Optimal Technique in Cardiac Anesthesia Recovery

Optimaal herstel na cardiochirurgie: de invloed van cardio-anesthesie techniek

Vesna Svirčević

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Optimaal herstel na cardiochirurgie: de invloed van cardio-anesthesie techniek

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Chapter 1

Introduction and Objectives of this Thesis

History

The early history of cardiac anesthesia is that of the history of general anesthesia which follows surgical developments. Experimental cardiac surgery on animals started in the late 19th century and was soon followed by operations on humans needed after traumatic injury to the heart.[1] First records of valve surgery are from 1913 and in the mid-thirties first interest in revascularization of the myocardium was described.[2-4] Cardiac surgery and anesthesia changed significantly after the World War II. However, it was not until 1953 that the first cardiac operation using total cardiopulmonary bypass was performed.[5] Although several publications had previously dealt with various aspects of cardiac anesthesiology, it was the first publication of a cardiac anesthesia textbook in 1979, that had made cardiac anesthesia the leading subspecialty of anesthesiology.[6,7] Nowadays cardiac anesthesia is a complex and comprehensive field of medicine, which incorporates many aspects of the specialties of anesthesiology, cardiology, and cardiac surgery. Monitoring modalities have always been a part of the anesthesia practice and have provided us with data to improve our therapeutic interventions. Over the past few decades, these monitors have become more sophisticated, with the use of ultrasound and other imaging technologies for monitoring, diagnosis, and helping to guide the surgical procedures.

Fundamental principles of anesthesia for cardiac surgery include maintaining hemodynamic stability and minimizing myocardial ischemia.[8] Traditional anesthetic techniques aimed to decrease cardiovascular stress during cardiac surgery and provide hemodynamic stability without myocardial depression in patients with compromised cardiac function.[9,10] This anesthesia technique consisted of the administration of high-dose opioids and long-acting muscle relaxants resulting in prolonged controlled mechanical ventilation for twelve to twenty-four hours postoperatively. In the intensive care unit, a time-based protocol was used, in which the patient was sedated and ventilated overnight and weaned from mechanical ventilation the following morning.

Fast track cardiac anesthesia

The concept of fast-track cardiac anesthesia (FTCA) emerged in the 1990s and has since then become a widespread technique. FTCA can be defined as a management protocol involving the perioperative care of patients with the goal of allowing rapid recovery following cardiac surgery. Patients are weaned and extubated on the basis

of specific physiologic parameters, such as body temperature, mental status, and pulmonary function, instead of the time parameter. It requires a team of health care providers to interact with the patient at various phases, from admission to discharge.[11] The necessary elements of the fast-track program are choice and the titration of short-acting anesthetic drugs, standardized surgical procedures, early extubation, postoperative normothermia and pain control, early ambulation and discharge.[12] Fast-track cardiac anesthesia avoids high-dose, long-acting narcotic techniques but still effectively manages postoperative pain. A major component of FTCA is early extubation, which can vary from extubation in the operating room to extubation within the first 8 postoperative hours in the intensive care unit (ICU).[13] Regardless of the timing of extubation, the patient must meet standard respiratory, hemodynamic, and temperature criteria before being weaned from the ventilator.[14] Cardiac surgery is a costly burden on the health care budget. A major part of the costs is due to the postoperative stay in the intensive care unit and the hospital.[15] With FTCA rapid recovery after cardiac surgery can be achieved, resulting in shorter ICU and hospital stay. Hence, a decrease in hospitalization time leads to a reduction in cost and better utilization of the hospital resources.[15]

Thoracic epidural anesthesia

Pain is a well-known cause of adrenergic response that increases both myocardial and global oxygen consumption. Undertreated surgical pain prolongs recovery and may result in postoperative complications.[16] The excellent analgesia that is associated with high thoracic epidural anaesthesia (TEA) may prevent respiratory complications by facilitating early tracheal extubation.[17-19] Through sympathycolysis, TEA may enhance coronary perfusion, improve myocardial oxygen balance and reduce the incidence of tachyarrhythmias and perioperative myocardial ischemia.[20,21] Along with these potential benefits of TEA, there is a risk for potential harm caused by an epidural hematoma that may develop after an epidural puncture and catheter insertion, especially in patients who need full heparinisation for cardiopulmonary bypass.[22] An epidural hematoma may compress the spinal cord and lead to permanent neurological injury including paraplegia if not detected and evacuated promptly.

Other potential unwanted side effects are hypotension secondary to sympathicolysis induced by anesthetic blockade and epidural abscess or infection.[47-53]

Outcomes after cardiac surgery: mortality, morbidity and health related quality of life

Patient outcomes after cardiac surgery are affected by many factors including co morbidity, disease severity, effectiveness of treatment, and chance.[23,24] Risk-prediction models play an important role in current cardiac surgical practice as they may be used for patient counseling and treatment selection, to examine medical provider quality, and to serve as the fundament for continuous quality improvement.[25,26] Although operative mortality is obviously the most important clinical endpoint, other non-fatal postoperative complications can significantly impact the patients' functional state and quality of life.[27] It is believable that the identification of risk factors and calculation of adjusted morbidity rates for cardiac surgery procedures could provide valuable insights on decision making and contribution to improved quality of care.[28]

Advances in anesthesiology and surgery techniques and critical care medicine have resulted in reduced risks of perioperative complications over the last decades resulting in a shift of interest towards health-related quality of life endpoints.[29-31] These endpoints can help to define the benefits and risks associated with cardiac operations as well.[32]

Objectives of this Thesis

The aim of this thesis is to evaluate fast-track cardiac anesthesia techniques and investigate their impact on postoperative mortality, morbidity and quality of life. The following topics will be discussed in the thesis.

1. Is fast track cardiac anesthesia a safe technique for cardiac surgery?
2. Does thoracic epidural anesthesia have an effect on mortality and morbidity after cardiac surgery?
3. Does thoracic epidural anesthesia have an effect on quality of life after cardiac surgery?
4. Do we need thoracic epidural anesthesia as a component of fast track cardiac anesthesia?
5. What is quality of life after cardiac surgery?
6. What are the risk factors for poor quality of life after cardiac surgery?

Overview of this Thesis

In **Chapter 2** data of 7989 consecutive patients undergoing elective cardiac surgery were retrospectively analyzed. Outcomes of patients undergoing fast track cardiac anesthesia were compared with patients undergoing conventional high-dose opioid cardiac anesthesia. The primary outcome measure was the incidence of in-hospital mortality. Secondary outcome measures were the incidence of in-hospital acute myocardial infarction, renal failure, and stroke. The duration of mechanical ventilation and length of hospitalization in the intensive care unit and postoperative ward were compared as well. Multivariate logistic and linear regression were used to correct for baseline differences across the two patient groups.

In **Chapter 3** a randomized controlled trial is described comparing thoracic cardiac anesthesia with fast track cardiac anesthesia. 654 elective cardiac surgical patients were randomly assigned to combined FTCA and TEA versus FTCA alone. Follow-up was at 30 days and one year after surgery. The primary endpoint was 30-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke. All data were analyzed according to the intention-to-treat principle using the chi-square statistic, Kaplan-Meier curves for graphic comparison and linear mixed models for repeated measures.

Chapter 4 presents the Cochrane review on possible additional value of thoracic epidural analgesia for cardiac surgery. Cochrane Reviews in the *Cochrane Database of Systematic Reviews* answer clinical questions about the effectiveness of treatments meant for policy-makers, patients, their advocates and carers, to make well-informed decisions about health care**.** Data were analyzed using Cochrane's ReviewManager including Peto method with odds ratios and Mantel–Haenszel with risk ratios.

Randomized studies comparing outcomes in patients undergoing cardiac surgery with either general anesthesia alone or general anesthesia in combination with TEA were retrieved from PubMed, Science Citation index, EMBASE, CINHAL, and Central Cochrane Controlled Trial Register databases in **Chapter 5** After identifying 28 trials including 2731 patients meta-analysis was performed. Sensitivity analyses were presented with L'Abbe plots. A metaregression as well as subgroup analyses based on year of publication and time to extubation were performed. In addition, the presence of small study effects, indicative of biases related to selective

reporting and selective publication of studies, was assessed with plots and Peters regression test.

Possible risk factors for a poor quality of life after cardiac surgery are presented in **Chapter 6**. Health related quality of life was measured and compared at baseline, 30 days and one year after cardiac surgery. Data from 2709 consecutive patients undergoing elective cardiac surgery were retrospectively analyzed. Multivariable linear regression modelling was used to assess risk factors contributing to a decrease in health related quality of life.

In **Chapter 7** the results as described in the previous chapters are discussed and put into perspective.

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Chapter 2

Fast-Track Anesthesia and Cardiac Surgery: *A Retrospective Cohort Study of 7989 Patients*

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Abstract

Background

Fast-track cardiac anesthesia (FTCA) has been widely implemented but its safety has not been evaluated in sufficiently powered studies.

Methods

We compared outcomes of patients undergoing FTCA with a historical control group undergoing conventional high-dose opioid cardiac anesthesia (CCA). The primary outcome measure was the incidence of in-hospital mortality. Secondary outcome measures were the incidence of in-hospital acute myocardial infarction, renal failure, and stroke. We also compared duration of mechanical ventilation and length of hospitalization in the intensive care unit and postoperative ward.

Results

The CCA group comprised 4020 patients and the FTCA Group 3969 patients. The patients in the FTCA group were slightly older, had more comorbidities, and were more likely to undergo valve surgery than the CCA group. The incidence of in-hospital mortality was 1.9% in the CCA group and 2.3% in the FTCA group. Compared with the CCA group, the crude odds ratio for mortality in the FTCA group was 1.20 (95% confidence interval 0.88–1.64, $P = 0.25$) and the adjusted odds ratio was 0.92 (95% confidence interval, 0.65–1.32, $P = 0.66$). The incidence of myocardial infarction and stroke in the CCA and FTCA groups were 5.2% and 5.5% ($P = 0.61$), and 0.9% and 1.3%, ($P = 0.06$), respectively, whereas the incidence of acute renal failure was similar in both groups (0.8%, $P = 0.84$). The duration of mechanical ventilation was shorter in the FTCA patients compared with the CCA group (6 vs 12 h, $P \leq 0.001$), but their median intensive care stay was 1 h longer (23 vs 22 h, $P \leq 0.001$). Although the median duration of hospitalization was 6.0 days in both groups, the 90th percentile of the hospitalization time was 13 days in the CCA group and 18 days in the FTCA group ($P \leq 0.001$).

