Anesthetic Technique (Sufentanil Versus Ketamine Plus Midazolam) and Quantitative Electroencephalographic Changes After Cardiac Surgery

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Objectives: Cardiac surgery involving cardiopulmonary bypass is associated with neurologic deterioration. Several interventions, including anesthetic techniques, have been designed to limit ischemic brain damage and have been evaluated in animals. Markers of neurologic injury may facilitate the assessment of these interventions in humans.

Design: A blinded randomized prospective study comparing 2 anesthetic techniques (one sufentanil-based, the other ketamine and midazolam–based) in patients undergoing cardiac surgery. Quantitative electroencephalography was used to detect postoperative neurologic injury.

Setting: Major teaching hospital.

Participants: Forty-two patients aged 18 to 70 years undergoing cardiac surgery.

Interventions: Patients were anesthetized with either a sufentanil-based or a ketamine and midazolam–based technique for cardiac surgery with cardiopulmonary bypass. Quantitative electroencephalography was performed preoperatively as well as 5 to 6 days postoperatively.

Measurements and Main Results: Quantitative electroencephalography outcome did not differ ($p > 0.05$) between the 2 groups. It showed significant deterioration between preoperative and postoperative assessments with a decrease in faster and an increase in slower frequencies. In addition, the alpha attenuation index decreased. This may reflect a decrease in alertness. Both the intergroup comparisons and the assessment of individual changes failed to reveal significant differences between the anesthetic techniques. The adjuvant use of isoflurane correlated with less deterioration of quantitative electroencephalographic variables.

Conclusions: The use of either sufentanil-based or ketamine and midazolam–based anesthetic techniques for cardiac surgery with cardiopulmonary bypass had no effects on a marker of postoperative neurologic injury (ie, quantitative electroencephalography).

THE MANIFESTATIONS of cerebral injury after cardiac surgery, to some extent ascribable to the effects of cardiopulmonary bypass (CPB), include postoperative delirium, stroke, and cognitive changes.[1] Potential methods to identify neurologic injury include clinical examination, neuropsychologic testing, electroencephalographic (EEG) changes, magnetic resonance imaging, and chemical markers.

The neuroprotective properties of ketamine have been shown in animals[2] but have not, to the authors' knowledge, been confirmed in humans. Ketamine binds to the phencyclidine area on the N-methyl-D-aspartate (NMDA) receptor complex and inhibits Na^+ and Ca^{2+} influx through NMDA-associated ion channels.[3] Opioids may also protect the brain by decreased cerebral oxygen consumption, noncompetitive NMDA antagonism,[4] or hypoxic preconditioning.[5] The $GABA_A$ agonist midazolam has been shown to be neuroprotective in animals.[6] Ketamine, like other NMDA-receptor antagonists, may be neurotoxic to the posterior gyrus cinguli and retrosplenic cortex. M_1 anticholinergic drugs and $GABA_A$ agonists like benzodiazepines prevent this effect.[7]

Toner et al[8] and Chabot et al[9] have shown that quantitative electroencephalography (QEEG) changes correlated with neuropsychologic deterioration after cardiac surgery. Chabot et al[9] found that patients whose neuropsychologic performance remained stable 1 week after CPB were correctly classified by the changes in the 1 week postoperative QEEG, with a specificity of 78.9%, and those whose neuropsychologic performance deteriorated, with a sensitivity of 87.6%. The respective specificity and sensitivity of the 1-week postoperative QEEG and neuropsychologic deterioration 3 months postoperatively were 87% and 100%. The alpha attenuation index (AAI) is an index of EEG reactivity and its deterioration may indicate reduced alertness; it has been related to reduced performance in tasks requiring vigilance.[10] An advantage of electrophysiologic testing with the QEEG is that it, unlike neuropsychologic evaluation, does not require literacy and motivation.

