Volatile Anesthetics Reduce Mortality in Cardiac Surgery

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Objectives: **A recent meta-analysis suggested that volatile anesthetics reduce postoperative mortality after cardiac surgery. Nonetheless, whether volatile anesthetics improve the outcome of cardiac surgical patients is still a matter of debate. The authors investigated whether the use of volatile anesthetics reduces mortality in cardiac surgery.**

Design, Setting, and Interventions: **A longitudinal study of 34,310 coronary artery bypass graft interventions performed in Italy estimated the risk-adjusted mortality ratio for each center. A survey was conducted among these centers to investigate whether the use of volatile anesthetics showed a correlation with mortality.**

Measurements and Main Results: **All 64 eligible centers provided the required data. The median unadjusted 30-day mortality among participating centers was 2.2% (0.3-8.8), whereas the median risk-adjusted 30-day mortality was 1.8% (0.1-7.2). Risk-adjusted analysis showed that the use of volatile anesthetics was associated with a significantly lower rate of risk-adjusted 30-day mortality (β = −1.172 [−2.259, −0.085], R^2 = 0.070, p = 0.035). Dichotomization into centers using volatile anesthetics in at least 25% of their cases or in less than 25% yielded even more statistically significant results (p = 0.003). Furthermore, a longer use of volatile anesthetics was associated with a significantly lower death rate (p = 0.022); and exploring the impact of the specific volatile anesthetic agent, the use of isoflurane was associated with significant reductions in risk-adjusted mortality rates (p = 0.039).**

Conclusions: **This survey among 64 Italian centers shows that risk-adjusted mortality may be reduced by the use of volatile agents in patients undergoing coronary artery bypass graft surgery.**

KEY WORDS: halogenated anesthetics, volatile anesthetics, total intravenous anesthesia, coronary artery bypass graft surgery, cardiac anesthesia, cardiac surgery, myocardial damage, mortality

ALL VOLATILE ANESTHETICS have cardiac depressant effects that decrease myocardial oxygen demand and may, therefore, have a beneficial role on the myocardial oxygen balance during ischemia. Recently, experimental evidence clearly has shown that in addition to these indirect protective effects, volatile anesthetic agents also have direct protective properties against ischemic myocardial damage.[1] The implementation of these properties during clinical anesthesia can provide an additional tool in the treatment or prevention, or both, of ischemic cardiac dysfunction in the perioperative period.

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A recent meta-analysis showed that desflurane and sevoflurane reduce postoperative mortality and the incidence of myocardial infarction (MI) after cardiac surgery with significant advantages in terms of postoperative cardiac troponin (cTn) release, need for inotropic support, time on mechanical ventilation, intensive care unit (ICU) stay, overall hospital stay, and survival.[2] This was the first study to show that the choice of an anesthetic plan can result in lower mortality and morbidity in patients undergoing surgery and was in contrast with previous meta-analyses[3,4] that included other volatile agents such as isoflurane. Multicenter, randomized clinical trials (RCT) had previously shown that, in comparison to propofol, the use of desflurane can reduce the postoperative release of cardiac troponin I (cTnI), the need for inotropic support, and the number of patients requiring prolonged hospitalization after coronary artery bypass graft (CABG) surgery, either with[5] or without[6] cardiopulmonary bypass.

Whether volatile anesthetics improve the outcome of cardiac surgical patients is still a matter of debate. Only Jakobsen et al,[7] in a retrospective, nonrandomized study including more than 10,000 cardiac surgical patients, confirmed that patients without preoperative unstable angina or recent myocardial infarction have lower postoperative mortality after sevoflurane anesthesia than after total intravenous anesthesia (TIVA).

Evidence in noncoronary surgical settings is even more contradictory. Even if Cromheecke et al[8] observed a protective effect of volatile agents in aortic replacement surgery, Landoni et al[9,10] found no advantage in using a preconditioning protocol with volatile anesthetics in patients undergoing mitral surgery

or coronary stenting procedures. Interestingly, patients with concomitant coronary artery disease undergoing mitral surgery showed a marked decrease in postoperative cTnI release when preconditioned with desflurane.[8] The same group conducted a meta-analysis of 79 RCTs comparing volatile anesthetics with TIVA in noncardiac surgery and found that none reported any postoperative major cardiac event or death.[11] De Hert et al[12] found no evidence of protective action of volatile agents in vascular surgery. According to the recent American College of Cardiology/American Heart Association guidelines, volatile anesthetics should be considered for patients at risk for myocardial ischemia[13] undergoing noncardiac surgery, despite the lack of evidence in this setting.[14]

Seccareccia et al[15] conducted a longitudinal study of 34,310 CABG interventions performed between 2002 and 2004 in 64 Italian cardiac surgical centers. They estimated a risk-adjusted mortality ratio for each center. Because initial reports[2,7] and guidelines[13] suggested a beneficial outcome in patients using volatile agents and while awaiting large randomized controlled studies to be performed, the authors have conducted a national survey among the same 64 cardiac surgical centers in order to investigate whether the use of volatile anesthetics in that time period showed a correlation with the risk-adjusted mortality ratio for each center (reported by the web site http://bpac.iss.it/).

