

Can Lidocaine Protect Against Cerebral Dysfunction of Cadiopulmonary Bypass in Hypertensive Patients ?

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Objective : The objective of this study is to investigate whether intraoperative administration of lidocaine can reduce the incidence of cerebral dysfunction in hypertensive patients undergoing cardiac surgery with CPB .

Methods: Fifty Hypertensive patients scheduled for cardiac surgery with CPB were enrolled randomly into 2 groups: lidocaine group and control group. They were subjected to the same method of anaesthesia, same monitoring process and same CPB and myocardial preservation technique. Lidocaine group received 2 mg.kg-1 lidocaine bolus dose over 5 min. and then infusion of 4 mg.min-1 starting at skin incision till the end of surgery. The control group received normal saline at the same volume, rate and time. A battery of neurocognitive tests were performed at the preoperative and predischage days. Jugular bulb oxygen saturation (Sjo2) and S-100 b protein were determined at different measuring points.

Results : The results of this study revealed that the incidence of postoperative cognitive dysfunction was significantly less in lidocaine group. Sjo2 was significantly reduced during rewarming in control group and not in lidocaine group. S-100 b protein was elevated significantly after one hour of CPB in both groups, but the elevation was more significant in control group.

Conclusion : We can conclude that lidocaine has a protective effect against cerebral insult of CPB in hypertensive patients. it prevents jugular bulb desaturation during rewarming and reduce the release of S-100-b protein.

Despite the technological advances in cardiac-surgery, anaesthesia, monitoring devices and CPB, the period of bypass still contributes to significant morbidity in many patients. In particular cerebral injury is a significant problem for patients and their care givers. Postoperative stroke and cognitive dysfunction are still seen in up to 4.9% and 5.9% respectively(1,2). It is proved that cardiac surgical patients exhibit more neurocognitive problems than non cardiac surgical control(3,4).

Hypertensive patients are more vulnerable to cerebral insult due to impairment of cerebral autoregulation mechanisms. Two major mechanisms have been proposed to explain the occurrence of cerebral dysfunction after cardiac surgery: intraoperative cerebral embolism and hypoperfusion(5).

Considerable evidence suggests a correlation between the intraoperative embolic load and postoperative neuropsychological dysfunction(6,7). Moreover, low perfusion pressure and rewarming during CPB cause an imbalance between oxygen supply and demand of the brain manifested by Jugular venous desaturation(8). In both mechanisms ischemic injury is the common pathway causing cerebral dysfunction. S-100 protein "an ischemic marker" has been

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reported to be increased significantly during CPB and it has a high predictive value with respect to early postoperative neuropsychological disorders(9).

Strategies to prevent embolic brain injury in cardiac operations included: arterial filters(10), reduced manipulation of atheromatous aorta(11), improved removal of residual air and debris from the heart after open chamber procedures(12), and prevention of bubble formation in CPB(13). There is also interest in pharmacologic cerebral protection. Although some agents such as thiopental, Ca⁺⁺ channel blockers, and N-methyl-D-aspartate antagonists have been shown to protect against ischemic brain injury *in vivo*; they are only effective at high concentrations. The neurotoxic and systemic effects of these agents have limited their routine use as neuroprotective agents(14).

Previous studies found that lidocaine at low concentration could protect against anoxic brain damage *in vitro* without affecting electro-physiological activity(15), reduce infarct size in a model of transient focal ischemia in rats(16), and improved cerebral protection provided by retrograde cerebral protection in dogs(17,18).

The objective of this study is to investigate whether intraoperative administration of lidocaine in the antiarrhythmic dose can reduce the incidence of cerebral dysfunction in hypertensive patients undergoing cardiac surgery with CPB.

Patients and Methods

This study was carried out in Cardiac Surgery Unit of Zagazig University Hospital. After informed consent, 50 hypertensive patients scheduled for elective valve replacement or CABG surgery with cardiopulmonary bypass (CPB) were allocated randomly into one of two groups: **group I**, the control group and **group II**, lidocaine group

Hypertension was defined as arterial blood pressure of $\geq 140/90$ for at least 6 months before surgery.

Exclusion criteria included: emergency surgery, history of neurological or psychiatric disease, DM, renal impairment, active liver disease, age > 70 years, preoperative heart failure or ejection fraction $\leq 40\%$, inability to perform neurocognitive tests.

Neuropsychological Testing

Neurocognitive test battery was administered the day before surgery, and the day before hospital discharge (9th day).