No previous human studies have compared a sufentanil-based anesthetic technique with a ketamine and midazolam–based technique in terms of markers of neurologic injury after cardiac surgery. The aim of this study was to compare the preoperative and postoperative QEEG changes in patients receiving either a sufentanil-based or a ketamine and midazolam–based anesthetic for cardiac surgery with CPB.

Methods

The study was performed with institutional ethics committee approval and written informed consent. Patients, surgeons, CPB technologists, those performing and analyzing the QEEG, and the data analyst were blinded regarding the anesthetic technique. The same anesthesiologist administered all the anesthetics and was not blinded to the prescribed anesthetic technique. The cohort consisted of 42 patients; 21 for coronary artery bypass graft (CABG) surgery and 21 for valve replacement surgery. The 21 CABG and the 21 valve replacement patients were randomized (by the statistician) separately to receive either sufentanil or ketamine plus midazolam as the primary anesthetic technique. Patients aged 18 to 70 years scheduled for elective first-time cardiac surgery were included. An ejection fraction <40%, psychosis, active neurologic disease, carotid artery bruits, a history of syncope, a transient ischemic neurologic deficit, a previous cerebrovascular accident, renal failure (serum urea >10 mmol/L or serum creatinine >180 μmol/L), liver disease, known diabetes mellitus, or a random blood glucose >11.1 mmol/L excluded a patient from the study.

The doses of midazolam, ketamine, and sufentanil were based on those reported in the literature.[11, 12, 13 and 14] These doses have been proposed to ensure a sufficient depth of anesthesia and may, but are not intended to, be neuroprotective. Patients received an oral dose of midazolam of 0.2 mg/kg 2 hours preoperatively. Those in the sufentanil group were induced with sufentanil, 0.7 μg/kg/min, until loss of responsiveness to a command to keep their eyes open or a minimum dose of 2 μg/kg. This was followed by sufentanil, 3 μg/kg/h. In the ketamine-midazolam group, patients received 15 μg/kg of alfentanil before induction with ketamine, 0.7 mg/kg/min, plus midazolam, 70 μg/kg/min, until loss of consciousness, or minimum doses of 2.0 and 0.2 mg/kg, respectively. This was followed by ketamine, 2 mg/kg/h, plus midazolam, 0.2 mg/kg/h. After induction of anesthesia, patients were paralyzed with vecuronium, 0.15 mg/kg. Isoflurane was administered as an adjuvant anesthetic in both groups. Administration of isoflurane and vecuronium were guided by clinical observations.

The surgeon palpated the aorta to determine the sites of cannulation and grafting. Echocardiographic examination of the aorta was not done. The procedures were performed during hypothermic (nasopharyngeal temperature 30°C) nonpulsatile (Cobe roller pump; Cobe, Lakewood, CO) CPB. The pump circuit was primed with crystalloid (Na^+ 130 mmol/L, K^+ 4 mmol/L, Mg^{2+} 1.5 mmol/L, HCO_3^- 27 mmol/L, Cl^- 110 mmol/L). A membrane oxygenator (Monolyth-Pro oxygenator and reservoir; Sorin Biomedica, Saluggia, Italy) and an uncoated pump circuit with a 40-μm filter in the arterial cannula (Dideco perfusion tubing systems; Sorin Biomedica) were used. Patients were heparinized with heparin, 500 IU/kg. The activated coagulation time was kept >400 seconds. Blood pressure during CPB was kept between 50 and 70 mmHg. At pressures <50 mmHg, pump flow was increased up to 4 L/min/m^2 after which phenylephrine was given.[15] Hypertension was treated by lower flows and the addition of isoflurane to the pump fresh gas. Anterograde cold (4°C) crystalloid cardioplegia was used in all patients. Cardiotomy suction blood was returned to the pump. Rewarming was active with a maximum temperature of 38°C in the heat exchanger. Epinephrine, nitroglycerin, phenylephrine, and volume expanders were used as considered necessary.

