00	--
P-value[2]	--	--	
Attention:			
Preoperative	4.00 ± 1.24	4.02 ± 0.95	0.920
24h Postoperative	3.98 ± 1.27	3.43 ± 1.11	0.042
P-value[2]	0.323	0.001	
Recall:			
Preoperative	2.85 ± 0.43	2.70 ± 0.46	0.136
24h Postoperative	2.83 ± 0.45	1.92 ± 0.66	0.001
P-value[2]	0.660	0.001	
Language:			
Preoperative	6.00 ± 0.00	5.95 ± 0.32	0.320
24h Postoperative	6.00 ± 0.00	5.95 ± 0.32	0.320
P-value[2]	--	--	
Executive function:			
Preoperative	2.28 ± 1.22	2.42 ± 1.13	0.570
24h Postoperative	2.28 ± 1.22	2.42 ± 1.13	0.570
P-value[2]	--	--	
Total MMSE score			
Preoperative	28.12 ± 2.09	28.07 ± 1.87	0.911
24h Postoperative	28.08 ± 2.20	26.67 ± 2.31	0.007
P-value[2]	0.421	0.001	

P-value 1 between Group L and Group C and P-value 2 between preoperative and 24h Postoperative in each group. P-value was significant if < 0.05.

Table (4): Comparison of Lactic Arterial between Groups (mmol/L)

	Group L (n= 40)	**Group C (n= 40)**	**P-value**
30 min after extubation	2.09 ± 0.27	2.15 ± 0.27	0.364
Mean change	1.02 ± 0.28	1.06 ± 0.25	0.591
Percent of change	48.61 ± 9.37	48.81 ± 8.20	0.922

Comparison of lactic arterial between Group L and Group C 30 min after extubation in each group using Independent samples t-test. P value was significant if < 0.05.

Figures

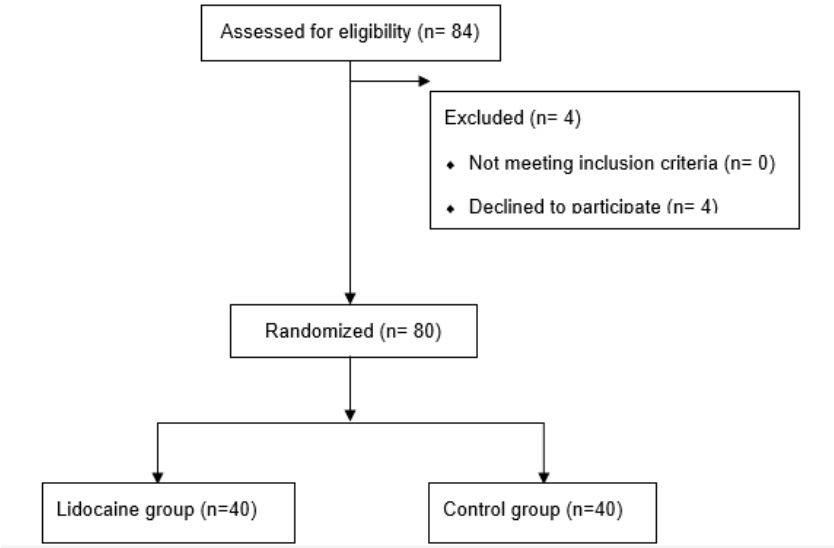

Figure (1): The Flow Diagram

It showed that 84 patients were initially enrolled, and finally, 80 patients were included in the final study cohort.

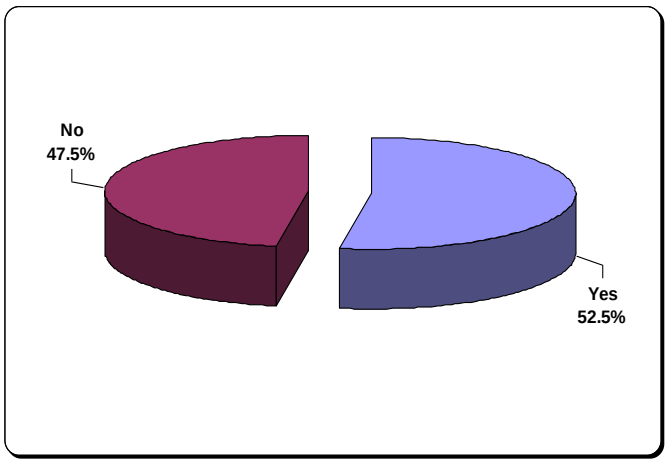

Figure (2): Postoperative Cognitive Dysfunction (POCD) Incidence in Group C.