Conclusions

These data from 7989 cardiac surgical patients showed no evidence of an increased risk of adverse outcomes in patients undergoing FTCA.

High-dose opioid anesthesia (e.g., on fentanyl 25–100 μg/kg or sufentanil 2.5–10 μg/kg) was introduced into cardiac surgery almost 40 yr ago in an attempt to provide hemodynamic stability without myocardial depression in patients with compromised cardiac function.[1] It was also assumed that the prolonged intensive analgesia resulting from conventional cardiac anesthesia (CCA) would reduce postoperative myocardial ischemia.[2] Over the past decade, fast-track cardiac anesthesia (FTCA) has gained popularity because it facilitates early tracheal extubation that may lead to a decreased length of hospitalization in the intensive care unit (ICU) and postoperative ward.[3,4] FTCA is based on the administration of relatively small amounts of short-acting opioids, supplemented with either propofol or volatile anesthetics.[5,6] It has been reported that the risk of cardiovascular complications after FTCA is comparable with CCA.[7–9] Nonetheless, the safety of FTCA has not been thoroughly evaluated, because the studies performed to date enrolled too few patients to adequately assess the relative risk for low-frequency complications, such as mortality. The two largest studies comparing FTCA with CCA, in fact, comprised only 1012 and 404 patients[10,11] yielding results with limited statistical power. Meta-analyses evaluating FTCA included randomized trials with predominantly low-risk patients and may have been subjected to publication bias and other limitations inherent with this analytic approach.[12,13]

Thus, the aim of this study was to compare the incidence of mortality, myocardial infarction, stroke, and renal failure between cardiac surgical patients undergoing FTCA and historical controls undergoing CCA.

Methods

Design and Patients

The study was designed as a retrospective observational study. Because of the retrospective nature of the study, formal evaluation by the institution's ethical committee and informed consent were waived. Eligible patients were consecutive patients who underwent elective cardiac surgery at a single institution (Isala Clinics, Zwolle, The Netherlands). During the first period (January 2000 until May 2003) patients received CCA. In June and July 2003 our institution gradually introduced

FTCA. Patients having surgery in these 2 mo were not analyzed. Patients undergoing surgery from August 2003 to December 2006 comprised the second group of patients receiving FTCA. Only patients operated on in June and July 2003, and patients undergoing emergency surgery, were excluded from the analyses.

Anesthesia Techniques

During the first period of study (CCA), patients were premedicated with midazolam 15 mg orally. Induction of anesthesia was with the combination of the opioid sufentanil 2–4 μg/kg and midazolam 0.05–0.1 mg/kg with pancuronium 0.1 mg/kg. Anesthesia was maintained with sufentanil 0.5–2.0 μg/kgxh and midazolam 0.1 mg/kgxh.

After the introduction of FTCA, patients were premedicated with midazolam 7.5 mg orally. Induction of anesthesia was with remifentanil 1–3 μg/kg and propofol 1–2 mg/kg with the muscle relaxant pancuronium 0.1 mg/kg. Some patients also received a low dose of midazolam (up to 5 mg) at induction. Anesthesia was maintained with remifentanil 5–10 μg/kgxh and propofol 1–4 mg/kgxh or sevoflurane (end-tidal concentration 0.5–1.5 volume percent). Upon completion of the operation, morphine 0.1–0.2 mg/kg was administered.

In the ICU after surgery, the CCA patients were sedated with midazolam 2–4 mg/h, and the FTCA patients with propofol 1–2 mg/kgxh. In both the FTCA and CCA groups, sedation was stopped when the patient was hemodynamically stable (no or minor inotropic support and urinary output >0.5 mL/kgxh), peripheral temperature >35°C, and arterial oxygen saturation ≥93% with an fractional inspired oxygen concentration of ≤40%. If a patient could not be weaned from the ventilator and the Ramsey score was >3, additional IV injections of midazolam or lorazepam were administered.

Senior anesthesiologists were responsible for the anesthetic management of the patients during their operations and their postoperative care in the ICU. There were no changes in the staff of senior anesthesiologists during the study period. Tracheal extubation criteria and ICU discharge criteria remained similar throughout the study period.

Surgical Procedures

All patients underwent surgery through a median sternotomy. In patients undergoing cardiac surgery using cardiopulmonary bypass (CPB), myocardial protection was

achieved with antegrade blood or crystalloid cardioplegia. One surgeon used the combination of retrograde and antegrade crystalloid cardioplegia for aortic valve surgery. CPB was managed using nonpulsatile flow applied by centrifugal pump and with the α-stat principle. A 40-μM filter was placed in the arterial line. Heparin was given to maintain the activated clotting time >480 s throughout CPB. Nasopharyngeal temperature was monitored and body temperature reduced to 28°C–34°C during CPB, followed by rewarming to a rectal temperature of 36°C before separation from CPB. After weaning from CPB, protamine 300 U/kg was administered. At the conclusion of surgery, all patients were transported to the ICU.

Outcomes

The primary outcome measure was the incidence of mortality during hospitalization. Secondary outcome measures were the incidence of acute myocardial infarction, stroke, and renal failure, as well as duration of mechanical ventilation, length of hospitalization in the ICU, and total hospitalization.

In coronary artery bypass graft surgery patients, acute myocardial infarction was defined as myocardial specific creatine kinase (CKMB) >120 U/L (five times upper reference limit) plus a peak CKMB/CK ratio >10%, or pathological new Q waves on a postoperative electrocardiogram (ECG).[14] To avoid false-positive diagnoses after valve surgery, CKMB value ≥180 U/L (7.5 times upper reference limit) plus a peak CKMB/creatine kinase ratio >10% was used as the criteria to diagnose myocardial infarction. Preoperative CKMB was not measured, but CK and CKMB were measured in all patients shortly after arrival in the ICU and 4 h later. Measurements were repeated at 4 h intervals when a CKMB level was >50 U/L, the percentage was >10% of total CK, and when CKMB was increasing between the first and second measurement. These measurements were continued until the CKMB level was decreasing. In the ICU, all patients were continuously monitored with 12-lead ECG. Shortly after arrival, a 12-lead ECG was printed and examined by the attending physician. This was repeated before ICU discharge. Additional 12-lead ECGs were printed and examined if myocardial injury was suspected.

According to the second international consensus conference of the acute dialysis quality initiative group, acute renal failure was defined as an increase in postoperative serum creatinine of at least three times the preoperative value, or a

serum creatinine >4 mg/dL associated with an acute increase of serum creatinine of at least 0.5 mg/dL.[15] Creatinine was measured in all patients before surgery and at least once daily as long as they were in the ICU.

Stroke was defined as a new motor or sensory deficit of central origin or unexplained coma. The diagnosis of stroke was made after physical examination by a neurologist and usually confirmed by head computed tomography scan.

Data Collection

Clinical data for the patients were prospectively registered in a dedicated electronic research database from admission until hospital discharge. In the operating room, the attending anesthesiologist documented the patients' demographic data and intraoperative data on a dedicated form and also entered these variables in an electronic database (Microsoft Access). Although the patients were admitted to the ICU, relevant data (duration of ventilation, length of ICU stay, medication, complications, and routine laboratory measurements) were collected by the ICU medical staff on another dedicated data form. After transfer to the step-down ward, additional data (length of hospital stay, medication, and complications in the ward) were recorded by nurses from the research team. These research nurses subsequently entered the data from the dedicated forms into the electronic research database. Because the demographic and intraoperative data were already entered into the database by the attending anesthesiologist, the nurses did not reenter these data but only compared these electronic and written variables. After the patient's discharge from the hospital, all data collection forms were rechecked by another member of the research team to confirm accuracy of the data entry. The final data were transferred into an SPSS database, from which further analyses could be performed.

Statistical Analysis

The rates of mortality, myocardial infarction, stroke, and acute renal failure in the FTCA and CCA group were compared using the χ^2 test and are presented as odds ratio with 95% confidence interval (CI). Continuous outcome measures were compared using the two-sample *t*-test or the Mann–Whitney test, where appropriate, and are expressed as medians with 10th and 90th percentile. For binary outcome measures, multivariable logistic regression analysis was used to correct for baseline

and intraoperative differences (confounders) between the two treatment groups. Based on the literature[16] and clinical expertise, we considered the following pre- and perioperative characteristics as potentially related to our study outcomes and thus as potential confounders of the association between FTCA and the study outcomes: age, gender, hypertension, diabetes mellitus, chronic obstructive pulmonary disease, peripheral vascular disease, preoperative renal failure, preoperative neurological deficit, left ventricular ejection fraction (LVEF), use of cardiovascular drugs, type of surgery, number of anastomoses, duration of CPB, cross-clamp time, off-pump surgery, and additive (i.e., standard) Euroscore.[16] This approach was also used for studying the association with the secondary dichotomous outcomes. For the continuous secondary outcome variables (i.e., duration of mechanical ventilation and duration of hospitalization in the ICU, and total duration in hospital) we used linear regression. As these three duration outcomes were all nonnormally distributed, we first applied a natural log-transformation and compared the mean log(duration) between the FTCA and CCA group using univariable linear regression. Subsequently, for each of these outcomes, multivariable linear regression on the log(duration) was used to adjust this difference in mean log(duration) for the potential confounders.

Statistical analysis was performed with SPSS software version 13. Although very limited, some patients did have missing values for one or more covariates (confounders) ranging from 0.1% for age to 2.6% for LVEF (Table 1). Missing data seldom occur completely at random. Deleting subjects with a missing value does not only lead to loss of statistical power but also commonly leads to biased results. Therefore, imputing missing values is generally preferred to complete case analysis.[17–20] Missing covariate or confounder data were thus (single) imputed using a regression model (logistic regression for dichotomous covariates, linear regression for continuous covariates, and polytomous regression for categorical covariates) approach with addition of a random error component before conducting the analyses (S-PLUS, professional edition, version 6.2). The imputation model, i.e., the model to impute missing covariate data, included all other covariates including the outcome variables, as it has extensively been reported that imputation of missing covariate data should always be done with all available data including the outcome.[17–20] Missing outcome variables were not imputed.