Using the α-stat blood gas strategy, normocapnia ($PaCO_2$ 31-39 mmHg at this altitude) was maintained throughout the procedure. End-tidal PCO_2 was monitored before and after CPB but not during CPB. Isoflurane concentration (%) was monitored in the end-tidal gas before and after CPB and in the fresh gas flow (dial reading) during CPB.

A QEEG was obtained 1 to 2 days preoperatively and repeated 5 or 6 days postoperatively. This was in accordance with Chabot et al[9] who repeated the QEEG 1 week postoperatively. Multiple-channel EEG recordings with a digitizing rate of 200 Hz were performed using a Cz reference. Artifacts and any periods of drowsiness were excluded from the analysis. Fast Fourier transform was applied off-line using EEGFOCUS version 2.0 software (MEGIS Software, GmbH, Munich, Germany). The epoch length was 2.6 seconds, and the bandpass was set at 1.6 to 30 Hz. The results were summed into 4 frequency bands: delta 1.6 to 4 Hz, theta 4 to 8 Hz, alpha 8 to 13 Hz, and beta 13 to 35 Hz. Results were expressed on an amplitude (μV) scale. The absolute value for each frequency band was used to derive the relative amplitude expressed as a percentage. In addition to the alpha/theta amplitude ratio, the AAI was calculated. The peak frequency of the amplitude spectrum (PS) >2 Hz was included. The PS of the amplitude spectrum was automatically determined and visually confirmed. The AAI was obtained by dividing the alpha amplitude with eyes closed by the alpha amplitude with eyes opened to provide an index of the reactivity of the EEG. In the current study, analysis was confined to parieto-occipital EEG changes because these changes have been reported to be particularly sensitive to the effects of cardiac surgery.[16 and 17]

The percentage change in a QEEG parameter was calculated for each patient: $\Delta x\% = (x \text{ postoperative}/x \text{ preoperative} - 1)100$. A decrease and an increase in the relative % of the higher frequencies (beta amplitude, alpha amplitude), alpha/theta ratio, PS, and AAI were expressed as negative and positive values, respectively. An increase and decrease in the relative delta and theta amplitudes were expressed as negative and positive changes, respectively. The criterion for deterioration of an EEG parameter was an increase of ≥20% of delta or theta or a decrease of ≥20% of alpha, beta, PS, alpha/theta ratio or AAI. At least 2 of these criteria had to be met to determine EEG deterioration. These criteria are similar to those applied by Toner et al.[8] A clinical neurologic examination was performed preoperatively and before discharge; patients were also questioned about intraoperative awareness.

Continuously monitored parameters (eg, blood pressure, heart rate, temperature, isoflurane concentration) were recorded every 5 minutes. For both the continuous and intermittent measurements (blood gas analysis), means and medians (where applicable) of all the recorded values over time were determined. Because there were only minor differences between means and medians, the former were used. Total doses of drugs were recorded.

Calculation of the sample size was based on the primary aim; the determination of the influence of the anesthetic technique on a marker of neurologic injury, the QEEG; or, the detection of whether treatment groups differ with respect to change from a baseline. A difference of 20% between groups, with respect to a change from baseline, was regarded as clinically relevant. The standard deviation of change from baseline was set to 20%[18] (ie, the range of change in individual patients as expected from 10% to 90%). This approximates 4 standard deviations. Based on these assumptions, a sample of 42 patients (21 per group, balanced for each type of operation) had a power to detect such a difference in excess of 85% at the 0.05 level of significance using a 2-sample *t* test. The paired *t* test was used for changes in all patients. Categoric data were compared using the 2-sided Fisher exact test. H_0 was rejected at the 0.05 level of significance when $p \leq 0.05$. Correlations were done using the Spearman correlation coefficient (ρ).