Neurological Tests

Included motor, sensory and cranial nerves examination .

Cognitive Function Assessments

Cognitive functions were assessed in several behavioral areas:

- 1-The short module of Randet memory test(19): requires subject to recall the details of short story immediately after it has been read to him and after 30 minutes delay.
- 2-The digit span subtest of Weschier Adult Intelligence Scale-revised (WAIS-R)(20): requires subjects to repeat a series of digits that have been orally presented to them both forward and in an independent test in reverse order.
- 3-The Benton revised visual retention test(21): requires the subject to draw from memory a series of geometric shapes following 10-seconds exposure.
- 4-The digit symbol sub-test of WAIS-R(20): requires subjects to reproduce within 90 seconds as many coded symbols as possible in blank boxes beneath randomly generated digits, according to scheme for pairing digits with symbols.
- 5-The trial making test (part B)(22): requires subjects to connect, by drawing a line, a series of numbers and letters in sequence (i.e. 1 - A, 2 - B) as quickly as possible.

Patients Management Anesthesia and CPB

All patients were premedicated with oral diazepam 10 mg the night before surgery and medazolam 0.05 mg.kg⁻¹ + morphine 10 mg 30 minutes before entering the operating room. After IV canulation and before anesthesia induction, arterial canulation (usually radial artery) was performed for continuous arterial pressure measurement and frequent blood gas analysis. Anesthesia was induced in all patients with fentanyl 10mg.kg⁻¹ and sleeping dose of thiopental 2 - 4 mg. kg⁻¹. Teracheal intubation was facilitated with pancuronium 0.15 mg. kg⁻¹. Anesthesia was maintained with propofole 6 - 12 mg. kg⁻¹, and intermittent doses of fentanyl 4 mg. kg⁻¹ \pm 0.5% isoflurane when necessary. After anesthesia induction a triple lumen CVP catheter was inserted through right internal jugular vein for CVP monitoring and drug administration, and a single lumen catheter was inserted retrogradly through the left internal jugular vein for jugular bulb blood sampling and its position was verified by X-ray.

Monitoring

Monitoring for all patients included: ECG, ABP, CVP, urine output, O₂ saturation, endtidal CO₂, ABG, and nasopharyngeal temperature.

Myocardial Preservation

It was fulfilled in all patients by moderate systemic hypothermia (32°C) and cold (4°C) crystalloid antegrade cardioplegia.

CPB

The bypass circuit included a roller pump, and a membrane oxygenator. It was primed with 1000 cc lactated ringér solution and 500 cc of hydroxyle starch, 50 mg heparin and 1 g.kg⁻¹ mannitol were added to the priming solution. The pump flow was non pulstile at a rate of 2 – 2.4 l.m⁻². min⁻¹. PCO₂ uncorrected for tempera-ture was maintained at 35– 40 mmHg. The patients were cooled to 32°C and hematocrit was kept at 22 – 25%. Mean arterial pressure during bypass was maintained at 50 – 80 mmHg by increasing pump flow or 4mg boluses of norepinephrin if hypotension occur and by increasing the depth of anesthesia for treatment of hyper-tension. Blood glucose level was maintained < 200 mg.dl⁻¹ using isulin infusion if needed. The re-warming rate was not more than 1°C core temperature per 3 minutes.

Tested Drug Administration

In lidocaine group, lidocaine was administered as a bolous of 2 mg.kg⁻¹ over 5 minutes started with skin incision followed by infusion of 4 mg. min⁻¹ untill the end of operation. Another dose of 4 mg.kg⁻¹ was added to the priming solution.

In control group, normal saline was added at the same time, volume and rate.

Blood Sampling

• Jugular bulb samples were withdrawn at the following points:

After induction of anesthesia, before establishment of CPB, at established cooling to 32°C, during rewarming at 35°C, one hour after the end of CPB and 6 hours after CPB.

• 5 ml of arterial blood were also withdrawn for protein S-100-b determination at the following points:

After induction of anaesthesia, before CPB, 30 minutes of CPB, one hour of CPB, 4 hours after CPB and 6 hours after CPB..

The samples were centrifuged and frozen till the time of analysis for protein S-100-b level. Protein S-100-b was measured with commercial Songetec S-100 R-kit (Songetec Medical – Sweden). This is a monoclonal, 2–site immunoradiometric assay. The Songetec assay measures the beta subunit of protein S-100 which is

specific for Schwann and glial cell damage. The sample is intubated with I125 monoclonal antibody to S-100 protein. A concentration of > 0.2 mg.L⁻¹ is considered pathological.

