Cardiothoracic Anesthesia, Respiration and Airway

Propofol offers no advantage over isoflurane anesthesia for cerebral protection during cardiopulmonary bypass: a preliminary study of S-100ß protein levels

[L'anesthésie au propofol, comparé à l'isoflurane, n'a pas d'avantage pour la protection cérébrale pendant la circulation extracorporelle : une étude préliminaire des niveaux de protéines S-100ß]

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Purpose: Despite advances in anesthesia, cardiopulmonary bypass (CPB) and surgical techniques, cerebral injury remains a major source of morbidity after cardiac surgery. We compared the effects of two different anesthetic techniques, isoflurane *vs* propofol on neurological outcome by serum S-100ß protein and neuropsychological tests after coronary artery bypass grafting (CABG).

Methods: Twenty patients undergoing CABG, randomly allocated into two groups, were enrolled in this prospective, controlled, preliminary study. Isoflurane was used in group I and propofol in group P. Neurological examination and a neuropsychologic test battery consisting of the mini mental state examination (MMSET) and the visual aural digit span test (VADST) were obtained preoperatively and on the third and sixth postoperative days. Blood samples for analysis of S-100ß protein were collected before anesthesia (T1), after heparinization (T2), 15 min into CPB (T3), after CPB (T4) and at the 24th hr postoperatively (T5).

Results: Postoperative neurological examinations of the patients were normal. VADST performance declined significantly on the third day ($P < 0.05$) in both groups, and there were no significant differences on VADST and MMSET scores between the two groups. In group P, S-100ß protein levels increased significantly at T3 and T4 compared to preoperative and isoflurane levels ($P < 0.05$).

Conclusions: Despite reports about the neuroprotective effects of propofol, S-100ß protein levels were significantly elevated in group P. Although there was no deterioration in neuropsychological outcome, propofol appeared to offer no advantage over isoflurane for cerebral protection during CPB in this preliminary study of 20 patients.

Objectif : *Malgré les progrès de l'anesthésie, la circulation extracorporelle (CEC) et les techniques chirurgicales, les lésions cérébrales demeurent une importante source de morbidité postchirurgie cardiaque. Les effets neurologiques comparés de l'isoflurane et du propofol sont présentés par l'analyse des protéines sériques S-100ß et des test neuropsychologiques après un pontage aortocoronarien (PAC).*

Méthode : *Notre étude préliminaire, prospective et contrôlée a porté sur 20 patients, répartis au hasard en deux groupes, qui devaient subir un PAC. L'isoflurane a été utilisé dans le groupe I et le propofol dans le groupe P. L'examen neurologique et une batterie de tests neuropsychologiques, comprenant le mini-examen de l'état mental (MMSET pour mini mental state examination) et le test visuel et auditif de mémoire des chiffres (VADST pour visual aural digit span test), ont été réalisés avant l'opération et aux jours trois et six postopératoires. Les échantillons sanguins nécessaires à l'analyse des protéines S-100ß ont été prélevés avant l'anesthésie (T1), après l'héparinisation (T2), 15 min après le début de la CEC (T3), après la CEC (T4) et 24 h après l'opération (T5).*

Résultats : *Les examens neurologiques postopératoires étaient normaux. La performance au VADST a décliné significativement au jour trois ($P < 0,05$) chez tous les patients. Il n'y a pas eu de différence intergroupe significative des scores de VADST et de MMSET. Dans le groupe P, les niveaux de protéines S-100ß ont augmenté à T3 et T4, comparés aux niveaux préopératoires et aux niveaux observés avec l'isoflurane ($P < 0,05$).*

Conclusion : *Malgré des études rapportant les effets neuroprotecteurs du propofol, les niveaux de protéines S-100ß ont été signi-*

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ficativement élevés dans le groupe P de notre étude. Aucune détérioration neuropsychologiques n'a été observée, mais le propofol ne semble pas offrir d'avantage sur l'isoflurane pour la protection cérébrale pendant la CEC.