Results

Data are presented as means ± standard deviation. There were neither double valve replacements nor valve replacement combined with CABG surgery. There were 10 valve replacements and 11 CABG patients in the sufentanil group and 11 valve replacements and 10 CABG patients in the ketamine-midazolam group. Preoperative and intraoperative findings are summarized in Table 1.

Table 1. Descriptive Statistics for Pre- and Intraoperative Variables (Means ± SD)

Variable	Sufentanil	Ketamine-Midazolam	*p*
Age (y)	47 ± 14	47 ± 12	NS
Body mass (kg)	76 ± 20	79 ± 16	NS
Mitral and aortic valve replacements	9 and 1	8 and 3	NS
CABG	11	10	NS
Time (min)			
Before CPB	57 ± 21	56 ± 25	NS
CPB	76 ± 22	79 ± 21	NS
After CPB	58 ± 11	58 ± 10	NS
Ejection fraction (%)	61 ± 12	59 ± 11	NS
Mean blood pressure (mmHg)			
Before CPB	77 ± 10	85 ± 14	0.0242
During CPB	58 ± 8	57 ± 6	NS
After CPB	72 ± 13	77 ± 7	NS
Pump flow (L/min/m^2)	3.1 ± 0.4	2.9 ± 0.3	NS
Peripheral resistance during CPB (dyne/s/cm^5/m^2)	1557 ± 298	1578 ± 265	NS
Central venous pressure (mmHg)			
Before CPB	7 ± 3	7 ± 3	NS
After CPB	9 ± 3	10 ± 3	NS
Isoflurane (%) during whole procedure	0.12 ± 0.10	0.18 ± 0.19	NS
Number of patients who received isoflurane	11/21	10/21	NS
End-tidal PCO_2 (mmHg)			
Before CPB	32 ± 2	30 ± 2	0.0281
After CPB	33 ± 2	32 ± 3	NS
$PaCO_2$ (mmHg)			
Before CPB	34 ± 5	34 ± 4	NS
During CPB	34 ± 3	33 ± 3	NS
After CPB	36 ± 4	35 ± 4	NS
Blood glucose during CPB (mmol/L)	6.8 ± 1.5	7.3 ± 1.3	NS
Core temperature (°C)			
Before CPB	36.1 ± 0.4	35.6 ± 0.5	0.0009
During CPB	32.1 ± 1.2	32.4 ± 2.0	NS
Maximum during CPB	37.3 ± 0.5	37.3 ± 0.3	NS
After CPB	36.1 ± 0.4	36.4 ± 0.6	0.0451
Hematocrit (%)			
Before CPB	38 ± 3	37 ± 6	NS
During CPB	29 ± 4	26 ± 5	0.0252
Minimum during CPB	28 ± 4	24 ± 5	0.0089
After CPB	30 ± 4	29 ± 4	NS
Fluid balance (mL/kg)			
Crystalloid	47 ± 16	43 ± 19	NS
Colloid	0.6 ± 1.8	0.3 ± 1.3	NS
Blood transfusion	5 ± 6	5 ± 6	NS
Blood loss	9 ± 3	8 ± 2	NS
Blood transfusion/blood loss ratio	0.7 ± 0.7	0.5 ± 0.6	NS
Urine output (mL/h)	18 ± 10	22 ± 16	NS

Abbreviation: NS, not significant.

The mean arterial blood pressure was significantly lower in the sufentanil group than in the ketamine-midazolam group before CPB (77 ± 10 mmHg and 85 ± 14 mmHg, respectively; $p = 0.0242$). $PaCO_2$ did not differ significantly between groups during any of the stages of surgery. End-tidal PCO_2 before CPB

was (statistically) significantly higher in the sufentanil than in the ketamine-midazolam group (32 ± 2 mmHg and 30 ± 2 mmHg, respectively; $p = 0.0281$) but did not differ significantly after CPB.

There were no significant differences between anesthetic techniques regarding transfusion of blood and other fluids, blood loss, and urinary output. The hematocrit was higher in the sufentanil than in ketamine-midazolam group during CPB (29% ± 4% and 26% ± 5%, respectively; $p = 0.0252$).