METHODS

A National Health System analysis to evaluate adjusted performance indicators in Italy was performed in 2002 to 2004 to compare 30-day mortality after CABG surgery among cardiac surgery centers, adjusting by confounding risk factors, as reported in detail in Seccareccia et al.[15]

Briefly, a list of all public and private cardiac surgery centers in Italy for adult patients was prepared, and a reference person from each center was contacted and invited to participate in the study. Patients considered were 15 to 99 years old who underwent an isolated CABG surgery (not associated with other cardiac or extracardiac procedures) between January 1, 2002, and September 30, 2004. For each participating cardiac surgery center, a sample of records was randomly selected from the electronic archive. Independent observers, following specific standardized operating procedures, visited each center and compared contents of the records transmitted to those reported in the original clinical charts. These procedures allowed assessment of the reliability and completeness of the database and to maintain constant quality control. The completeness of data in each center was evaluated by comparing them with hospital discharge records supplied by regional and national health information systems. Cardiac surgery centers with fewer than 100 CABG operations per year were excluded from the analytic database. Moreover, only centers that provided data continuously for at least 6 months and who had fewer than 5% of patients lost to follow-up were considered to calculate the algorithm required for the risk-adjustment procedure.

Risk-adjusted mortality rate was obtained as follows[15]: univariate analyses and multivariable analyses were performed on candidate predictive variables in order to determine significant associations with the outcome (30-day mortality). The entire dataset was finally used in estimating the definitive coefficients and calculate their p values to provide more precise parameter estimates. By applying the best predictive algorithm back to each center's dataset, the expected number of deaths of that center was estimated. The risk-adjusted mortality rate was then calculated by dividing, for each center, the observed number of deaths by the expected number of deaths and by multiplying this ratio by the average mortality rate of the whole sample.

Table 1. Questionnaire on the Use of Volatile Agents Administered in the 64 Italian Centers

1. What was, between 2002 and 2004, the average prevalence of use of volatile anesthetics in your center during coronary artery bypass graft surgery procedures (mutually exclusive)? Answers could be: 100%, >75%, 25%-75%, <25%, none.
2. Which were, between 2002 and 2004, the volatile anesthetics employed in your center during coronary artery bypass graft surgery procedures (nonmutually exclusive)? Answers could be: desflurane, isoflurane, sevoflurane, none.
3. Which was, between 2002 and 2004, the average duration of use of volatile anesthetics for each specific procedure (mutually exclusive) in your center? Answers could be: all of the operation, only part of the operation, only incision/sternotomy, no use.

Stemming from Seccareccia et al,[15] a standardized questionnaire was administered by a senior anesthesiologist (E.B.) in 2006 to all the 64 centers that participated in the longitudinal outcome study of the Italian Ministry of Health. The proposed questions focused on practice patterns used during 2002 to 2004 and are shown in Table 1. The aim of the questionnaire was not disclosed to the participants. The primary endpoint of the study was 30-day risk-adjusted all-cause mortality, as defined previously by Seccareccia et al.[15]

Continuous variables are reported as median (minimum and maximum values) when appropriate. Categoric variables are reported as n (%). To appraise the impact of the use of volatile anesthetics on the 30-day risk of all-cause mortality, as well as taking into account the baseline patient risk profile, a linear regression analysis was performed using risk-adjusted mortality rate as the dependent variable and details on volatile anesthetics as the dependent variable. Specific details on model building, calibration, and discrimination of the multivariable model used to generate risk-adjusted mortality rates are reported in the study by Seccareccia et al. Furthermore, the authors conducted additional sensitivity analyses by forcing into the multivariable linear regression model the annual procedural caseload per each center, weighting it according to a weighted least squares method, as well as building a generalized linear model with weighted least squares for caseload, volatile anesthetics as random-effect covariate, and risk-adjusted mortality rate as the dependent variable. Such analyses yielded regression coefficients (β) with 95% confidence intervals, R^2, and p values for hypothesis testing. All computations were performed with SPSS 11.0 (SPSS, Chicago, IL), with hypothesis testing set at the 2-tailed 0.05 level.

RESULTS

All 64 eligible centers replied and provided the required data. Data entry had a median of 21 months (6-32) because a number of hospitals began performing cardiac surgery procedures only after the beginning of the study. During the study period, a total of 34,310 CABG surgery procedures were performed, with a median per single center of 471 (116-2,058). A summary of patient characteristics, reported in detail in Seccareccia et al,[15] are available in Table 2. The median unadjusted 30-day mortality among participating centers was 2.2% (0.3-8.8); whereas median risk-adjusted 30-day mortality was 1.8% (0.1-7.2).

Replies to the survey showed that 25 (39.1%) centers were using volatile anesthetics during all procedures, 8 (12.5%) in >75% of them, 6 (9.4%) in between 25% and 75% of them, 15 (23.4%) in fewer than 25% of cases, and 10 (15.6%) in none.