ALTHOUGH advances in surgical techniques, anesthetic and intensive care management, and perfusion technology have substantially reduced the mortality and morbidity rate related with cardiopulmonary bypass (CPB) operations, transient neurological and neuropsychological dysfunctions continue to occur.[1]

The diagnosis of cerebral injury currently relies on clinical neurological examination, computed axial tomography or magnetic resonance imaging. However, these methods are not always suitable for the unconscious and artificially ventilated, or hemodynamically unstable and thus unable to cooperate. The identification of a biochemical serum marker to assist in diagnosis of cerebral injury would potentially be useful.[2,3]

It has been reported that S-100ß protein is an early marker for cerebral injury during cardiac operations. S-100ß subunits are present in glial and Schwann cells and, recently, elevated levels have been detected after cardiac operations complicated by neurological injury.[4,5] The appearance of S-100ß in serum indicates both neuronal damage and increased permeability of the blood-brain barrier.[6]

Neuropsychological testing is one of the best methods currently available for assessing changes in intellectual function after a cerebral insult and has identified persistent mild, moderate or severe deterioration in 19% to 38% of patients who undergo CPB.[7]

Although proposal of mechanisms by which anesthetics or other drugs may produce cerebral protection are controversial and changing rapidly, isoflurane and propofol have been shown to decrease neuronal injury during ischemia by decreasing cerebral oxygen consumption. Propofol protects the brain from neuronal damage induced by brain ischemia and plays a role in the inhibition of neuronal death. Although various surgical techniques and pharmacological methods of brain protection have been evaluated, the effects of different anesthetic regiments on neurological outcome after cardiac surgery remain unclear. In this preliminary study, we evaluated the effect of propofol and isoflurane anesthesia on neuropsychological test performance and S-100ß protein levels in patients undergoing coronary artery bypass grafting (CABG).

Methods

After obtaining University Ethical Committee approval and patient informed consent, we studied 20 male patients undergoing CABG. Patients included had a sufficient educational level to participate in neuropsychological testing, were below 70 yr of age, had a good ventricular function (as defined by an ejection fraction > 50% and left ventricular end-diastolic pressure < 15 mmHg), presented no major non-cardiac impairment that could interfere with recovery such as renal, psychiatric or neurological disease, had time for the preoperative interview and a normal carotid Doppler ultrasonography.

Patients with unstable angina, hepatic and renal insufficiency, additional valve disease, reoperation, preoperative insertion of an intra-aortic balloon pump (IABP), requiring re-exploration for any reason (hemostasis, tamponade, etc.,) necessitating pharmacological support and/or IABP to wean from CPB were excluded from the study.

Twenty patients were randomly classified into two groups by a concealed envelope method. They were premedicated with diazepam 10 mg *po.* Induction of anesthesia was performed with etomidate 0.2 $mg \cdot kg^{-1}$ and fentanyl 0.1 $\mu g \cdot kg^{-1}$. Vecuronium bromide 0.1 $mg \cdot kg^{-1}$ was administered to facilitate endotracheal intubation. Oxygen and nitrous oxide were used (3–3 $L \cdot min^{-1}$) during the maintenance of anesthesia for all patients. After induction, isoflurane was used in group I and a propofol infusion in group P. Isoflurane was administered at a concentration of 1 to 1.5% until CPB and 0.5 to 1% during CPB. Propofol was infused at a rate of 6 $mg \cdot kg^{-1} \cdot hr^{-1}$ until CPB and 3 $mg \cdot kg^{-1} \cdot hr^{-1}$ during CPB. All patients were monitored with the bispectral index (BIS) and the anesthetics titrated in order to keep BIS between 40 and 50.