Statistical Analysis

Data are represented as mean ±SD. Changes from pre-operative to pre-discharge on neuropsychological tests was assessed with paired t-test. Significant impairment was defined as decline of one or more standard deviation or more than 20% of preoperative test.

One way ANOVA was used for intergroup comparisons, while repeated measures ANOVA was used for intragroup comparisons. P< 0.05 was considered SIGNIFICANT.

Results

Fourty seven patients completed the study. Two patients died due to non-neurological complications, one in the control group and one in the lidocaine group. One patient in the control group refused to complete the neurocognitive tests. Demographic, preoperative and operative data of the patients of the 2 groups are listed in table (1).

Table (1): Demographic, preoperative and operative data of both study groups

Parameter	Control group (n=23)	Lidocaine group (n=24)
Age (years)	43±1	39.7±12.
Gender, male (%)	13 (56.5)	15 (62.5)
Weight (kg.)	63±11	64±
Preoperative MAP (mmHg)	110±1	116±12.
Type of surgery		
AVR	11	13
DVR	8	7
CABG	4	4
Ischemic time (min.)	100.8±2	98.6±1
CPB time (min.)	130±2	121±1
Epinephrin (mµg.kg-1/min)	0.07±0.00	0.083±0.01

No significant difference was found between the patients of the two study groups as regard age, weight, preoperative and operative parameters.

No patient in the two study groups showed motor or sensory defects. When compared to preoperative tests, postoperative cognitive performance tested by digit span forward, digit span backward, Benton visual retention, digit symbol and trial making part were significantly reduced in control group ($p < 0.05$). Twelve patients (52.1%) in control group showed impairment of > 2 cognitive tests while in lidocaine group only 6 patients (25%) showed impairment of > 2 cognitive tests (Table 2).

Table (2): Neurological test scores (mean \pm SD)

Test	Group	Preoperative	Predischarge
Randt immed	Control	8.1 \pm 3.	8.3 \pm 3.
	Lidocaine	8.3 \pm 3.	8.5 \pm
Randt delayed	Control	6.2 \pm 3.	5.7 \pm 3.7
	Lidocaine	6.3 \pm 3.	5.1 \pm 3.4
Digit span. Forward	Control	7.4 \pm 1.	7 \pm 1.4
	Lidocaine	7.35 \pm 2.	7.2 \pm 1.
Digit span backward	Control	5.6 \pm 2.	5.1 \pm 2.3
	Lidocaine	5.4 \pm	5.33 \pm 1.
Benton visual retention	Control	5.3 \pm 2.	4.8 \pm 2.
	Lidocaine	5.1 \pm 2.	5 \pm 1.
Digit symbol	Control	39 \pm 1	33 \pm 14
	Lidocaine	37 \pm 1	35 \pm 10.3
Trial making test (b β)	Control	138 \pm 7	159 \pm 82
	Lidocaine	136 \pm 7	140 \pm 7

* $P < 0.05$ in comparison with preoperative vlaue.

Jugular bulb oxygen saturation (Sjvo2) was significantly elevated in the two groups at established cooling to 32°. On the other hand, during rewarming to 35° control group showed a high significant reduction in Sjvo2 ($p < 0.001$), while the reduction in the lidocaine

group was non-significant ($p > 0.05$). At this point, there was a jugular bulb desaturation in control group (Sjvo2 = 43.8 \pm 2.7%) while in lidocaine group there was no desaturation (Sjvo2 = 67 \pm 18.7%). (Table 3).

Table (3): Jugular bulb saturation at different measuring points (mean \pm SD)

Time	Control group	Lidocaine group
1	63.7 \pm 15.2	61.2 \pm 15.3
2	66.6 \pm 10.8	70 \pm 2
3	75.6 \pm 17.4%	85.4 \pm 9.8%**
4	43.8 \pm 2.8%*	67 \pm 18.9%°
5	56.4 \pm 14	66 \pm 13%
6	55.6 \pm 6	63.4 \pm 7.9%

1-After anesthesia induction.

2-Before establishment of CPB.

3-At established cooling (32°)

4-During rewarming (35°).

5-One hour after the end of CPB.

6-6 hours after the end of CPB.