Table 1. *Baseline characteristics and intra-operative data*

	CCA group n=4020	FTCA group n=3969	p-value	Missings, %
Age, mean (SD), y	65.3 (10.3)	66.2 (10.5)	0.32	0.1
Gender male, %	70.5	70.5	0.98	0.2
Euroscore, Median (10^{th};90^{th})	5 (1-9)	5 (2-10)	≤ 0.001	0
Pulmonary disease, %	14.0	14.1	0.92	0
Hypertension, %	42.3	49.6	≤ 0.001	0
Diabetes mellitus, %	17.6	22.1	≤ 0.001	0
Peripheral vascular disease, %	10.1	10.8	0.29	0
Renal failure, %	1.2	1.8	0.04	0.3
Neurological disease, %	8.1	8.8	0.23	0
LVEF <20, %	3.9	5.0	0.02	0.6
Preoperative medication use, %				
diuretics	23.2	22.7	0.56	0
beta blockers	74.4	66.8	≤ 0.001	0
calcium antagonists	33.3	21.5	≤ 0.001	0
Statines	29.3	34.3	≤ 0.001	0
ACE inhibitors	32.2	34.1	0.07	0
CABG, %	66.0	59.3	≤ 0.001	0
CABG off pump, %	9.0	8.1	0.18	0
Number of anastamoses, Median (10^{th};90^{th})	3 (0-5)	3 (0-5)	0.03	0
Aortic valve replacement, %	22.8	27.5	≤ 0.001	0
Mitral valve replacement, %	13.7	19.3	≤ 0.001	0
Other surgical procedure, %	1.2	1.6	0.04	0
ECC time, Median (10^{th};90^{th}), min	90 (45-196)	99 (49-215)	≤ 0.001	0
Aortic cross-clamp time, median (10^{th}; 90^{th})(min)	61 (36–127)	68 (40–138)	≤0.001	0

CCA denotes conventional cardiac anesthesia; FTCA denotes fast track cardiac anesthesia; LVEF denotes left ventricular ejection fraction; CABG denotes coronary artery bypass graft; ECC denotes extracorporal circulation

Results

The CCA group comprised 4020 patients and the FTCA Group 3969 patients. Baseline characteristics of the two groups are presented in **Table 1**. Although the median Euroscore was 5 in both groups, the 90th percentile of the Euroscore was 9 in the CCA group and 10 in the FTCA group, reflecting a higher risk profile in the FTCA group ($P < 0.001$). The FTCA group included more patients with hypertension, diabetes, renal failure, poor LVEF, and fewer patients using cardiovascular drugs preoperatively. Furthermore, the FTCA group had a median duration of CPB of 99 min vs 90 min in the CCA group ($P < 0.001$). There were no substantial differences between the two groups in age, gender, chronic obstructive pulmonary disease, peripheral vascular disease, or neurological disease. In the CCA group, 2655 (66.0%) patients underwent elective coronary artery bypass graft surgery versus 2360 (59.3%) in the FTCA group ($P < 0.001$).

Outcomes

Crude and adjusted mortality for the CCA and FTCA groups are listed in **Table 2**. There was no difference in the incidence of in-hospital mortality between the CCA and FTCA groups (CCA group, 1.9% vs FTCA group, 2.3%, crude odds ratio, 1.20, 95% CI 0.88–1.64, $P = 0.25$). This lack of difference in mortality rate persisted after adjusting for confounding variables (odds ratio, 0.92; 95% CI, 0.65–1.32, $P = 0.66$). We also performed a stratified analysis based on preoperative risk. After stratifying the patients into three different risk groups (Euroscore 1–4, 5–9, and >10), the actual and predicted mortality were compared. Across the three strata, the predicted mortality was higher than the actual mortality in both the CCA and FTCA group, but there were no differences between the two groups (**Fig. 1**).

The frequency of myocardial infarction, stroke, and renal dysfunction for the CCA and FTCA groups are listed in **Table 3**. There was no difference between the two groups in the rates of these complications.

The duration of mechanical lung ventilation, hospitalization in the ICU and total hospitalization are listed in **Table 4**. The FTCA group had a significantly shorter duration of mechanical ventilation ($P \leq 0.001$) compared with the CCA group, as

Table 2. *Crude and adjusted odds ratio for mortality, FTCA versus CCA group*

	Odds Ratio	(95% CI)
Crude	1.20	(0.88, 1.64)
Adjusted for age and female gender (1)	1.14	(0.83, 1.55)
Adjusted for 1 + duration of ECC (2)	0.96	(0.70, 1.34)
Adjusted for 2 + DM (3)	0.96	(0.69,1.33)
Adjusted for 3 + hypertension (4)	0.97	(0.70,1.34)
Adjusted for 4 + LVEF (5)	0.94	(0.67,1.32)
Adjusted for 5 + betablokkers	0.92	(0.66,1.29)
Adjusted for all confounders*	0.95	(0.67,1.35)

CCA denotes conventional cardiac anesthesia; FTCA denotes fast track cardiac anesthesia;
An odds ratio of >1.00 indicates an increased risk of mortality in the FTCA group.
*adjusted for differences in age, gender, hypertension (HT), diabetes mellitus (DM), pulmonary disease, peripheral vascular disease, renal failure (RF), neurological disease, left ventricle ejection fraction (LVEF), use of cardiovascular drugs, type of surgery, number of anastomoses, duration of extracorporal circulation and off-pump surgery.

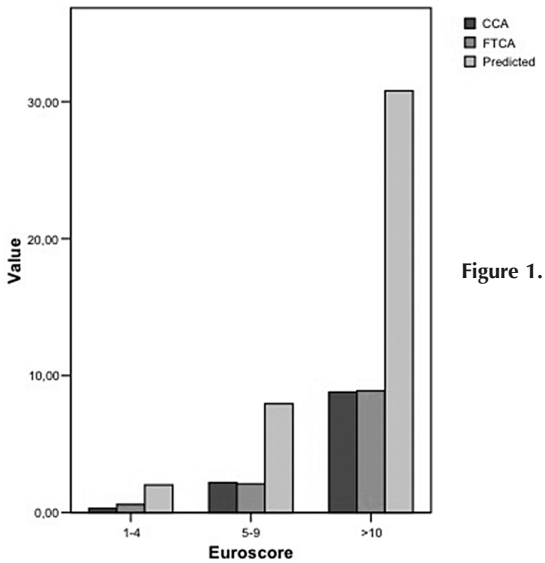

Figure 1. *Predicted mortality (%) and actual mortality (%) in CCA and FTCA group, in three different risk strata. CCA = conventional cardiac anesthesia; FTCA = fast-track cardiac anesthesia. Because of the stratification according to risk, the predicted risks of mortality are similar in the CCA and FTCA group.*

Table 3. *Iincidences and odds ratios of myocardial infarction, renal failure and stroke*

	CCA group n=4020	FTCA group n=3969	crude odds ratio	p-value	adjusted odds ratio*	p-value
Myocardial infarction	5.2%	5.5%	1.07	0.61	0.96	0.76
Renal failure	2.5%	3.1%	1.27	0.08	1.02	0.88
Stroke	0.9%	1.3%	1.52	0.06	1.31	0.24

CCA denotes conventional cardiac anesthesia; FTCA denotes fast track cardiac anesthesia;
An odds ratio of >1.00 indicates an increased risk in the FTCA group.
*adjusted for differences in age, gender, hypertension, diabetes mellitus, pulmonary disease, peripheral vascular disease, preoperative renal failure, neurological disease, left ventricular ejection fraction, use of cardiovascular drugs, type of surgery, number of anastomoses, duration of extracorporal circulation and off-pump surgery.

Table 4. *Mean and median ventilation time, intensive care and hospital stay, Geometric mean and estimated ratios of continuous outcomes*

		Duration of mechanical ventilation (h)	Duration of ICU stay (h)	Duration of hospital stay (days)
CCA n=4020	Mean (SD)	17.0 (43.3)	55.1 (195.5)	11.5 (63.2)
	Median (10^{th};90^{th})	12 (7-19)	22 (18-71)	6 (4-13)
	Geometric mean*	12.2	29.1	6.6
FTCA n=3969	Mean (SD)	13.3 (49.2)	74.3 (276.2)	13.5 (64.3)
	Median (10^{th};90^{th})	6 (3-16)	23 (18-95)	6 (4-18)
	Geometric mean*	6.7	31.1	7.3
Estimated ratio** (95% CI)	Unadjusted	0.55 (0.53,0.56)	1.07 (1.03,1.11)	1.10 (1.07,1.14)
	Adjusted***	0.52 (0.51,0.54)	1.07 (1.02,1.11)	1.09 (1.06,1.13)

Conventional cardiac anesthesia (CCA) versus fast track cardiac anesthesia (FTCA)
*Geometric mean = Exp (mean log duration time)
**Estimated ratio = ratio of the geometric mean in CCA versus FTCA
***adjusted for differences in age, gender, hypertension, diabetes mellitus, pulmonary disease, peripheral vascular disease, preoperative renal failure, neurological disease, left ventricle ejection fraction , use of cardiovascular drugs, type of surgery, number of anastomoses, duration of ECC and off-pump surgery

expressed by a ratio of geometric means significantly smaller than 1. For example, the ratio between the mean log (duration of mechanical ventilation) after adjustment for confounding was 0.53, implying that the mean log (mechanical ventilation) was 0.53 times shorter in the FTCA group. In contrast, the duration of hospitalization in the ICU ($P \leq 0.001$) and total duration of hospitalization was longer ($P \leq 0.001$) in the FTCA group compared with the CCA group, after adjustment for confounding.

Discussion

In this study, we compared the hospital outcomes of 3969 patients undergoing FTCA with 4020 historical control patients undergoing CCA. We found no differences in the frequency of hospital mortality or other major complications between patients receiving FTCA and patients receiving CCA.

Many cardiac surgical centers have embraced FTCA protocols to reduce ICU bed use and to reduce hospital costs associated with postoperative care.[9,10,21] It has been argued, however, that FTCA should not be adopted until further evidence of its safety is available, in particular because the prolonged intensive analgesia resulting from CCA is thought to reduce postoperative myocardial ischemia.[2] A number of randomized trials have indicated that FTCA is not associated with a higher risk for myocardial ischemia or other perioperative complications compared with conventional anesthetic methods.[5,6,10] However, the largest study to date included only 1012 patients, and thus did not contain enough statistical power to exclude a higher risk for mortality.[11] The authors of this article calculated that a sample size of 7844 patients would be needed to detect a possible difference in myocardial infarctions.[11] A meta-analysis of randomized trials evaluating FTCA included 10 trials with 1800 patients.[12] No differences were observed in 30-day mortality, myocardial infarction, or renal failure, but the authors recognized that even this meta-analysis was underpowered.[12] A later meta-analysis included 27 studies with 2821 patients.[13] Both meta-analyses predominantly included low-risk patients and were not designed to evaluate the safety of FTCA.

