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Cerebral Protective Effect of Magnesium During CABG Assessed by Cerebral Oximetry and Cognitive P300 Visual Evoked Potentials

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Abstract: Cardiac-surgery-associated neurological complications and cognitive deficits are preoccupations in cardiac surgery because of their frequency, variety and long-term impact. The study aimed at evaluation of the efficacy of intravenous magnesium sulphate as a neuroprotective agent in patients undergoing Coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB). 30 patients were admitted for on pump coronary artery bypass grafting categorized into two groups, Group I n=15 patients received magnesium sulphate before induction of anaesthesia and group II n=15 patients received saline. Intraoperative Cerebral oximetry as well as cognitive P300 visual evoked potentials, 1 day pre- & 3 days postoperatively were assessed for the patients. There was a significant decrease in the P300 latency in the magnesium group postoperatively (p-value= 0.008) as compared to their preoperative values, while the postoperative P 300 amplitude showed a significant higher level in the magnesium group compared to that of the control group (p-value= 0.0241). Regarding the cerebral oximetry values there were no significant differences between both studied groups. The study showed that magnesium may play a role in decreasing the incidence of postoperative cognitive dysfunction (POCD) following cardiac surgery. P300 evoked potential could a useful tool in the to assess POCD

Key words: Magnesium · Cerebral oximetry · P300 Visual evoked potentials · CABG

INTRODUCTION

Cardiac-surgery-associated neurological complications are common, multifactorial and often preventable if they are detected early [1, 2]. Neurologic injury after cardiopulmonary bypass (CPB) remains a devastating complication of cardiac surgery. Possible causative factors include hypoperfusion, lack of pulsatile flow and cerebral embolization [3].

Magnesium is critical to cellular energy metabolism [4]. Inorganic magnesium ion (Mg^{2+}) blocks synaptic transmission by preventing the release of neurotransmitters and blocking N-methyl-D-asparate (NMDA)-coupled calcium channels, thereby inhibiting calcium entry into neurons [5]. Both in vitro [6] and in vivo experiments [7, 8] suggest that magnesium ions reduce the neuronal damage brought about by ischemia or excitatory amino acids. But despite favorable results in preclinical studies, the neuroprotective effects of Mg^{2+} are still controversial. Differences in dosage, time of administration and hypothermia are contributing factors to the conflicting results [9].

The P300 wave, a long-latency event-related potential, is known to be associated with psychological processing of stimulus information and thus can provide a quantification of impaired cognitive brain function. It can be considered as a neuropsychological correlate of information processing, such as stimulus evaluation, alertness and memory updating [10].

The use of the P300 technique has proved to be even more sensitive than electroencephalogram and standard psychometric tests for detecting sub-clinical impairment of cognitive brain function [11].

This study aimed at evaluating the efficacy of intravenous magnesium sulfate as a neuroprotective agent, decreasing the neurocognitive changes in patients undergoing coronary artery bypass grafting with cardiopulmonary bypass.

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MATERIALS AND METHODS

After being approved by the Institutional Review Boards (IRBs) of Kasr-Al-Aini hospital, the present study was conducted on 30 patients admitted for on pump coronary artery bypass grafting. Patients with a history of cerebrovascular event, impaired renal function (serum creatinine > 1.2 mg/dL), heart block, muscular dystrophy, or carotid artery stenosis over 30% narrowing by carotid duplex scan were excluded from this study. After a written informed consent for participation in the study the patients were randomly assigned into two groups, group (I) n=15 patients received 4gram magnesium sulphate over 20 minutes before induction of anaesthesia, group (II) n=15 patients received normal saline as placebo and they served as control group.

Cerebral Oximetry Setup for Each Patient: The forehead was degreased with an alcohol/acetone wipe then the sensors were placed bilaterally on the patient's forehead and the sensor cable was connected to sensors before or after placement. The right and left channel measurements were observed. Alarm limits were set. Status messages were observed on screen for troubleshooting assistance. *Baseline rSo_2* (defined as the average saturation value over one min. period before induction of anaesthesia beginning approximately 3 min. after sensors application) was measured, as well as *Regional cerebral oxygen saturation (rSo_2)* which was continuously monitored using near infrared spectroscopy (NIRS) (INVOS somanetics Inc., Tyco. USA).