The core temperature (nasopharynx) of all patients during CPB was 32.2° ± 1.6°C and did not differ between groups. Before CPB, core temperatures were significantly higher in the sufentanil group than in the ketamine-midazolam group (36.1° ± 0.5°C and 35.6° ± 0.4°C, respectively; $p = 0.0009$). After CPB, the temperatures were significantly lower in the sufentanil than in ketamine-midazolam group (36.1° ± 0.4°C and 36.4° ± 0.6°C, respectively; $p = 0.0451$).

There was no significant difference between the 2 groups regarding the mean isoflurane concentration administered or the number of patients who received isoflurane. In all patients, the concentration of isoflurane administered during the whole operation was 0.15% ± 0.15% and during CPB 0.10% ± 0.15%. There were also no differences between the groups regarding the mean doses of cardiac drugs (Table 2).

Table 2. Drugs Administered Intraoperatively (Means ± SD)

Variable	Sufentanil	Ketamine-Midazolam	*p*
Epinephrine total dose (μg/kg)	4 ± 2	4 ± 1	NS
Number of patients who received epinephrine	21/21	21/21	NS
Nitroglycerin total dose (μg/kg)	10 ± 9	11 ± 9	NS
Number of patients who received nitroglycerin	19/21	20/21	NS
Phenylephrine (μg/kg)	1 ± 1	1 ± 1	NS
Number of patients who received phenylephrine	10/21	9/21	NS
Isoflurane concentration (%) administered			
During whole procedure	0.12 ± 0.10	0.18 ± 0.19	NS
During CPB	0.09 ± 0.14	0.11 ± 0.17	NS
Number of patients who received isoflurane			
During whole procedure	11/21	10/21	NS
During CPB	7/21	9/21	NS

Abbreviation: NS, not significant.

There were no significant differences in preoperative QEEG variables between the 2 groups of patients; nor were there significant differences in the percentage change between the groups (Table 3). QEEG deterioration (≥2 parameters deteriorating ≥20%) did not differ between the sufentanil and ketamine-midazolam groups (14/21 [66.67%] and 13/21 [61.90%], respectively; $p = 0.5000$).

Table 3. Percentage Changes (Means ± SD) Between the Baseline and Postoperative Assessments in QEEG Variables in the Sufentanil (n = 21) and Ketamine-Midazolam (n = 21) Groups

Variable	Sufentanil	Ketamine-Midazolam	*p*
Δbeta%	−12.36 ± 14.2	−12.64 ± 11.1	0.9434
Δalpha%	−2.1 ± 24.4	−4.3 ± 15.3	0.7346
Δdelta%	−25.6 ± 40.4	−24.9 ± 31.3	0.9485
Δtheta%	−26.2 ± 22.8	−21.3 ± 22.8	0.4936
Δalpha/theta%	−18.4 ± 33.7	−18.2 ± 21.2	0.9821
ΔPS%	−4.8 ± 15.2	−8.3 ± 13.4	0.4474
ΔAAI%	−14.9 ± 32.7*	−25.7 ± 23.0†	0.2225

Abbreviations: Δalpha%, percentage change of relative alpha; PS, peak spectrum. The same for relative beta, relative delta, relative theta, alpha/theta%, and alpha attenuation index (AAI).

* n = 19.

† n = 20.