To our knowledge, the present cohort study is the first to evaluate the safety of FTCA in a large number of patients including all types of (elective) cardiac surgery.

The results are in accordance with previous studies and meta-analyses,[12,13] insofar as we found no effect of FTCA on perioperative mortality or other major complications. The present analysis of almost 8000 patients has resulted in comparatively narrow 95% CIs, reflecting more precise estimates of the risks of FTCA. Because of its retrospective design, however, this study is liable to many more sources of bias than the smaller randomized studies.

As expected, the duration of mechanical ventilation was shorter in the patients receiving FTCA. Surprisingly, this did not result in a shorter ICU stay. An explanation could be that most FTCA patients had their tracheas extubated in the afternoon and early evening after surgery, meeting the ICU discharge criteria at a time when hospital procedures prevented transfer to the postoperative ward. Even so, patients in the FTCA group were discharged from the hospital later than CCA patients. We have no explanation for this finding, other than that the higher rates of comorbidity in the former group required more postoperative care, or that there was a higher rate of other complications not collected in this study in the FTCA group (e.g., postoperative atrial fibrillation).

The present study has several limitations, particularly its retrospective design. Moreover, the control subjects were operated on earlier than the FTCA subjects. This means that time effects and many other sources of bias could have influenced the results. The limited number of complications and processes of care collected for this study do not preclude that factors other than anesthetic technique might have confounded the results. More risk factors were present in the FTCA group, which reflects the gradual increase over time in age and comorbidity of cardiac surgery patients. We have corrected for a large number of possible confounders, but it is likely that other, unknown, confounders are still present. Because it is not possible to correct for differences in unknown risk factors, it is conceivable that the present analysis underestimates or overestimates the safety of FTCA.

In conclusion, the present retrospective study of 7989 cardiac surgical patients showed no evidence of an increased risk of adverse outcomes in patients undergoing FTCA.

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Chapter 3

Thoracic epidural anesthesia for cardiac surgery: *a randomized trial*

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Abstract

Background

The addition of thoracic epidural anesthesia (TEA) to general anesthesia (GA) during cardiac surgery may have a beneficial effect on clinical outcomes. TEA in cardiac surgery, however, is controversial because the insertion of an epidural catheter in patients requiring full heparinization for cardiopulmonary bypass may lead to an epidural hematoma. The clinical effects of fast-track GA plus TEA were compared with those of with fast-track GA alone.

Methods

A randomized controlled trial was conducted in 654 elective cardiac surgical patients who were randomly assigned to combined GA and TEA *versus* GA alone. Follow-up was at 30 days and 1 yr after surgery. The primary endpoint was 30-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke.

Results

Thirty-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke was 85.2% in the TEA group and 89.7% in the GA group (P = 0.23). At 1 yr follow-up, survival free from myocardial infarction, pulmonary complications, renal failure, and stroke was 84.6% in the TEA group and 87.2% in the GA group (P = 0.42). Postoperative pain scores were low in both groups.

Conclusions

This study was unable to demonstrate a clinically relevant benefit of TEA on the frequency of major complications after elective cardiac surgery, compared with fast-track cardiac anesthesia without epidural anesthesia. Given the potentially devastating complications of an epidural hematoma after insertion of an epidural catheter, it is questionable whether this procedure should be applied routinely in cardiac surgical patients who require full heparinization.

High thoracic epidural anesthesia (TEA) during cardiac surgery promotes sympathicolysis and attenuates the stress response to surgery.[1,2] TEA may also enhance coronary perfusion.[3] TEA may therefore improve myocardial oxygen balance and reduce the incidence of tachyarrhythmias.[1] Through the same mechanism, the incidence of perioperative myocardial infarction could be reduced.[4] Moreover, the excellent analgesia that is associated with TEA facilitates early tracheal extubation and may prevent respiratory complications.[5–7] Along with these potential benefits of TEA, however, there is a risk for potential harm caused by an epidural hematoma that may develop after an epidural puncture and catheter insertion, especially in patients who need full heparinization for cardiopulmonary bypass.[8] An epidural hematoma may compress the spinal cord and lead to permanent neurologic injury including paraplegia if not detected and evacuated promptly.

Most randomized controlled studies on TEA in cardiac surgery have compared TEA with traditional opioid-based general anesthesia (GA). Over the last two decades, however, fast-track cardiac anesthesia has gained widespread popularity. Fast-track cardiac anesthesia is based on lower doses of shorter acting opioids and hypnotics than conventional cardiac anesthesia. Like TEA, fast-track cardiac anesthesia therefore facilitates early tracheal extubation and may decrease length of intensive care and hospital stay, but without the need to insert an epidural catheter.[9–11]

Despite the apparent advantages of both techniques separately, few studies have directly compared TEA and fast-track cardiac anesthesia. We therefore designed a randomized controlled trial to compare the effect of fast-track GA with TEA versus fast-track GA alone on major complications in patients undergoing elective cardiac surgery.

Materials and Methods

Study Population

The study was designed as a randomized clinical trial and is reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement.[12] The local human research ethics committees of the two participating centers (METC Isala Clinics, Zwolle, The Netherlands and METC MST, Enschede, The Netherlands)

approved of the study, and written informed consent was obtained from all patients. Patients were eligible if scheduled for elective cardiac surgery, including off-pump procedures. Exclusion criteria were age less than 18 yr, patient refusal, severe aortic valve stenosis, active neurologic disease, cutaneous disorders at the epidural insertion site, and preoperative impaired coagulation status precluding safe insertion of an epidural catheter (see **appendix 1**). Patients were randomly assigned the day before surgery to the GA group or the combined GA and TEA group. The random-allocation sequence was concealed and computer-generated in permuted unequal blocks, accessible through an Internet site. It was not possible for either the patient or the care providers to be blinded for treatment allocation. Major sensory differences are associated with epidural block, which are readily apparent to the patient, that preclude the patient from being blinded. Inserting a thoracic epidural catheter and treating the GA group with placebo infusion and the TEA group with bupivacaine/morphine infusion, "sham epidural," was rejected because of ethical and practical reasons.

Anesthetic and Operative Management

Patients allocated to the epidural group received a thoracic epidural catheter at least 4 h before heparinization. The epidural catheter was inserted in the thoracic 2–3 or thoracic 3–4 intervertebral space. The location of the catheter was verified before induction of GA with a test dose of lidocaine (Xylocain 2%, 3 ml). Before the start of GA, an epidural injection of 0.1 ml/kg was administered of a solution of 0.08 mg/ml morphine and 0.125 mg/ml bupivacaine, followed by a continuous infusion of 4–8 ml/h of the same solution. The GA technique for both groups consisted of 0.1–0.3 mg/kg etomidate, 0.15 mg/kg pancuronium, and 100–200 μg remifentanil at induction, followed by a continuous infusion of 1–4 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol or 1–1.5% sevoflurane, and 0.01 $mg \cdot kg^{-1} \cdot h^{-1}$ remifentanil. Hypnotic depth was monitored electroencephalographically with a bispectral index monitor. The bispectral index was kept between 40 and 60.

All patients underwent surgery through a median sternotomy. During cardiopulmonary bypass (CPB), myocardial protection was achieved with antegrade blood or crystalloid cardioplegia. One surgeon used a combination of retrograde and antegrade crystalloid cardioplegia for aortic valve surgery. CPB was managed

using nonpulsatile flow applied by a centrifugal pump and with the α-stat principle. A 40-μm filter was placed in the arterial line. Activated clotting time was kept more than 480 s throughout CPB. Body temperature was reduced to 28°–34°C during CPB, followed by rewarming to a temperature of 36°C before separation from CPB. After weaning from CPB protamine 300 U/kg was administered. At the conclusion of surgery, all patients were transported to the intensive care unit (ICU).

In the ICU sedation was continued until the patient had complied with the criteria for stopping the sedation listed in **appendix 2**. Postoperative analgesia in the TEA group was continued through the epidural catheter with continuous infusion of bupivacaine/morphine. The GA group received an injection of 0.2 mg/kg morphine 1 h before the end of the operation. In the ICU an infusion of 1–4 mg/h morphine was continued. The patients were extubated as soon as the extubation criteria listed in **appendix 2** were met. In the TEA group, the epidural catheter was removed before transfer to the general ward and after infusion of a 0.15-mg/kg morphine bolus. Postoperatively, all patients received paracetamol, 1 g every 6 h.

Outcomes

The primary endpoint was defined as 30-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke. The definitions of these complications are listed in **appendix 3**. All components of the primary endpoint were evaluated by an independent event committee blinded for randomization, consisting of a cardiologist, cardiothoracic surgeon, nephrologist, pulmonologist, and a neurologist. Secondary outcome measures were the combined endpoint at 1 yr and the occurrence of each component of the primary endpoint separately at 1 and 12 months. We also compared postoperative cardiac arrhythmias, resternotomy, transient ischemic attack, postoperative cardiac enzyme release, duration of mechanical ventilation, length of stay in the ICU, and total length of stay in the hospital. In addition, the time needed for a patient to meet the criteria of being nursed at the Medium Care level (**appendix 4**) was evaluated. A 10-cm visual analog scale[13] was used to assess patient comfort and pain control. Finally, we used the Euroquol[14] and ShortForm-36[15] questionnaires to assess quality of life 30 days after the operation.

Sample Size

The power calculation was based on the following: The primary endpoint was 30-day survival free from major complications, i.e., survival free from myocardial infarction, pulmonary complications, renal failure, and stroke. Based on the complication rate in our institution in 2003 and our experience during a pilot study in 30 patients, it was estimated that this would be present in the GA group in 85% of patients. An improvement to 92.5% with use of epidural block was considered clinically relevant and possibly achievable considering previously published studies.[3,16,17] With the (two-sided) α error set at 0.05 and the β error set at 0.2 (power of 80%), 304 patients per treatment group were needed. Taking into account a 5% loss to follow-up, we decided to recruit 320 patients per group.

Statistical Analysis

The aim of the main analysis was to compare the incidence of the primary outcome measure (30-day survival free from major complications) in both patient groups. Kaplan-Meier curves were used for graphic comparison. The primary outcome was compared using the chi-square statistic and presented as relative risk (RR) with 95% CI.

The secondary analyses included the comparison of each component of the primary outcome at 1 and 12 months and in-hospital complications, again by means of the chi-square test. The comparison of postoperative cardiac enzyme release was performed using linear mixed models for repeated measures. Continuous outcome measures include length of stay in the ICU, costs of care, and quality of life. Normally distributed data are presented as means with SD and were compared with a two-sample t test. Nonnormally distributed data are presented as medians with 10^{th} and 90^{th} percentile, and were compared using the Wilcoxon nonparametric test.