In our study, cerebral desaturation was recorded as one of the following two values: (1) a decrease in absolute rSO_2 values to less than 50% and (2) a decrease in the relative rSO_2 value of 30% compared with the individual baseline value.

Therapeutic approaches for reduced cerebral tissue saturation were taken as increasing cerebral blood flow (increasing arterial $PaCO_2$ tension), decreasing the cerebral metabolic rate for oxygen (anaesthesia), increasing the oxygen content (red cell transfusion), slower re-warming and increasing the flow rate if the patient is on pump [3].

The Cognitive P300 Visual Evoked Potential: It was measured for all patients at the Clinical Neurophysiology Unit in Kasr Al-Ainy Hospital 1 day before and 3 days after the operation. The machine used to record the responses was Nihon Kohden, Neuropack MEB-9200G/K EP/EMG measuring system (Neuropack M1) 4-channels version 08.11. The examiner was blind to whether patients belonged to the magnesium or control groups.

Subjects were seated comfortably and instructed to avoid excessive movements of face and neck. The recording electrodes were surface disc electrodes placed after properly cleaning the skin. The active and ground electrodes were applied on the scalp and forehead corresponding respectively to Cz and Fpz positions of the 10-20 international system of electrode placement. The reference electrode was applied over the mastoid process. The electrodes impedance was kept below 5 Kohms, The gain was initially set to 50 μv per (vertical) division, monitor time was 200 msec per (horizontal) division. The band pass was 0.1 – 50 Hz.

A total of 200 visual stimuli were presented to the eyes through goggles. 80% of stimuli were presented regularly to both eyes (frequent, non target stimulus) whereas the remaining 20% were presented to one eye (rare, target stimulus) randomly intermixed at a rate of 0.5/second.

The patient was instructed to press a trigger button as quickly as possible whenever the rare stimulus occurred. To verify reproducibility of the response, the procedure was repeated at least once. The responses were displayed on a screen and could be printed out.

Many different components of the event related potential have been identified. For measurements the P3 (300) (Figure 1) of the response to the rare stimulus was taken as follows:

The latency was calculated as the time taken to reach the peak of the component (in milliseconds) [10].

The amplitude was measured in microvolt from the peak of P3 component to the preceding wave (N200) [10].

Statistical Methods: Data were analyzed by Microsoft Office 2003 (excel) and Statistical Package for Social Science (SPSS) version 16. Parametric data was expressed as mean ± SD and non parametric data was expressed as number and percentage of the total. Comparing the mean ± SD of 2 groups was done using paired and unpaired student's t test. *P value < 0.05 is considered significant.*