* $p < 0.05$ in comparison with baseline

** $p < 0.001$ in comparison with baseline

° $p < 0.05$ in comparison with control group

Serum protein S-100 b started to elevate during CPB in both groups, but the elevation was more significant in control group. It reached its peak one hour of CPB. This peak level was 7.5mg.L⁻¹ ($p < 0.001$) in control group while it was only 3 mg.L⁻¹ in lidocaine group. The level of S-100 b protein was still significantly elevated in control group 6 hours after CPB, but in lidocaine group it almost returned to its baseline value 6 hours after CPB (TABLE 4).

Table (4): Serum S-100 ? protein (?g.L-1) at different measuring points (mean \pm SD)

	Control group	Lidocaine group
1	0.1 \pm	0.13 \pm 0.
2	0.12 \pm .1.	0.15 \pm 0.
3	0.5 \pm 0.3	0.43 \pm 0.5
4	7.5 \pm 4.1**	3 \pm 1.9
5	5.5 \pm 5.2***°	0.6 \pm 0.8
6	3.5 \pm 0.7*	0.17 \pm

1-After induction. 2- Just before CPB

3- 30 min of CPB 4- 1 hour of CPB.

5- 4 hours after CPB 6- 6 hours after CPB

* $p < 0.05$ in comparison with baseline

** $p < 0.001$ in comparison with baseline

° $p < 0.05$ in comparison with other group

°° $p < 0.001$ in comparison with other group

Discussion

Neurological and neurocognitive problems after cardiac surgery remain irritating causes of postoperative morbidity and prolonged hospitalization. Although technological advances over the past decades have greatly improved the safety of cardiac surgery, the incidence of postoperative cognitive dysfunction remains frequent (1,3). The prevailing opinions about the cause of neurobehavioral complications are that they result from hypoperfusion, embolism, inflammation or a combination of the three (23,24). A strategy to ameliorate the damaging processes and reduce the risk of adverse neurobehavioral outcomes may require further improvement of the techniques in cardiac surgery, CPB, and peri-operative patient management. Another possible treatment that is attracting more attention is the pharmacological cerebral protection. Hypertensive patients may need more care for neuroprotection as hypertension might impair the cerebral autoregulation mechanism and so it is considered a risk factor for post-bypass cerebral insult (25). The effect of lidocaine in protecting the ischemic brain have been demonstrated by many animal and human studies (16). The possible mechanisms for cerebral protection by lidocaine include deceleration of ischemic trans-membrane ion shift, reduction of cerebral metabolic rate (26), and reduction of ischemic excitotoxin release (27).

The results of the present study confirmed that there was significant incidence of cognitive dysfunction after cardiac surgery (52.1% in control group and 25% in lidocaine group). This is in agreement with many studies who reported neuro-cognitive dysfunction after CPB in normotensive patients (28,29). However the incidence of cognitive dysfunction is higher in the present study (52.1% in control group) because of hypertension. Moreover, our results demonstrated that intraoperative administration of lidocaine significantly reduced the incidence of early postoperative cognitive dysfunction in hypertensive patients.

Wang et al (2002) (30) also proved the protective effect of lidocaine against early postoperative cognitive dysfunction in normotensive patients. In this study, lidocaine prevent jugular bulb desaturation during rewarming. Jugular bulb oxygen saturation indicates the global balance of cerebral metabolic rate and cerebral blood flow and is used to estimate the adequacy of flow/metabolism coupling in the brain, and so lidocaine might reduce cerebral metabolism during the period of supply-demand uncoupling. The relation between jugular desaturation ($Sjvo_2 < 50\%$) and cognitive dysfunction was suggested by Croughwell et al (31). In this study, there was a significant elevation of protein S-100 b level one

hour after CPB in both study groups but the elevation was more significant and persisted for longer duration in control group. The level of protein S-100 b in control group was still significantly elevated 6 hours after CPB, while in lidocaine group it returned to its pre-bypass level. The beta sub-unit of protein S-100 is highly brain specific and is well-established marker of cerebral injury after cardiac surgery with CPB (32,33). So, the results of this study give a biochemical proof that cerebral insult in lidocaine group is less than that in control group.

Further investigations at the cellular level will be required to detect the mechanism by which lidocaine protect against cerebral injury and define the effective intracellular concentration.

We can conclude that lidocaine has neuroprotective effect in hypertensive patients undergoing cardiac surgery with CPB. Considering its relative safety, wide use as antiarrhythmic drug, and wide availability, it may be used routinely for neuroprotection especially in high risk patients even if its effect is small or transient.

Study limitations: Small number of patients. Also, the delayed neurocognitive effect of CPB was not assessed in this study.

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