All data were analyzed according to the intention-to-treat principle, i.e., based on randomization. Statistical analysis was performed with SPSS software version 15 (SPSS Inc., Chicago, IL).

Results

From March 2004 to September 2007, we evaluated 4,920 patients for study participation in two hospitals. Six hundred fifty-six patients were randomly assigned, and 632 patients received the allocated treatment (**Figure 1**). One patient was

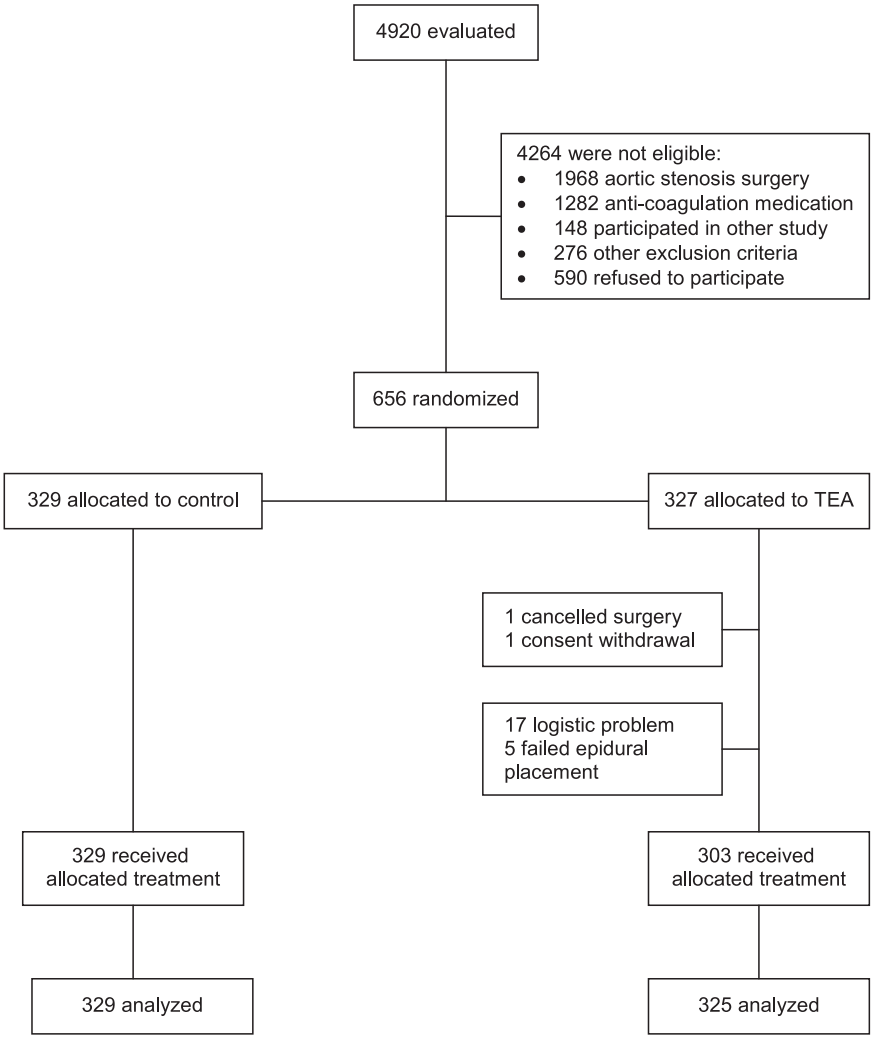

Figure 1. *Trial profile. TEA thoracic epidural anesthesia.*

Table 1. *Baseline characteristics and intra-operative data*

	TEA group n=325	GA group n=329	Missing data, %
Age (years)	65 (52-77)	64 (52-77)	0.4
Gender male	266 (82)	277 (84)	0.3
Euroscore	3 (0-7)	3 (1-7)	2.3
Weight (kg)	85 (66-102)	83 (67-100)	0
COPD	51 (16)	46 (14)	0
Hypertension	185 (57)	170 (52)	0
Diabetes mellitus	71 (22)	74 (22)	0
Peripheral vascular disease	33 (10)	27 (8)	0
Renal failure	2 (0.6)	1 (0.3)	0
Neurological disease	8 (2)	10 (3)	0
LVEF <20%	12 (4)	12 (4)	0.5
CABG	297 (91)	293 (89)	0
CABG off pump	47 (14)	41 (12)	0
Number of anastomoses	4 (2-5)	4 (2-5)	0
Aortic valve replacement	18 (6)	12 (4)	0
Mitral valve replacement	61 (19)	52 (16)	0
Other cardiac surgical procedure	13 (4)	12 (4)	0
CPB time (min)	87.5 (56-165)	92 (58-165)	0
Aortic cross clamp time (min)	58 (36-110)	61 (39-123)	0

Data are n (%) or median (interquartile range).

CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease. Neurological disease = history of stroke or other neurological dysfunction severely affecting ambulation or day-to-day functioning;
CPB = cardiopulmonary bypass; GA = general anesthesia; LVEF = left ventricular ejection fraction;
TEA = thoracic epidural anesthesia.

Table 2. *Primary Endpoint and separate components after 30 day and 1 year follow-up*

Endpoint	30 day follow-up TEA group n=325	GA group n=329	RR (95% CI)	*p* value*
Postoperative death	2 (0.6)	1 (0.3)	2.02 (0.18-22.2)	0.56
Pulmonary complications	30 (9.2)	19 (5.8)	1.60 (0.92-2.78)	0.12
Acute myocardial infarction	16 (4.9)	16 (4.9)	1.01 (0.52-1.99)	0.98
Renal failure	12 (3.7)	5 (1.5)	2.43 (0.87-6.82)	0.14
Stroke	2 (0.6)	1 (0.3)	2.02 (0.18-22.2)	0.56
Any event	48 (14.8)	34 (10.3)	1.43 (0.95-2.16)	0.23

Data are n (%). * X^2 test.

A risk ratio of >1.00 indicates an increased risk in the TEA group. CI = confidence interval; GA = general anesthesia;
RR = relative risk; TEA = thoracic epidural anesthesia.

excluded because his surgery was canceled, and one patient withdrew his consent after randomization. Twenty-two patients allocated to the TEA group did not have an epidural catheter placed: 17 patients because of logistic reasons and five patients because the attending anesthesiologist was unable to place the catheter in the epidural space. These 22 patients were analyzed according to their random assigments. The number of isolated coronary artery bypass graft patients in the TEA group was 236, of whom 47 underwent an off-pump procedure. The number of isolated coronary artery bypass graft patients in the GA group was 241, of whom 41 underwent an off-pump procedure. No patient suffered an epidural hematoma or abscess. Patient and surgical characteristics are listed in **table 1**.

Primary Outcome Measure

Thirty-day follow-up was complete. The frequency of events is shown in **table 2** and illustrated by the Kaplan-Meier curve (**Figure 2**). Thirty-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke was 85.2% in the TEA group and 89.7% in the GA group (RR 0.95; $P = 0.23$).

Secondary Outcome Measures

At 30-day follow-up, two patients had died in the TEA group and one in the GA group ($P = 0.56$). Thirty patients in the TEA group and 19 patients in the GA group had suffered a pulmonary complication ($P = 0.12$), and in both groups, 16 patients had a myocardial infarction ($P = 0.98$). Renal failure occurred in five patients in the GA

1 year follow-up TEA group n=325	GA group n=327	RR (95% CI)	*p* value*
3 (0.9)	7 (2.1)	0.43 (0.11-1.65)	0.21
33 (10.2)	21 (6.4)	1.58 (0.94-2.67)	0.11
17 (5.2)	18 (5.5)	0.95 (0.50-1.81)	0.88
12 (3.7)	5 (1.5)	2.41 (0.86-6.78)	0.10
5 (1.5)	4 (1.2)	1.26 (0.34-4.64)	0.73
50 (15.4)	42 (12.8)	1.20 (0.82-1.75)	0.42

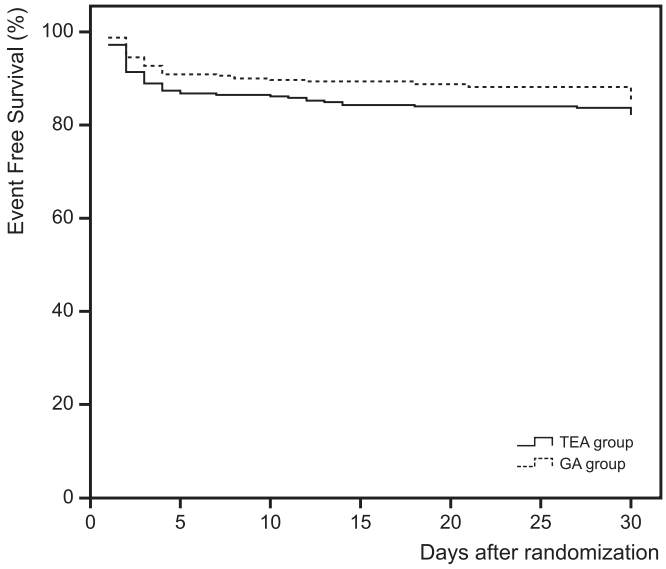

Figure 2. *Thirty-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke, P = 0.22 by the log-rank test. GA = general anesthesia; TEA = thoracic epidural anesthesia.*

group and in 12 patients in the TEA group (P = 0.14). Two patients in the TEA group and one patient in the GA group suffered a stroke (*P* = 0.56). At 1-yr follow-up, two patients were lost to follow-up. Fifty (15.4%) patients in the TEA group had died or had at least one complication, compared with 42 (12.8%) in the GA group (*P* = 0.42).

The incidence of cardiac arrhythmias was similar across the two groups (**table 3**). A total of 156 (48%) patients in the TEA group and 173 (53%) in the GA group developed supraventricular arrhythmia postoperatively (P = 0.24). This was 32 (10%) versus 46 (14%) for ventricular arrhythmia (*P* = 0.12).

None of the patients in the TEA group suffered a transient ischemic attack versus 6 (2%) patients in the GA group (*P* = 0.04). Resternotomy was necessary in seven (2%) patients in the TEA group and 13 (4%) patients in the GA group. No significant difference of creatine kinase muscle-brain isoenzyme plasma concentration was found (the difference of GA in comparison with TEA group for all measurements was 0.32 U/l, P = 0.52).