Discussion

In the present study we found that IV lidocaine administration at a loading dose of 1 mg/ kg infused over 5 minutes after induction of anesthesia followed by a continuous infusion at 1.5 mg/kg/h until the end of surgery in patients underwent elective arthroscopic rotator cuff repair (ARCR) under general anesthesia in beach chair position (BCP) reduced the incidence of early postoperative cognitive dysfunction (POCD) with no effects on the hemodynamic stability, the post-extubation serum lactate levels, the length of hospital stay, and with no significant side effects.

The beach chair position is commonly used for arthroscopic and open shoulder surgery. This technique positions the shoulder in an anatomic upright position, facilitating shoulder

joint access and visualization[14]. The position also provides improved airway access, diminished bleeding, and reduced risk of brachial plexus injury. Despite these advantages, there are multiple reports of significant neurologic complications, including severe brain damage and death[6]. The definitive etiology of these complications remains unproven, but it is hypothesized that they occur secondary to cerebral ischemia[15].

In vitro and animal studies have demonstrated that Lidocaine is neuroprotective against hypoxia and ischemia. The underlying mechanism is unclear and may be multifactorial, including inhibition of sodium influx, preservation of cellular mitochondria and Adenosine triphosphate (ATP), and reduction of neuroinflammation. Lidocaine at higher concentrations (>300 μM) inhibits acid-sensing ion channels and the transient receptor potential ion channel subfamily M, member 7 (TRPM7) channels[16].

The effect of perioperative IV Lidocaine on the incidence of short-term cognitive function after non-cardiac and cardiac surgeries has been investigated. However, clinical studies focused on preventing POCD by using Lidocaine remain controversial, given the application of various inconsistent diagnostic criteria and neurologic endpoints.

Chen et al. studied the effect of IV Lidocaine on early POCD in elderly patients following spine surgery using the mini-mental state examination (MMSE) test. They found that compared with the preoperative MMSE scores, those three days after surgery significantly decreased in the control group. The MMSE scores in the lidocaine group were markedly higher than those in the control group three days after surgery. They concluded that Lidocaine may be an effective neuroprotective agent in treating early POCD in elderly patients undergoing spine surgery[17].

Guo et al. investigated the neuroprotective effects of Lidocaine on early POCD in elderly patients undergoing orthopedic surgery. They reported that the MMSE scores were significantly decreased on the third day after surgery (24.91±2.62) compared with preoperative values (26.95±2.97) in the control group ($P < 0.05$). However, the MMSE scores were not significantly different between the third day after surgery (27.22±3.14) and preoperative values (27.41±3.08) in the lidocaine group ($P > 0.05$). Moreover, the decreased level of MMSE scores was greater in the control group than in the lidocaine group (2.31, 95% confidence interval: 1.53-3.09 vs 0.46, 95% confidence interval: 0.26-0.65; $P < 0.05$). They concluded that Lidocaine had neuroprotective effects on early POCD in elderly patients undergoing orthopedic surgery[3].

Wang et al. found that intraoperative administration of Lidocaine significantly decreased the occurrence of early POCD after coronary artery bypass surgery[9].

Hashemi et al. evaluated the cognitive effect of Lidocaine in elderly patients undergoing urologic or orthopedic surgeries. MMSE test was used to evaluate cognitive state at discharge time, six hours, and 24 hours after surgery. They found that the mean MMSE scores at discharge from the 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, six hours, and 24 hours after the operation. The mean MMSE scores and frequency

distribution of intensity of cognitive impairments were not significantly different between the two groups at different times. They concluded that bolus IV lidocaine, before extubation, did not affect cognitive states in elders undergoing urologic or orthopedic surgeries[18].