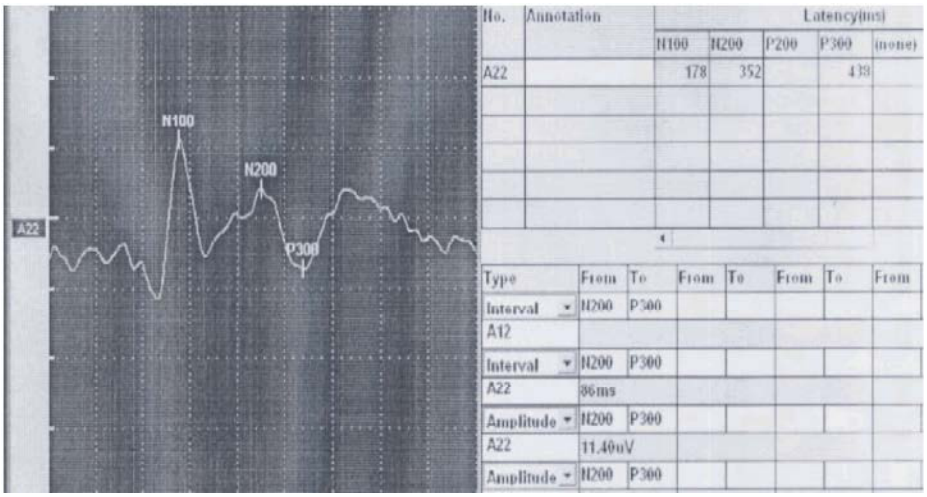

Fig. 1: The trace of the P300 response in one of the patients

RESULTS

There was no statistically significant difference detected between both groups regarding their demographic and operative data (Table 1). Also there was no statistically significant difference ($p > 0.05$) between both groups regarding the clinical data (levels of hematocrite, random blood sugar, blood pressure, nasopharyngeal temperature, peripheral oxygen saturation, arterial blood gases (PO2, PCO2).

There was no statistically significant difference between the two groups as regards the regional cerebral oxygen saturation, which was monitored before and after 15 minutes of induction, also 15 min after bypass and after weaning from bypass as well as after sternal closure (Table 2).

The amplitude and latencies of the P300 waves both pre and postoperatively were compared separately in each group and the results revealed no statistically significant change from before to after the operation in both groups except for a significant decrease in the postoperative P 300 latency in the magnesium group (p-value=0.008) (Table 3). In addition comparison of both groups showed no statistically significant difference detected between them except for the post operative P300 amplitude which was significantly higher in patients of group I than that of the controls, p-value=0.024 (Table 4).

Two cerebral desaturation episodes (defined as <50%) were reported in our study, one in the control group & one in the magnesium group, in T3 (on CPB). This was not associated with any significant change in the parameters of the P300 in the postoperative readings.

DISCUSSION

The application of magnesium in clinical trials aimed at treating acute cerebral ischemia. Therefore, recent studies of MgSO4 focused on its neuroprotective effects in cerebral ischemia. For example, the administration of MgSO4 in brain ischemia reduces the infarct size, ischemic brain tissue and acidosis. Furthermore, it was demonstrated that various neuroprotective functions of magnesium in brain ischemia include a decrease in the presynaptic release of glutamate and a blockade of the NMDA receptors with the calcium entry via the voltage-gated channels [12].

The use cognitive P300 to assess POCD after cardiac surgery was found in other studies [13, 14]. Some used more than one neurocognitive test for the assessment of cognitive function [13, 15].

In our study no significant difference was detected in the P 300 latency between both studied group either pre or postoperatively except for a significant decrease (P=0.008) in its value in the magnesium group postoperatively compared to the preoperative value, while the postoperative P 300 amplitude showed a significant higher value (P=0.024) in the magnesium group compared to that of the control group. Regarding the regional oxygen saturation there was no significant difference between both studied groups.

These findings might suggest that the magnesium may have beneficial effect as neuroprotector in cardiac surgery, but it may have no role in improving cerebral oxygenation.

Table 1: Demographic and operative data of both groups

	Group I (Magnesium)	Group II (Control)	P value
Age in years	54.07±5.23	54.93±5.77	0.89
Sex (M:F)	12:3 (80:20%)	11:4 (73.3:26.7%)	0.68
Weight in kg	85.4±6.09	85.8±8.68	0.73
Ejection fraction	55.07±2.93	57.47±3.16	0.067
Cardiopulmonary bypass time	107±9.28	107.07±14.06	0.876
AXC	86.2±9.54	86.4±12.76	0.963
Tridil (µg/kg/m)	2.53±0.81	2.67±1.07	0.713

Table 2: Regional oxygen saturation in the studied groups

RSO2 before induction of anaesthesia	Group I (Magnesium)	Group II (Control)	P value
Right	71±4.07	70.6±3.05	0.771
Left	70.67±2.15	69.53±2.16	0.175
RSO2 15 min. after induction of anaesthesia			
Right	69.53±3.18	66.8±5.95	0.144
Left	69.87±2.45	67.2±6.17	0.15
RSO2 15 min. after the start of CPB			
Right	69±3.16	67.6±2.87	0.23
Left	69.33±2.91	68.2±2.48	0.278
RSO2 15 min. after separation from CPB			
Right	69.93±2.02	69.93±2.43	0.99
Left	69.93±2.26	70±1.79	0.932
RSO2 after sternal closure			
Right	70.67±2.02	70.47±2.09	0.799
Left	70.73±1.29	70.33±1.35	0.429