Table 3. *The effect of TEA versus GA on Secondary Endpoints*

Endpoint	TEA group n=325	GA group n=329	RR (95% CI)	*p* value
VT	32 (10)	46 (14)	0.73 (0.48-1.12)	0.12*
SVT	156 (48)	173 (53)	0.91 (0.78-1.06)	0.24*
Cardiac arrest	1 (0.3)	3 (0.9)	0.34 (0.04-3.23)	0.62*
TIA	0 (0)	6 (2)	0.50 (0.46-0.54)	0.04†
Resternotomy	7 (2)	13 (4)	0.55 (0.22-1.35)	0.26*
Epidural haematoma or abscess	0	0		

Data are n (%). * X^2 test. † Fisher exact test.

A risk ratio of >1.00 indicates an increased risk in the TEA group. CI = confidence interval; GA = general anesthesia; RR = relative risk; SVT = supraventricular tachycardia; TEA = thoracic epidural anesthesia; TIA = transient ischemic attack; VT = ventricular tachycardia;

The duration of mechanical ventilation, length of stay in the ICU, total length of stay in the hospital, and the time until the patient met the criteria of being nursed at the Medium Care level were similar for both groups and are listed in **table 4**.

Median pain scores on the first postoperative day were 2 in the TEA group and 3 in the GA group ($P < 0.001$). On the second and third day after surgery, the median pain scores were 2 in both groups (**table 4**). There were no marked differences in self-reported quality of life at 1 month between the TEA and GA group (data not presented).

Our per protocol analysis showed results similar to the intention-to-treat analysis: 30-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke was 85.7% in the TEA group and 88.4% in the GA group (RR 0.97; 95% CI 0.92–1.03; $P = 0.40$).

We have performed an additional subgroup analysis for the coronary artery bypass graft patients who underwent an off-pump procedure. In the TEA group, there were 47 off-pump procedures, and in the GA group, 41 off-pump procedures; in each group, there were four events that resulted in RR of 0.88 (95% CI 0.23–3.33; $P = 0.84$) for survival free from events.

Table 4. *The effect of TEA versus GA on duration of mechanical ventilation, ICU and hospital stay and pain at rest*

	TEA group n=325	GA group n=329	*p* value
Duration of mechanical ventilation, (h)	5 (3-12)	5 (3-11)	0.58
Duration of ICU hospitalisation (h)	22 (17-46)	22 (17-44)	0.21
MC level reached (h)	5 (3-16)	5 (3-21)	0.82
Duration of hospitalisation (days)	6 (4-10)	6 (4-11)	0.62
VAS day 1	2 (0-6)	3 (0-7)	<0.001
VAS day 2	2 (0-5)	2 (0-6)	<0.001
VAS day 3	2 (0-5)	2 (0-5)	0.86

Data are medians (interquartile range). * Wilcoxon rank sum test.

GA = general anaesthesia; ICU = intensive care unit; MC = medium care; TEA = thoracic epidural anaesthesia; VAS = visual analogue scale pain score.

Discussion

This randomized trial in 654 cardiac surgical patients evaluated the effect of TEA on major clinical outcomes at 1- and 12-month follow-up. The principal finding was that we were not able to show a measurable benefit of TEA combined with GA, compared with GA alone. There was even a trend toward a higher number of major complications in the TEA group. In addition, the duration of mechanical ventilation, length of stay in the ICU, length of stay in the hospital, and quality of life at 30-day follow-up were similar for the two groups. Statistically significant lower pain scores were observed in the TEA group on the first and second postoperative days, but the absolute pain scores were very low in both study groups.[18]

The use of TEA in cardiac surgery is controversial because the need for systematic heparinization during cardiopulmonary bypass may increase the risk of epidural hematoma.[8] This devastating complication is believed to be rare, but the incidence is likely to be underreported.[19,20] Furthermore, hypotension due to TEA-associated sympathicolysis, both intraoperatively and postoperatively, might have

deleterious effects for patients with carotid artery stenosis. The use of TEA also has logistic and manpower implications because of the need to insert the epidural catheter several hours before surgery, more postoperative monitoring, and consequently increased costs.

The use of TEA for cardiac surgery is nevertheless still being advocated, because a trial by Scott et al.[1] in 420 patients and a systematic review by Liu et al.[21] reported benefits of TEA on pulmonary complications and cardiac arrhythmias. There are several plausible explanations as to why the current study could not confirm the benefits of TEA that were found in older studies. This includes the play of chance and publication bias.

A more likely explanation, however, is that the older studies compared TEA with a light GA to conventional anesthesia with high-dose, long-acting opioids. In contrast, the current study compared TEA with fast-track general cardiac anesthesia that is based on lower doses of short-acting opioids and showed that both anesthetic techniques offer the same benefits of early extubation and a low rate of pulmonary complications. The fact that early tracheal extubation with a reduction in pulmonary complications can also be achieved using fast-track general cardiac anesthesia[22] without TEA, makes TEA less relevant. Although TEA is also thought to reduce the incidence of perioperative myocardial infarction through sympathicolysis,[1–4] our results do not confirm these previously reported cardioprotective effects of TEA.

Although this study is the largest randomized clinical trial to date evaluating TEA in cardiac surgery, there are several limitations. First, to facilitate early mobilization of the patients, we removed the epidural catheter within 48 h after surgery. This time span is shorter than in most previous study protocols, in which the epidural catheter remained in situ for 4 days. As a result, one might argue that we provided insufficient perioperative sympathicolysis, although most ischemic complications occur within the first 48 h postoperatively. This may also explain the absence of a positive effect on the incidence of tachyarrhythmias, although one could also argue that there are better and less invasive alternatives for preventing postoperative arrhythmias, such as -blockers or amiodarone.[23] A second limitation of the study is that the median Euroscore in both groups was low, representing a relatively healthy population of cardiac surgical patients. Sicker patients are thought to benefit more from TEA,[24] but unfortunately, these patients also most often have

contraindications for the application of this technique, in particular because of an impaired coagulation status. Twenty-six percent of our patient population was not eligible for the TEA technique because their clinical condition required the perioperative continuation of their anticoagulation therapy. Another 40% was not eligible owing to severe aortic valve stenosis, leaving only 34% of our patient population eligible for TEA.

The study was powered for a combined endpoint, survival free from major complications. The validity of combined endpoints depends on similarity in patient importance, treatment effect, and number of events across the components of the combined endpoint. Pulmonary complications occurred more frequently, but repeating the analyses without the pulmonary complication component, resulted in a point estimate that reflects no benefit of TEA (RR 1.14; 95% CI 0.61-2.13; P = 0.61). However, because of the lower number of events in this analysis, the CI is even wider and therefore an actual benefit of TEA still cannot be excluded with these data. This also applies to the subgroup analysis of the coronary artery bypass graft patients who underwent an off-pump procedure: the CI is wide and an actual benefit of TEA in off-pump patients cannot be excluded. A final limitation of the current study is that the definitions of myocardial infarction and renal failure, which were prospectively set at the time of the study design, are now considered outdated. When we applied the newer definitions in a post hoc analysis, this did not change the results.[25,26]

In conclusion, we were unable to demonstrate a clinically relevant benefit of TEA on the frequency of major complications after elective cardiac surgery, compared with fast-track cardiac anesthesia without epidural anesthesia. Given the potentially devastating complications of an epidural hematoma after insertion of an epidural catheter, it is questionable whether this procedure should be applied routinely in cardiac surgical patients who require full heparinization.

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Appendix 1: Impaired coagulation status precluding safe insertion of an epidural catheter

Insertion of an epidural catheter is not allowed if a patient meets any of the following criteria:

1. History of a bleeding disorder
2. Preoperative laboratory investigations:
    - International Normalized Ratio >1.8
    - Platelet count $<80x10^9/l$
    - activated partial thromboplastin time >1.5 normal value
    - Ureum >15mmol/l
3. Use of any of the following medication:
    - Platelet aggregation inhibitors
        - Clopidogrel administered in the last 120 hours
        - Acetylsalicylic acid administered in the last 72 hours or, if combined with low molecular weight heparines
        - GPIIB/IIIa-receptorantagonists administered in the last 48 hours
    - Coumarine derivatives associated with an International Normalized Ratio > 1.8
    - Low molecular weight heparin
        - Therapeutic dosage administered in the last 24 hours
        - Prophylactic dosage administered in the last 10 hours
    - Intravenous Heparine infusion associated with an activated partial thromboplastin time > 1.5 times the normal value
    - Thrombolytic/ Fibrinolytic agents

It is allowed to include a patient in the trial if it is expected that his or her coagulation status is restored at the time of catheter insertion. The criteria above were checked again at the time of catheter insertion, if a patient was randomized to thoracic epidural anesthesia group.

Appendix 2: Intensive care unit protocols

Criteria for discontinuing the sedation in the Intensive care unit

- Core temperature >36°C
- Difference core/skin temperature <5°C
- Hemodynamic stability without the use of major doses of vasoactive medication
- Chest drain output <1.5 ml/kg/h

Criteria for extubation

- Presence of deglutition reflex
- Breathing minute volume > 80ml/kg/min
- Breathing frequency > 10/min and < 20/min
- Oxygen saturation > 94% with Fraction of Inspired Oxygen ≤ 40%

Appendix 3: Definitions of the components of the primary endpoint

Endpoint	Definition
Postoperative death	Death from any cause within 30 days of surgery
Pulmonary complication	• Pneumonia: clinical symptoms consistent with pneumonia and (1) positive microbiologic criteria of pneumonia, or (2) positive radiographic criteria of pneumonia:27 1. clinical symptoms: chest pain, cough, or typical ausculatory findings, with or without fever or leukocytosis 2. microbiologic criteria: (a) purulent expectorated sputum with identification by microscopy or culture of a predominant suspected pathogen; or (b) transtracheal aspirate with identification by microscopy or culture of a predominant suspected pathogen; or (c) pleural fluid or direct lung aspirate with identification by microscopy or culture of a predominant suspected pathogen; or (d) positive blood culture with identification by microscopy or culture of a predominant suspected pathogen, in absence of another source of bacteriemia 3. radiographic criteria: the presence of a new infiltrate on chest radiograph • Prolonged artificial ventilation: patient intubated for >24h postoperatively
Acute myocardial infarction	Creatine kinase muscle-brain isoenzymes >75 U/l (5 times upper limit of normal level) and peak creatine kinase muscle-brain isoenzymes /creatine kinase ratio of >10% or a new Q wave infarction
Renal failure	Rise in serum creatinine of 50% of the preoperative value, or need for hemofiltration or dialysis

Stroke	A new motor or sensory deficit of central origin, persisting more than 24 hours, preferably confirmed by computed tomography -scan; resulting in a drop of two points on the Rankin scale

Appendix 4: Intensive care and medium care level criteria

	Intensive care	**Medium care**	**Time**
Breathing			
Detubation	NO ☐	YES ☐	___:___
Saturation >92%	NO ☐	YES ☐	___:___
Hemodynamics			
According level	NO ☐	YES ☐	___:___
Dobutamine <25mg/h			
Dopamine <20mg/h			
Noradrenaline <120 g/h			
Milrinone <0.4mg/h			
Nitroglycerin <2mg/h			
Nicardipine <4mg/h			
Ketanserin <4mg/h			
Temperature			
>36˚C	NO ☐	YES ☐	___:___
Drainproduction			
<1ml/h/kg	NO ☐	YES ☐	___:___
Urineproduction			
>0.5ml/h/kg	NO ☐	YES ☐	___:___
Consciousness			
Ramseyscore 2-3	NO ☐	YES ☐	___:___
Each of the 7 criteria "YES"			___:___

patient has reached the "Medium care level"

Chapter 4

Epidural Analgesia for Cardiac Surgery

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Abstract

Background

A combination of general anaesthesia (GA) with thoracic epidural analgesia (TEA) may have a beneficial effect on clinical outcomes by reducing the risk of perioperative complications after cardiac surgery.