Heparin sulphate 3 $mg \cdot kg^{-1}$ was administered prior to CPB and supplemented as needed to maintain an activated clotting time of at least 400 sec. CPB was conducted with a roller pump and membrane oxygenator, a 40-µ arterial line filter and non-pulsatile perfusion (at a flow rate of 2.4 $L \cdot min^{-1} \cdot m^2$ normothermia and above 1.6 $L \cdot min^{-1} \cdot m^2$ during hypothermia). The circuit was primed with 1000 to 1500 mL of Ringer's lactate and 150 mL 20% mannitol. Antegrade cold St. Thomas crystalloid cardioplegia and topical ice slush were used for myocardial protection. Systematic cooling to approximately 28°C was used. Heparin sulphate was reversed with a corresponding dose of protamine sulphate at decannulation. The mean arterial pressure (MAP) was maintained at a target range of 40 to 60 mmHg.

Hemodynamic management aimed at keeping a heart rate below 90 $beats \cdot min^{-1}$ and MAP above 60

mmHg with volume replacement, changes in anesthetic concentration or administration of nitroglycerin and ephedrine.

Distal coronary anastomoses were performed during a single period of aortic cross clamping. A tangential occluder replaced the cross clamp during the proximal anastomosis. Maximum care was exercised to remove particulate debris and de-air the aorta before weaning from CPB. A MAP of 65 to 85 mmHg was considered optimal. Left atrial pressure was generally kept below 12 mmHg. If bleeding was not excessive, the patients were weaned from mechanical ventilation and the trachea was extubated after additional rewarming in the intensive care unit.

For all patients, blood samples for analysis of S-100ß protein were collected before anesthesia (T1), after heparinization before CPB (T2), 15 min into CPB (T3), following protamine administration CPB (T4) and 24 hr postoperatively (T5). After centrifugation, the serum was kept at -20°C until analysis. The S-100ß protein was analyzed using a commercially available two-site immunoradiometric assay (Santec-100, IRMA kit, Bromma, Sweden). The ß chain as defined by the three monoclonal antibodies - SMST 12, SMSK 25, and SMSK 28 - is detected. After dilution with a phosphate buffer, the serum samples were incubated on plastic beads coated with monoclonal S-100 antibodies, thereby binding S-100ß protein to the beads. The beads were washed and reincubated with anti-S-100 antibodies labeled with I^{125}. The amount of radioactivity bound to immobilized S-100ß was measured in a gamma counter. Samples were analyzed in duplicate. The sensitivity of the assay was 0.2 $\mu g \cdot L^{-1}$. S-100ß protein levels in excess of 0.5 $\mu g \cdot L^{-1}$ are considered pathological.

A neurologist examined all patients one day prior to surgery and on the third and sixth postoperative days.

Neuropsychological testing was conducted by the same appropriately trained anesthesiologist blinded to anesthetic management. The neuropsychological tests were administered one day prior to surgery and on the third and sixth postoperative days.

The test battery at pretest and follow-up consisted of the following: 1) Mini mental state examination (MMSET): it includes a diagnostically valuable verbal retention test, tasks that assess basic orientation, short-term memory, ability to calculate and visio-motor ability. The number of correct responses scores the test. 2) Visual aural digit span test (VADST): this test assesses alertness, attention, concentration, and short-term memory. VADST mainly measures intersensory integration, sequencing and recall. It consists of four subtests: aural-oral subtest, visual-oral subtest, aural written subtest, and visual written subtest. With regard to the statement of consensus[8] on the assessment of neurobehavioural outcomes after cardiac surgery, the neuropsychiatric test battery should have its sensitivity and reliability confirmed in specific populations. The sensitivity and reliability of the MMSET and VADST have been established in a Turkish population.[9]

TABLE Demographic and surgical variables (mean ± SD)

	Group I (n = 10)	*Group P (n = 10)*
Age (yr)	56 ± 7.6	54.5 ± 5.9
Height (cm)	1.68 ± 0.06	1.66 ± 0.07
Weight (kg)	71.23 ± 8.78	68.36 ± 9.54
Duration of surgery (min)	243.0 ± 37.3	240.0 ± 50.17
Cross-clamp time (min)	32.0 ± 9.62	30.20 ± 11.36
Total bypass time (min)	58.90 ± 17.32	62.77 ± 30.32

n = number of patients; group P = propofol anesthesia; group I = isoflurane anesthesia.