Table 3: P300 latency and amplitude for both groups

Preoperative P300	Group I (magnesium)	Group II (Control)	
Latency (msec)	449.83 ± 35.87	415.6 ± 60.76	0.071
Amplitude(µv)	11.97±4.48	9.16±3.98	0.08
Postoperative P300	Group I (magnesium)	Group II (Control)	
Latency (msec)	404.83 ± 49.59	433.2 ± 46.49	0.117
Amplitude(µv)	12.55±3.69	9.14±4.13	0.0241*

* Statistically significant

Table 4: Comparison of the preoperative and postoperative P300 latency and amplitude for both groups

	Preoperative	Postoperative	p-value
Group I (magnesium) P300			
Latency (msec)	449.83 ± 35.87	404.83 ± 49.59	0.008*
Amplitude (µv)	11.97±4.48	12.55±3.69	0.701
Group II (Control) P300			
Latency (msec)	415.6 ± 60.76	433.2 ± 46.49	0.38
Amplitude(µv)	9.16±3.98	9.14±4.13	0.99

* Statistically significant

These data are in agreement with Bhudia *et al*. [16], who studied the protective effect of raising magnesium level in serum to 1.5 - 2 folds during cardiac surgical procedures using CPB. They reported safety of this protocol and better preservation of short-term memory along with prevention of re-emergence of primitive cerebellar reflexes. Despite the different patient population and methodology, this study strongly supports the safety and protective effect of magnesium on the cerebral outcome after cardiac surgery.

Also there are numerous studies that suggested the use of magnesium for neuroprotection [17-18].

In a systematic review by Care *et al*. [20], they stated that although human studies have confirmed that moderate hypermagnesemia (2.5 to 3 times the baseline) is well-tolerated, only modest elevation of CSF magnesium (blood–brain barrier penetration of the ion) occurs. However, current experimental evidence has yet to establish whether this modest elevation is sufficient for a neuroprotective effect.

In our study, we recorded two episodes of cerebral desaturation (<50%), one in the control group & one in the magnesium group, at T3(on CPB) and therapeutic approaches for a reduced cerebral tissue saturation were taken as slower re-warming, increasing cerebral blood flow (increasing arterial PaCO2 tension), decreasing the cerebral metabolic rate for oxygen (anaesthesia), increasing the oxygen content (red cell transfusion) and increasing the flow rate and they resulted in optimizing cerebral oxygenation in the following readings for the same patients.

Cerebral desaturation reported in our study intraoperatively (in 6.6%of patients) was associated with no significant increase in latency or decrease in amplitude in the results of postoperative readings of P300 when compared with the preoperative ones. This implies that there may be decreased incidence of POCD in the patients of our study, however, this should be supported by another neurocognitive test and needs follow up for longer periods.

This is in agreement with Negagar *et al*. [21] who did not find any correlation between cerebral oxygen saturation changes and postoperative neurologic complications using mini mental state examination (MMSE) scores. On the other hand Tournay-Jetté, *et al*. [22] stated that cerebral desaturation is associated with higher incidence of cognitive decline that is assessed by variable psychometric tests.

Magnesium has shown other beneficial effects in cardiac surgery. It could be used for prophylaxis against arrhythmia postoperatively in cardiac surgery where it reduces the risk of supraventricular arrhythmias after cardiac surgery by 23% (atrial fibrillation by 29%) and of ventricular arrhythmias by 48%, but has no effect on the length of hospital stay, perioperative myocardial infarction or mortality [23]. Magnesium sulfate in adult patients undergoing elective CABG surgery can decrease the amount of chest tube drainage in the early, i.e. 24 hours, postoperative period [24].