Objectives

The objective of this review was to determine the impact of perioperative epidural analgesia in cardiac surgery on perioperative mortality and cardiac, pulmonary or neurological morbidity. We performed a meta-analysis to compare the risk of adverse events and mortality in patients undergoing cardiac surgery under general anaesthesia with and without epidural analgesia.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 12) in *The Cochrane Library*; MEDLINE (PubMed) (1966 to November 2012); EMBASE (1989 to November 2012); CINHAL (1982 to November 2012) and the Science Citation Index (1988 to November 2012).

Selection criteria

We included randomized controlled trials comparing outcomes in adult patients undergoing cardiac surgery with either GA alone or GA in combination with TEA.

Data collection and analysis

All publications found during the search were manually and independently reviewed by the two authors. We identified 5035 titles, of which 4990 studies did not satisfy the selection criteria or were duplicate publications, that were retrieved from the five different databases. We performed a full review on 45 studies, of which 31 publications met all inclusion criteria. These 31 publications reported on a total of 3047 patients, 1578 patients with GA and 1469 patients with GA plus TEA.

Main results

Through our search (November 2012) we have identified 5035 titles, of which 31 publications met our inclusion criteria and reported on a total of 3047 patients. Compared with GA alone, the pooled risk ratio (RR) for patients receiving GA with TEA showed an odds ratio (OR) of 0.84 (95% CI 0.33 to 2.13, 31 studies) for mortality; 0.76 (95% CI 0.49 to 1.19, 17 studies) for myocardial infarction; and 0.50 (95% CI 0.21 to 1.18, 10 studies) for stroke. The relative risks (RR) for respiratory complications and supraventricular arrhythmias were 0.68 (95% CI 0.54 to 0.86, 14 studies) and 0.65 (95% CI 0.50 to 0.86, 15 studies) respectively.

Authors' conclusions

This meta-analysis of studies, identified to 2010, showed that the use of TEA in patients undergoing coronary artery bypass graft surgery may reduce the risk of postoperative supraventricular arrhythmias and respiratory complications. There were no effects of TEA with GA on the risk of mortality, myocardial infarction or neurological complications compared with GA alone.

Plain language summary

Epidural analgesia for heart surgery

The use of thoracic epidural analgesia (TEA) in heart surgery is controversial. TEA produces a high level of pain relief and may reduce some of the adverse effects that are associated with heart surgery. Along with these potential benefits of TEA there is a widespread fear that TEA could cause bleeding into the epidural space (haematoma). We have conducted a review of medical trials to compare the effect of general anaesthesia (GA) alone with GA in combination with epidural analgesia on major complications in patients undergoing elective heart surgery. We identified 5035 titles of which 31 publications met all the inclusion criteria. These 31 publications reported on a total of 3047 patients, 1578 patients with GA and 1469 patients with TEA as well as GA. The risks of death, heart attack and stroke were not statistically significant, however our analysis showed statistically significant reductions in the risk of arrhythmias and pulmonary complications. Despite this,

our findings must be viewed with caution. Epidural analgesia in heart surgery remains controversial in the absence of a sufficiently large and statistical significant effect on mortality, stroke, or myocardial infarction and while the risks are unclear.

Background

Description of the condition

Advances in anaesthesiology, surgery, extracorporeal perfusion techniques, and perioperative care medicine have resulted in a reduced risk of perioperative complications and subsequently have improved postoperative outcomes after cardiac surgery (Coriat 2001). The addition of thoracic epidural analgesia to general anaesthesia has been suggested to benefit patients after cardiac surgery in several trials (Royse 2003; Scott 2001). However, the technique is controversial because the insertion of an epidural catheter in patients requiring full heparinization for cardiopulmonary bypass may lead to an epidural haematoma.

Description of the intervention

A combination of general anaesthesia (GA) with thoracic epidural analgesia (TEA) may further improve outcomes after cardiac surgery (Djaiani 2000; Oxelbark 2001; Zarate 2000). TEA is a technique by which continuous infusion of local anaesthetic and opioid is given in the epidural space at high thoracic levels. TEA produces a high level of analgesia and may reduce the adverse effects that are associated with heart surgery.

A possible complication of TEA includes spinal cord compression, caused by a haematoma or abscess, which can result in paraplegia. Systemic anticoagulation is needed during cardiopulmonary bypass and may increase the incidence of epidural haematoma related to the use of an epidural catheter (Bang 2011; Ho 2000; Rosen 2004).

How the intervention might work

TEA may result in enhanced coronary perfusion, improved myocardial oxygen supply and a reduced incidence of dysrhythmias, via intense blockade of the

sympathetic nervous system (Royse 2003; Scott 2001). Through the same mechanism, the size of perioperative myocardial infarction may be reduced (Beattie 2003; Scott 2001; Turfrey 1997). TEA may also shorten the duration of tracheal intubation as well as the time spent in an intensive care unit and hospital, which could have major economic benefits (Bowler 2002; Nicholson 2002; Priestley 2002), and may prevent pulmonary complications (Ballentyne 1998; Stenseth 1996).

Why it is important to do this review

A previous meta-analysis of 15 trials by Liu et al (Liu 2004) demonstrated fewer respiratory complications and dysrhythmias in patients assigned to TEA, but failed to show an effect of TEA on mortality or myocardial infarction. However, more trials comparing TEA and conventional anaesthesia for cardiac surgery are now available (Hansdottir 2006; Lundstrom 2005), and these were considered for inclusion in the present review.

The present meta-analysis could elucidate whether or not TEA has a benefit on relevant outcomes such as mortality and myocardial infarction. It does not clarify the clinical costs of TEA, which range from patient discomfort during epidural puncture to paraplegia. When the meta-analysis shows a significant benefit on mortality or other very relevant outcomes, whilst catastrophic complications are not observed in the patient samples that are included, one can argue that TEA should be used; although the safety of the technique has not been completely quantified. On the other hand, if no relevant benefits can be demonstrated, one could argue that TEA should not be applied in cardiac surgery as long as its safety remains unclear.

Objectives

The objective of this review was to determine the impact of perioperative epidural analgesia in cardiac surgery on perioperative mortality and cardiac, pulmonary or neurological morbidity.

METHODS

Types of studies

We included randomized controlled trials (RCT).

Types of participants

We included adult patients undergoing general anaesthesia (GA) for cardiac surgery with and without thoracic epidural analgesia (TEA).

Types of interventions

We included trials that compared cardiac surgery with and without TEA. We excluded studies which compared cardiac surgery with and without spinal anaesthesia.

Types of outcome measures

We did a separate meta-analysis for each of the outcomes listed below. We measured all outcomes at two weeks and six months after surgery.

Primary outcomes

1. Risk of mortality
2. Risk of myocardial infarction

We defined myocardial infarction as myocardial specific creatine kinase (CKMB) measurement greater than 50 U/l and peak CKMB/creatine kinase ratio of greater than 10%, or a new Q wave infarction.

Secondary outcomes

1. Risk of in-hospital pulmonary complications (respiratory insufficiency or pneumonia)
2. Risk of cardiac events (supraventricular or ventricular dysrhythmias or cardiac arrest)
3. Risk of neurological complications (epidural haematoma or abscess, transient ischaemic attack or cerebrovascular accident)

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 12) in *The Cochrane Library*, MEDLINE (PubMed) (1966 to November 2012); EMBASE (1989 to November 2012); CINAHL (1982 to November 2012); and the Web of Science (SCI/SSCI) (1988 to November 2012) with relevant search terms relating to heart surgery procedures and neuraxial anaesthetic techniques.

We combined these search terms with a sensitive methodological filter (Appendix 1, see Chapter 5) for randomized trials, found in Chapter 6 of the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 (Higgins 2011).

Searching other resources

We screened reference lists from retrieved randomized trials, meta-analyses and systematic reviews to identify additional trials. We conducted a search by author for any individual who appeared as an author of two or more relevant articles.

We used PubMed's 'See related articles' function with relevant trial reports to search for additional references. In addition, we included the references of the following reviews on cardiac surgery and epidural analgesia (Ballentyne 1998; Chaney 1997; Liu 2004; Meissner 1997; Rodgers 2000).

Data collection and analysis

Selection of studies

Two authors (VS and MP) independently examined the titles and, where available, abstracts of studies identified using the search strategy, and handsearched reference lists. We retrieved any full studies that met our predefined inclusion criteria. If our judgements on inclusion or exclusion were split we discussed the article until we achieved consensus, with the help of a third review author (DD) where necessary.

Data extraction and management

For each title, abstract or full-text article, the two review authors (VS and MP) used

a standardized selection form (Appendix 2, see Chapter 5) to extract data independently. The review authors were not blinded to the authors' or journals' names. All included trials were thoroughly studied by the two authors using the data collection form. The items that were scored were also listed in a standardized form.