Sixty-four percent of all patients (27) showed QEEG deterioration; in 29% (12), it was unchanged; and in 7% (3), it was improved: 2 in the ketamine-midazolam group and 1 in the sufentanil group. The mean values of all parameters deteriorated significantly, but the largest changes were observed in the following: Δdelta% = −25% ± 36% ($p < 0.0001$), Δtheta% = −24% ± 23% ($p < 0.0001$), and ΔAAI% = −20% ± 28% ($p = 0.0007$). The Δbeta% was −13% ± 13% ($p < 0.0001$), Δalpha% = −3% ± 20% ($p = 0.0282$), Δalpha/theta% = −18% ± 28% ($p < 0.0001$), and ΔPS% = −7% ± 14% ($p = 0.0063$). The alpha attenuation index decrease probably reflects a decrease in alertness.[10] In 2 patients, a preoperative, and, in 1 patient a postoperative, spectral peak could not be identified, apparently because of the absence of a dominant alpha rhythm.

No significant correlation was found between any of the changes in QEEG variables and age, CPB time, intraoperative blood pressure, hematocrit, temperature, or $PaCO_2$. There were significant correlations between the mean isoflurane concentration measured during the whole operation and Δbeta% ($\rho = 0.46$, $p = 0.0033$), Δtheta% ($\rho = 0.50$, $p = 0.0015$), Δalpha/theta% ($\rho = 0.34$, $p = 0.0363$), and ΔPS% ($\rho = 0.33$, $p = 0.0395$).

No patient suffered any neurologic deficit or delirium as determined with a clinical physical examination postoperatively. Neither implicit nor explicit intraoperative awareness was reported.

Discussion

The main finding of this study was that QEEG changes did not differ significantly between sufentanil-based compared with ketamine and midazolam–based anesthetic techniques, both in respect to mean change and in the percentage of individual subjects showing significant deterioration. The QEEG deteriorated in 64% of all patients. The pattern of deterioration in respect to specific QEEG parameters, such as increases in relative delta and theta frequencies, as well as decreases in AAI and PS, are similar to those reported by Chabot et al.[9] The reason for improvement of the QEEG in 3 patients is not clear.

The assessment of postoperative cognitive function has been reviewed by Rasmussen et al.[19] The notion of 20% or 1 standard deviation deterioration in 20% of a battery of neuropsychologic tests as representing a significant change has been applied by Newman et al[18] and Stump.[20] The present authors are of the opinion that criteria for “significant change” may also be applied to markers such as the QEEG. Therefore, in this study, it was decided to regard a deterioration of ≥20% in 2 or more of 7 QEEG variables as the criterion of significant deterioration, which is similar to the criterion set by Toner et al.[8]

In this study, no sedative drugs (including opioids) were allowed for at least 24 hours before the preoperative and postoperative QEEG. It is therefore unlikely that residual effects of anesthesia, sedatives, or opioids affected the EEG 5 to 6 days postoperatively. Sleep deprivation could be a cause of some deterioration in QEEG parameters. Patients were questioned about sleep disturbances but did not report any. The EEG was carefully scrutinized for any signs of drowsiness, including changes in frequency of the EEG, and for occurrence of slow rolling eye movements. Any sections containing these changes were excluded from analysis.

Part of the explanation for the lack of difference between the effects of sufentanil and ketamine-midazolam on QEEG changes may be that both possess anti-NMDA properties. Other brain protective measures (hypothermia and isoflurane) might also have offered significant protection in both groups.

A post hoc finding of this study was the significant correlation between the mean isoflurane concentration and Δbeta%, Δtheta%, Δalpha/theta%, and ΔPS%. The concentration of isoflurane administered during the whole operation (0.18% ± 0.14%) and during CPB (0.10% ± 0.15%) was substantially less than 1 minimum alveolar concentration (1.2%) and did not differ significantly between the 2 groups. Apart from decreasing cerebral oxygen consumption, isoflurane may be neuroprotective by decreasing glutamate release,[21] by suppressing the increase of extracellular dopamine during cerebral ischemia,[22] or by preserving hippocampal Ca^{2+}/calmodulin-dependent protein kinase.[23]

Several intraoperative variables have been implicated in the production of changes in the markers of neurologic injury after cardiac surgery. Apart from blood pressure before CPB, end-tidal PCO_2 before CPB, temperature before and after CPB, and hematocrit during CPB, none of these variables differed significantly between groups (Table 1). Patients in both groups were relatively young (47 ± 14 years and 47 ± 12 years), which may explain the lack of difference in QEEG changes.