Statistical analysis

Data were analyzed with SPSS 10.0.5 for windows (SPSS Inc., Chicago, IL, USA) software. One sample Kolmogorov Smirnov test was used for testing the distribution of data. Comparisons between groups were done with the Mann-Whitney test. General linear model repeated measures analysis of variance was used for analyzing differences between groups and within time. The Wilcoxon signed ranks test was used for analyzing the differences within groups compared to baseline values. *P* values less than 0.05 were considered significant and a reduction in *P* values was used when multiple comparisons were made.

It was not possible to calculate sample size prior to initiating the study since the standard deviation of S-100ß levels after CABG are not well known. We performed a post hoc analysis, which demonstrated a power of 38% when groups were compared, 71% when time was compared, and 39% when time and group interaction were analyzed.

Results

The 20 patients are described in the Table. There were no significant differences in demographic characteristics and peroperative variables between the two groups. There was no significant difference between groups for MAP during CPB.

No overt neurological injury was detected in any of the patients. The neurological examinations of the patients on the third and sixth postoperative days revealed no pathological finding.

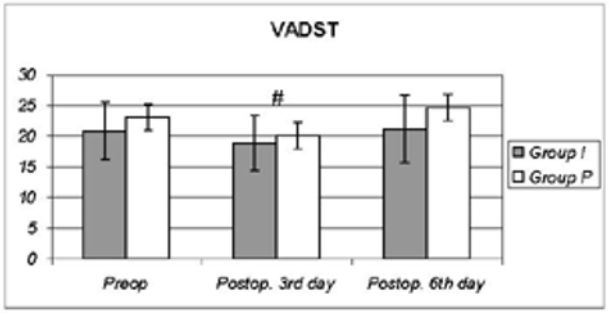

FIGURE 1 Visual aural digit span test (VADST) scores of two groups. #$P < 0.05$ *vs* preoperative and postoperative day six scores for both groups.

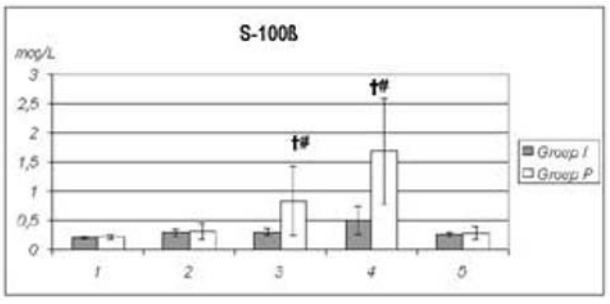

FIGURE 3 S-100ß protein levels of two groups (CPB; mean ± SD). T1 = preoperative value; T2 = after heparinization; T3 = 15 min following CPB; T4 = after CPB; T5 = postoperative 24 hr. †$P < 0.05$ *vs* T1 (preoperative values), †#$P < 0.05$ group I *vs* group P.

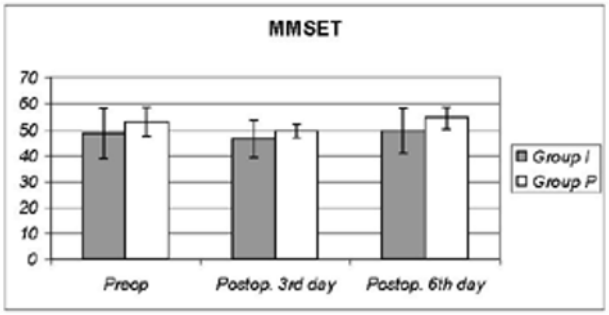

FIGURE 2 Mini mental state examination test (MMSET) scores of two groups.

The VADST scores showed a statistically significant decline in the total performance on the third postoperative day in both the isoflurane and propofol groups ($P < 0.05$), and returned to basal levels on the sixth postoperative day (Figure 1). This deterioration was seen in all the subtests of the VADST - aural stimuli, verbal stimuli, intersensory integration score (inter IS), and intrasensory integration score (intra IS; $P < 0.003$). Although a significant decrement was observed in intra IS and inter IS subgroups in group P, the decrement was seen only in intra IS subgroups in group I, when the groups were examined separately. The MMSET scores were increased in both groups at postoperative day six ($P > 0.05$; Figure 2). There were no statistically significant differences between the two groups in VADST and MMSET scores.