Magnesium may play a role in decreasing the incidence of POCD following cardiac surgery, so, it could be used as one of the pharmacological neuroprotective strategies for high risk patients. Cerebral oximetry is a valuable tool in multimodal brain monitoring in cardiac surgery as it may play a role in predicting cognitive decline postoperatively. P300 evoked potential could be a useful tool in the assessment of neuroprotector agents used in cardiac surgery and to assess POCD. Further prospective studies with larger sample size including off pump CABG and including patients with variable grades of cardiac dysfunction, the use of different types of cognitive tests and long term follow up for the patients are recommended.

REFERENCES

1. Arutiunian, O.M., A.G. Iavorovskii, V.A. Guleshov, E.F. Dutikova and A.A. Buniatian, 2010. Role of entropy-based neuromonitoring during cardiac surgery. Anesteziol Reanimatol., 5: 78-82.
2. Jiahai, M., W. Xueyan, X. Yonggang, Y Jianhong, H. Qunhui, L. Zhi, D. Juan and J. Xiuliang, 2012. Spectral entropy monitoring reduces anesthetic dosage for patients undergoing off-pump coronary artery bypass graft surgery. J Cardiothorac Vasc Anesth, 26: 818-21.
3. Kilo, J., M. Dzerny, M. Gorlitzer, D. Zimpfer, H. Baumer, E. Wolner and M. Grimm, 2001. Cardiopulmonary bypass affects cognitive brain function after coronary artery bypass grafting. Ann Thorac Surg, 72: 1926-32.
4. Lin, J.Y., S.Y. Chung, M.C. Lin and F.C. Cheng, 2002. Effects of magnesium sulfate on energy metabolites and glutamate in the cortex during focal cerebral ischemia and reperfusion in the gerbil monitored by a dual-probe micro-dialysis technique. Life Sci., 71: 803-811.
5. Kass, I.S., J.E. Cottrell and G. Chambers, 1988. Magnesium and cobalt, not nimodipine, protect neurons against anoxic damages in the rat hippocampal slice. Anesthesiology, 69: 710-715.
6. Greensmith, L., E.C. Mooney, H.J. Waters, D.G. Houlihan-Burne and M.B. Lowrie, 1995. Magnesium ions reduce motoneuron death following nerve injury or exposure to N-methyl-D-aspartate in the developing rat. Neuroscience, 68: 807-812.
7. Izumi, Y., S. Roussel, E. Pinadr and J. Seylaz, 1991. Reduction of infarct volume by magnesium after middle cerebral artery occlusion in rats. J. Cereb. Blood Flow Metab, 11: 1025-1030.
8. Marinov, M.B., K.S. Harbaugh, P.J. Hoopes, H.J. Pikus and R.E. Harbaugh, 1996. Neuroprotective effects of pre-ischemia intra-arterial magnesium sulfate in reversible focal cerebral ischemia. J. Neurosurg, 85: 117-124.
9. Meloni, B.P., H. Zhu and N.W. Knuckey, 2006. Is magnesium neuroprotective following global and focal cerebral ischemia? A review of published studies. Magnes. Res., 19: 123-137.