The significantly higher blood pressure before CPB in the ketamine-midazolam group (85 ± 14 mmHg *v* 77 ± 10 mmHg) may be explained by the maintenance of neural responses to hypotension during ketamine anesthesia.[24] An explanation for the lower hematocrit in the ketamine-midazolam group during CPB is not clear because the fluid balance did not differ between groups. Neither volume of blood transfused, blood loss, blood loss/transfusion ratio, nor volume of other intravenous fluids or urinary output differed significantly between these groups during any of the stages of the operations. The explanation may lie in the systemic inflammatory response that accompanies CPB, which may contribute to loss of intravascular fluid to the interstitial space. This fluid shift may bring about hemoconcentration. Ketamine is antiinflammatory because of suppression of nuclear factor κB expression at clinically relevant concentrations.[25] Nuclear factor κB is involved in the transcription of several genes, including those encoding the proinflammatory cytokines tumor necrosis factor α, interleukin 6, and interleukin 8.[26]

At this institution, CPB is performed at a target temperature of about 30°C with rewarming to normothermia. Using jugular bulb oxygen saturation, Shaaban et al[27] could not show a difference in brain oxygenation between CPB at 28°C and 34°C. Temperature was significantly higher in the sufentanil group before CPB (36.1° ± 0.4°C *v* 35.6° ± 0.5°C, $p = 0.0007$) but lower after CPB (36.1° ± 0.4°C *v* 36.4° ± 0.6°C, $p = 0.0323$). Because both groups were close to normothermia after CPB, these small differences were probably not significant from a neuroprotective point of view.

Neurologic outcome may not only be influenced by the anesthetic technique and surgical and CPB practice, but also by postoperative care. Patients may sustain further brain damage postoperatively because they are often cardiovascularly unstable and warm. Browne et al[28] have shown a significant correlation between hypoxemia 5 days postoperatively after cardiac surgery and cognitive decline. In this study, postoperative care of the patients was not controlled, which might have had an equalizing influence on outcome.

It is uncertain whether a favorable neuropsychologic outcome excludes neurologic impairment.[29] Diffusion-weighted magnetic resonance imaging has shown new brain lesions after cardiac surgery that were not reflected by persistent neurocognitive decline.[30] Chabot et al[9] are of the opinion that the lack of one-to-one correlation between QEEG and neuropsychologic changes may be because of the fact that deterioration in neurophysiologic function, is not necessarily responsible for a deterioration in neuropsychologic function, but rather points to the risk of suffering an unfavorable cognitive outcome. The markers of neurologic injury may also measure different endpoints, namely neuropsychologic function, electrophysiologic function, chemical marker elevation, magnetic resonance imaging changes, stroke, or death. These complexities may explain the divergent findings in previous studies.[31 and 32] No awareness was reported despite no additional midazolam in the sufentanil group and the low concentration of isoflurane needed. The question must, however, be asked if a lack of recall after cardiac surgery implies adequate anesthesia because amnesia also occurs after minor brain injury.

This study has several shortcomings. The combination of anesthetic drugs makes it difficult to separate the neuroprotective effects (if any). The authors considered it unethical to administer ketamine without midazolam and to withhold an inhalation agent when clinically necessary. Animal studies do not pose this problem. A sample consisting of patients scheduled for only 1 type of surgery might have been more informative regarding a drug effect. QEEG recordings using more leads, recordings at 3 months or 6 months postoperatively, and the inclusion of neuropsychologic tests would have broadened the scope of this study.

In conclusion, by using QEEG changes as a marker, this study was unable to show a difference between sufentanil-based and ketamine and midazolam–based anesthetic techniques regarding neurologic injury after cardiac surgery in humans.

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