S-100ß protein levels increased with the beginning of CPB in both groups. They reached maximum levels at the end of CPB and decreased to baseline levels at 24 hr postoperatively. The increase was not statistically significant in the isoflurane group but it was significantly higher in the propofol group ($P < 0.05$; Figure 3). A significant difference was observed between the two groups ($P < 0.05$).

Discussion

S-100ß protein, an early marker of brain damage, may be valuable to gauge the timing and extent of cerebral damage after CPB.[10] Recently elevated serum levels of S-100ß have been detected after adult cardiac operations complicated by neurological injury.[11] CPB is associated with the release of brain specific S-100ß protein indicating an injury to the blood-brain barrier or neuronal cell injury. Various techniques of neurological protection have been used during CPB and some methods, such as pharmacological protection, remain controversial. Initially, anesthetics were believed to produce cerebral protection through a reduction in metabolism that provided greater tolerance to periods of cerebral ischemia or embolic insults.[12]

We attempted to determine if the anesthetic management affects serum S-100ß protein levels, neuropsychological tests, and early neurological outcome after CABG. Propofol, is a rapidly acting *iv* anesthetic that suppresses brain electrical activity, and decreases cerebral oxygen consumption together with cerebral blood flow (CBF).[13] Anesthetics were proposed as cerebral protectors because of their ability to reduce cerebral metabolism, but recent studies have indicated that metabolic depression is not the only mechanism at work. Propofol decreases the cerebral metabolic

rate for oxygen ($CMRO_2$) and CBF while maintaining reactivity to changes in $PaCO_2$.[14] Newman *et al.*[15] studied the effect of burst suppression doses of propofol on CBF and cerebral metabolism during non-pulsatile hypothermic CPB in patients undergoing cardiac valvular surgery. These authors stated that propofol induces decreases in CBF and $CMRO_2$ but has no effect on cerebral oxygen extraction (COE).

Only a few reports on the effects of propofol on CBF and cerebral metabolism in humans are available. Ederberg *et al.*[16] demonstrated that propofol, at a plasma concentration of approximately 9 $\mu g \cdot mL^{-1}$, induces a 35% decrease in CBF velocity over a cerebral perfusion pressure range of 30 to 70 mmHg during moderate, hypothermic non-pulsatile CPB. The indirect vasoconstrictive effect of propofol, due to its effect on cerebral metabolism, is partly counteracted by its direct vasodilator effect, as indicated by a 10% decrease in COE. Furthermore, propofol improves the slightly impaired cerebral auto regulatory response seen during CPB.

Ito *et al.*[17] demonstrated that pharmacological agents that act directly on gamma-aminobutyric acid ($GABA_A$) receptors or that modulate $GABA_A$ receptor activity such as propofol, midazolam, muscimol are capable of suppressing the severity of brain injury following ischemia in gerbils. We used neuropsychological tests and neurologic examination besides S-100ß protein levels to examine the effects of anesthetic management on cerebral injury after CPB. It has been shown that neurocognitive dysfunction and S-100ß protein levels are moderately correlated.[18]

Recently Kilminster and colleagues[19] found that less S-100ß protein release was associated with worse neuropsychological test performance. In our study there was a significant decrease of VADST scores at postoperative day three but scores returned to baseline on postoperative day six. The propofol group was expected to have less S-100ß protein levels than the isoflurane group because of the brain protective action of propofol. However unexpectedly, we found that S-100ß protein levels were higher with propofol.

Despite the increase in S-100ß protein levels no difference in deterioration of neuropsychological test scores and neurological examination after the operation was seen between groups. We conclude that, using S-100ß levels as a marker of cerebral injury, propofol appears to offer no advantage over isoflurane for brain protection during CPB in this preliminary study of 20 patients.

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