10. Madl, C., G. Grimm, L. Kramer, R. Koppensteiner, M. Hirschl, W. Yeganehfar, M.M. Hirschl, A. Ugurluoglu, B. Schneider and H. Ehringer, 1994 Cognitive brain function in non-demented patients with low-grade and high-grade carotid artery stenosis. Eur. J. Clin Invest, 24: 559-564.
11. Grimm, M., M. Czerny, H. Baumer, J. Kilo, C. Madl, L. Kramer, A. Rajek and E. Wolner, 2000. Normothermic cardiopulmonary bypass is beneficial for cognitive brain function after coronary artery bypass grafting - a prospective randomized trial. Eur. J. Cardiothorac Surg, 18: 270-275.
12. Bhattacharya, P., A.K. Pandey and S. Paul, 2011. Minocycline and magnesium in combination may be a good therapeutic intervention for cerebral ischemia. Medical Hypotheses, 77: 1129-1131.
13. Buziashvili, Y.I., Y.A. Aleksakhina, S.G. Ambat and S.T. Matskeplishvili, 2006. Use of P300 Cognitive Evoked Potentials in the Diagnosis of Impairments of Higher Mental Functions after Cardiac Surgery in Conditions of Cardiopulmonary Bypass, 36(2).
14. Kunihara, T., D. Tscholl, F. Langer, G. Heinz, F. Sata and H.J. Schäfers, 2007. Cognitive brain function after hypothermic circulatory arrest assessed by cognitive P300 evoked potentials. European Journal of Cardio-thoracic Surgery?: Official Journal of the European Association for Cardio-thoracic Surgery, 32(3): 507-13.
15. Slater, J.P., T. Guarino, J. Stack, K. Vinod, R.T. Bustami, M. Brown, A.L. Rodriguez, C.J. Magovern, T. Zaubler, K. Freundlich and G.V. Parr, 2009. Cerebral Oxygen Desaturation Predicts Cognitive Surgery, ATS, 87(1): 36-45.
16. Bhudia, S.K., D.M. Cosgrove, R.I. Naugle, J. Rajeswaran, B. Lam, E. Walton, J. Petrich, R.C. Palumbo, A.M. Gillinov, C. Apperson-Hansen and E.H. Blackstone,2006. Magnesium as a Neuroprotectant in Cardiac Surgery, pp: 853-861.
17. Prapa, V., T. Xanthos, E. Koudouna, E. Bassiakou, I. Dontas and L. Papadimitriou, 2009. Evidence Suggesting the Beneficial use of Magnesium in Cerebral Ischaemia in an Experimental Model of Cardiac Arrest, pp: 1-7.
18. Sen, A.P. and A. Gulati, 2010. Use of Magnesium in Traumatic Brain Injury. NURT, 7(1): 91-99.
19. Kang, S.W., S.K. Choi, E. Park, S.J. Chae, S. Choi, H. Jin Joo, G.J. Lee and H.K. Park, 2011. Neuroprotective effects of magnesium-sulfate on ischemic injury mediated by modulating the release of glutamate and reduced of hyperreperfusion, Brain Research, 1371: 121-8. doi:10.1016/j.brainres.
20. Care, N., J.A. McKee, R.P. Brewer, G.E. Macy, C.O. Borel, J.D. Reynolds and D.S. Warner, 2005. Magnesium Neuroprotection is Limited in Humans With Acute Brain Injury, 4(5): 342-351. doi:10.1385/Neurocrit.
21. Negargar, S., A. Mahmoudpour, R. Taheri and S. Sanaie, 2007. The relationship between cerebral oxygen saturation changes and post operative neurologic complications in patients undergoing cardiac surgery, Pak. J. Med. Sci., 23: 380-385.
22. Tournay-Jetté, E., G. Dupuis, L. Bherer, A. Deschamps, R. Cartier and A. Denault, 2011. The relationship between cerebral oxygen saturation changes and postoperative cognitive dysfunction in elderly patients after coronary artery bypass graft surgery. Journal of Cardiothoracic and Vascular Anesthesia, 25(1): 95-104. doi:10.1053/j.jvca.
23. Shiga, T., Z. Wajima, T. Inoue and R. Ogawa, 2004. Magnesium Prophylaxis for Arrhythmias after Cardiac Surgery: A Meta-analysis of Randomized, Am. J. Med. 2004 Sep. 1; 117(5): 325-33. doi:10.1016/j.amjmed.
24. Dabbagh, A., S. Rajaei and M.H. Shamsolahrar, 2010. The effect of intravenous magnesium sulfate on acute postoperative bleeding in elective coronary artery bypass surgery. Journal of perianesthesia nursing: official journal of the American Society of PeriAnesthesia Nurses, 25(5): 290-5. doi:10.1016/j.jopan.