Klinger et al. evaluated the effect of IV lidocaine infusion compared to placebo (normal saline) on cognitive function after cardiac surgery at six weeks and one year post-operatively. They reported that IV lidocaine administered during and after cardiac surgery did not reduce postoperative cognitive decline at six weeks. At the one-year follow-up, there continued to be no difference in cognitive score change or cognitive deficit[19].

Peng et al. studied the effect of lidocaine administration as an IV bolus (1.5 mg/kg) after anesthesia induction followed immediately by infusion at 2 mg /kg/h until the end of surgery compared to normal saline using the MMSE before surgery, 24 hr, one week, one month, three months, and six months after surgery. They found that intraoperative infusion of Lidocaine does not significantly decrease the incidence of postoperative neuropsychological-cognitive decline in patients up to six months after supratentorial tumor surgery[20].

To date, no study has demonstrated the effect of Lidocaine on POCD in patients undergoing ARCR under general anesthesia in BCP.

In the current study, we investigated 80 patients who underwent ARCR under general anesthesia in BCP.

We reported that 21 (52.5 %) patients in Group C suffered from POCD, with no patient experiencing POCD in Group L. Patients in Group C experienced significantly lower attention, recall, and total MMSE score values than those in Group L at the 24 h postoperative evaluation. Additionally, there was a significant difference between preoperative and 24 h postoperative attention, recall, and total MMSE score values in Group C, whereas no difference was found in Group L. This suggests that Lidocaine had a neuroprotective effect in patients undergoing ARCR under general anesthesia in BCP.

Lidocaine is a local anesthetic and class IB antidysrhythmic agent. It closes the Na+ channels and prevents the signals from reaching the postsynaptic cell. On the other hand, IV lidocaine also blocks the sodium channels in the heart, which is used for treating ventricular arrhythmias[21, 22].

It was reported that IV administration of Lidocaine could effectively suppress the hemodynamic response to laryngoscopy and endotracheal intubation and maintain the baseline conditions of patients during anesthetic induction[21, 23].

The current study showed no significant differences between both groups in the intraoperative mean arterial pressure (MAP) and heart rate (HR). However, compared to Group L, Group C experienced a considerably higher rate of hypertension.

No patient in both groups experienced postoperative complications (hypotension, bradycardia, vomiting, or manifestation of drug toxicity).

Conclusion

IV lidocaine is safe and effective and has a neuroprotective effect on early POCD in patients who underwent ARCR under general anesthesia in BCP.

References:

1. **Öner K,** Okutan **AE, Ayas MS, Paksoy AE, Polat F**. Predicting postoperative pain with neutrophil/ lymphocyte ratio after arthroscopic rotator cuff repair. AsiaPacific J Sport Med Arthrosc Rehabil Technol. 2020 Apr;20:24–7.
2. **Provencher CDRMT, McIntire ES, Gaston TM, Frank RM, Solomon CDRDJ**. Avoiding complications in shoulder arthroscopy: pearls for lateral decubitus and beach chair positioning. Tech Shoulder Elb Surg. 2010;11(1):1–3.
3. **Guo X, Liu J, Liu L, Huang M, Chen H, Hui N, et al.** Neuroprotective effects of Lidocaine on early postoperative cognitive dysfunction and the possible mechanism. Int J Clin Exp Med. 2019;12:8746–52.
4. **Rains DD, Rooke GA, Wahl CJ.** Pathomechanisms and complications related to patient positioning and anesthesia during shoulder arthroscopy. Arthrosc J Arthrosc Relat Surg. 2011;27(4):532–41.
5. **Morrison DS, Schaefer RK, Friedman RL.** The relationship between subacromial space pressure, blood pressure, and visual clarity during arthroscopic subacromial decompression. Arthrosc J Arthrosc Relat Surg. 1995;11(5):557–60.
6. **Pohl A, Cullen DJ.** Cerebral ischemia during shoulder surgery in the upright position: a case series. J Clin Anesth. 2005;17(6):463–9. http://dx.doi.org/10.1016/j.jclinane.2004.09.012.
7. **Butterworth J, Hammon JW.** Lidocaine for neuroprotection: more evidence of efficacy. Anesth Analg. 2002; 95 (5): 1131–3.
8. **Evans DE, Kobrine AI, LeGrys DC, Bradley ME.** Protective effect of Lidocaine in acute cerebral ischemia induced by air embolism. J Neurosurg. 1984;60(2):257–63.
9. **Wang D, Wu X, Li J, Xiao F, Liu X, Meng M.** The effect of Lidocaine on early postoperative cognitive dysfunction after coronary artery bypass surgery. Anesth Analg. 2002;95(5):1134–41.
10. **Riedel B, Browne K, Silbert B.** Cerebral protection: inflammation, endothelial dysfunction, and postoperative cognitive dysfunction. Curr Opin Anesthesiol. 2014;27(1):89–97.
11. **Yoelin AB, Saunders NW.** Score disparity between the MMSE and the slums. Am J Alzheimers Dis Other Demen 2017; 32: 282-288.
12. **Casati A, Fanelli G, Pietropaoli P, Proietti R, Tufano R, Danelli G, et al.** Continuous monitoring of cerebral oxygen saturation in elderly patients undergoing major abdominal surgery minimizes brain exposure to potential hypoxia. Anesth Analg. 2005;101(3):740–7.
13. **Folstein MF, Folstein SE, McHugh PR.** "Mini-mental state": a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res. 1975;12(3):189–98.
14. **Tange K, Kinoshita H, Minonishi T, Hatakeyama N, Matsuda N, Yamazaki M, et al.** Cerebral oxygenation in the beach chair position before and during general anesthesia. Minerva Anestesiol 2010;76: 485-90.
15. **Dippmann C,Winge S, Nielsen HB.** Severe cerebral desaturation during shoulder arthroscopy in the beach-chair position. Arthroscopy 2010; 26(9 Suppl):S148-50. http://dx.doi.org/10.1016/j.arthro.2010.03.012
16. **Leng T, Gao X, Dilger JP, Lin J.** Neuroprotective effect of Lidocaine: is there clinical potential? Int J Physiol Pathophysiol Pharmacol. 2016;8(1):9-13.
17. **Chen K, Wei P, Zheng Q, Zhou J, Li J.** Neuroprotective effects of intravenous Lidocaine on early postoperative cognitive dysfunction in elderly patients following spine surgery. Med Sci Monit Int Med J Exp Clin Res. 2015;21:1402-07.

18. **Hashemi SJ, Heidari SM, Rahavi A.** Lidocaine administration before tracheal extubation cannot reduce postoperative cognition disorders in elderly patients. Adv Biomed Res 2013;2:81.
19. **Klinger RY, Cooter M, Bisanar T, Terrando N, Berger M, Podgoreanu M V, et al.** Intravenous Lidocaine does not improve neurologic outcomes after cardiac surgery: a randomized controlled trial. Anesthesiology. 2019;130(6):958–70.
20. **Peng, Y., Zhang, W., Zhou, X., Ji, Y., Kass, I. S., & Han, R.** Lidocaine did not reduce neuropsychological-cognitive decline in patients 6 months after supratentorial tumor surgery: A randomized, controlled trial. Journal of Neurosurgical Anesthesiology, 2016; 28(1), 6–13.
21. **Qi, D. Y., Wang, K., Zhang, H., Du, B. X., Xu, F. Y., Wang, L., et al.** Efficacy of intravenous Lidocaine versus placebo on attenuating cardiovascular response to laryngoscopy and tracheal intubation: a systematic review of randomized controlled trials. Minerva Anestesiol 2013; 79: 1423-1435. Doi: 10.4103/0366-6999.170260.
22. **Mesbah Kiaee M, Safari S, Movaseghi GR, Mohaghegh Dolatabadi MR, Ghorbanlo M, Etemadi M, et al.** The effect of intravenous magnesium sulfate and Lidocaine in hemodynamic responses to endotracheal intubation in elective coronary artery bypass grafting: a randomized controlled clinical trial. Anesth Pain Med 2014; 4: e15905. doi: 10.5812/aapm.15905.
23. **Hashemian AM, Zamani Moghadam Doloo H, Saadatfar M, Moallem R, Moradifar M, Faramarzi R, et al.** Effects of intravenous administration of fentanyl and Lidocaine on hemodynamic responses following endotracheal intubation. Am J Emerg Med 2018; 36: 197-201. doi: 10.1016/j.ajem.2017.07.069.