Assessment of risk of bias in included studies

Two review authors (VS and MP) independently assessed the quality of the studies according to the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.0.2 (Higgins 2011). We graded the risk of bias for each study in the categories of sequence generation, allocation concealment, blinding, incomplete outcome data and selective reporting. We graded each category as low risk (yes), high risk (no), or unclear risk of bias.

Measures of treatment effect

All outcomes were dichotomous. Both the sample sizes and the numbers of patients with events were summed across groups (Higgins 2011).

Unit of analysis issues

The odds were calculated per treatment group for all outcomes. The Peto odds ratio was used as the pooled measure of effect.

Dealing with missing data

We contacted the first authors of included trials to obtain missing data that were necessary for the meta-analysis.

Assessment of heterogeneity

When significant heterogeneity was suspected from the I^2 statistic (I^2 = 25% or higher) for heterogeneity, or from visual inspection of the results, we used a random-effects model for pooling. In this model the RR for every trial is weighted by the reciprocal of its variance, whereby studies with a smaller standard error were given more weight than those with a larger standard error. We have explored sources of heterogeneity by looking at possible differences in clinical and methodological factors across the trials.

Assessment of reporting biases

We assessed publication bias for the two primary outcomes by both graphical inspection of the funnel plot and statistical testing of plot asymmetry, using a 95% confidence interval.

Data synthesis

We used RevMan 5.1 for quantitative analysis. As all our outcomes were binary data, we related the numbers reporting an outcome in each group to the numbers at risk to derive a relative risk (RR) and 95% confidence interval, or as an odds ratio (OR) through the Peto method where appropriate. We applied the Peto method to obtain the OR for mortality as there were 15 trials with zero events, and for the myocardial infarction analysis as numbers of events were very small. As a general rule, we used a fixed-effect model for calculations of summary estimates and their 95% confidence intervals (CI).

Subgroup analysis and investigation of heterogeneity

We planned an exploratory subgroup analysis that included trials with two different methods of GA, the fast-track protocol (short-acting opioids) versus regular GA. We also performed a subgroup analysis on the results for mortality at the two-week period, for high and low risk of bias studies. A low risk of bias study was defined as a study where no categories or only the detection bias category (blinding of patient and medical personnel) were inadequate. A high risk of bias study was defined as a study where any of the other bias categories (sequence generation, allocation concealment, incomplete outcome data and selective reporting) were inadequate.

Sensitivity analysis

We conducted a sensitivity analysis in low risk of bias trials to estimate the robustness of the results for mortality at the two-week period.

Results

Description of studies

See Characteristics of included studies and Characteristics of excluded studies.

Results of the search

We identified 5035 titles, of which 4990 studies did not satisfy the selection criteria or were duplicate publications, from the five different databases (**Figure 1**).

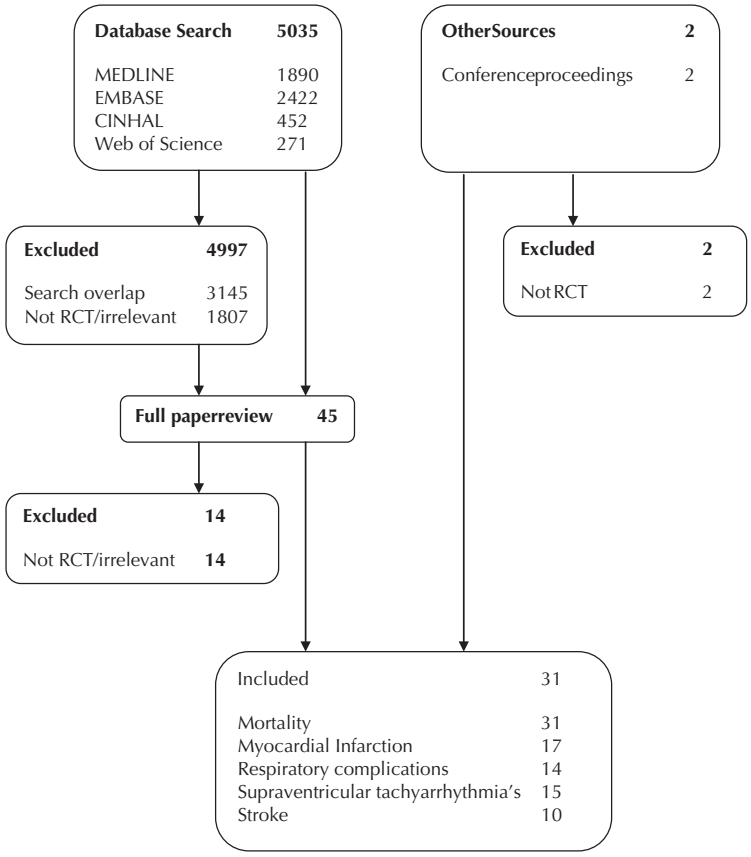


Figure 1. *Study flow diagram.*

Included studies

We performed a full review of 45 studies, of which 31 publications met our inclusion criteria (see Characteristics of included studies). These 31 publications reported on a total of 3047 patients, 1578 patients with GA and 1469 patients with GA plus TEA. There were no trials in languages other than English identified.

Excluded studies

We excluded 14 of the 45 assessed studies for the reasons shown in the table Characteristics of excluded studies.

Risk of bias in included studies

Incomplete data were rare and when present this was reported, making attrition bias minimal. Blinding of outcome assessors was rarely mentioned and was treated as a possible risk of detection bias.

Allocation (selection bias)

The risk of selection bias was unclear. We have included only randomized controlled trials in this meta-analysis, however the method of randomization and allocation concealment were not always clearly stated (**Figure 2; Figure 3**).

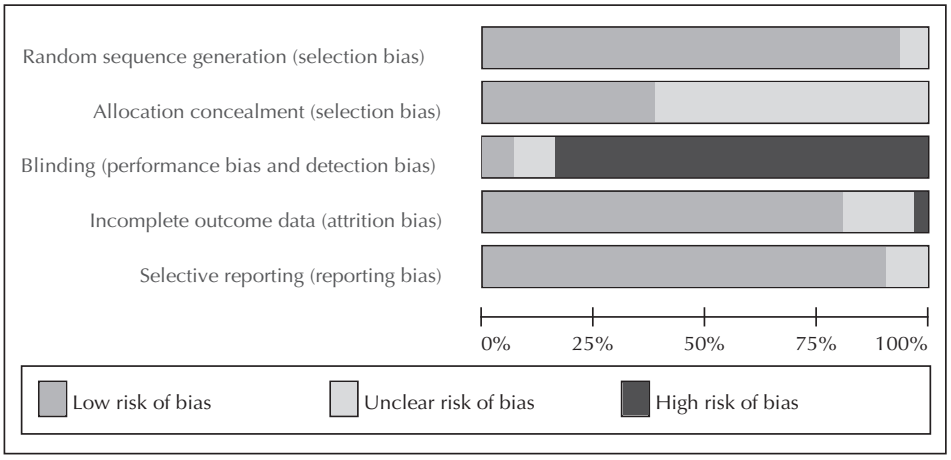


Figure 2. *Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.*

Blinding (performance bias and detection bias)

Performance bias was high in this meta-analysis as the patients and personnel were not blinded in 85% of the trials (**Figure 2; Figure 3**).

Incomplete outcome data (attrition bias)

There was a minimal possibility of attrition bias as the outcome data were not complete in six trials (see **Figure 2; Figure 3**).

Selective reporting (reporting bias)

There was a low risk of reporting bias (**Figure 2; Figure 3**).

Other potential sources of bias

Other potential sources of bias were not identified.

Effects of interventions

Mortality

All 31 studies reported mortality (see Characteristics of included studies). Of those studies, 29 (Bach 2002; Bakhtiary 2007; Barrington 2005; Berendes 2003; Brix-Christensen 1998; Caputo 2009;Caputo 2011; de Vries 2002; El-Baz 1987; Fillinger 2002; Hansdottir 2006; Heijmans 2007; Kendall 2004; Kilickan 2006; Kirno 1994; Lagunilla 2006; Liem 1992; Lundstrom 2005; Moore 1995; Nygard 2004; Onan 2011; Rein 1989; Royse 2003; Scott 2001; Sharma 2010; Stenseth 1994; Stenseth 1996; Svircevic 2011; Tenling 1999) reported on mortality

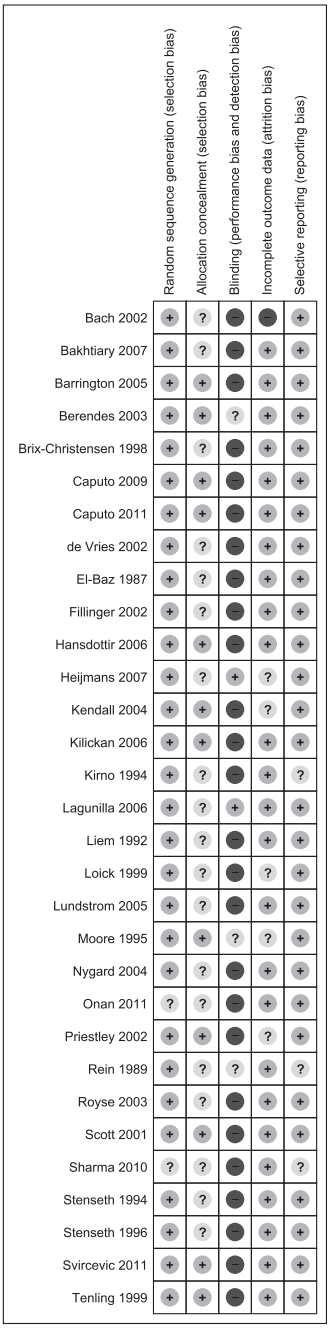


Figure 3. *Risk of bias summary: review authors' judgements about each risk of bias item for each included study*

within two weeks after surgery (**Analysis 1.1**), and two studies (Loick 1999; Priestley 2002) reported mortality after six-months follow-up (**Analysis 1.2**). Combining data from 29 studies showed no difference in the rate of mortality two weeks after surgery for patients receiving TEA with GA versus GA (OR 0.84; 95% CI 0.33 to 2.13) (**Analysis 1.1**). Of the 29 included studies, 17 did not provide an estimate resulting in the overall OR being based on 12 studies. The meta-analysis of studies that evaluated mortality six months after surgery included two studies with 170 patients (I^2 = 0%) and yielded an RR of 1.35 (95% CI 0.08 to 22.83) (Analysis 1.2).

Subgroup analysis showed that the risk of mortality at the two-week period in both low (Barrington 2005; Berendes 2003; Caputo 2009; Caputo 2011; Hansdottir 2006; Kilickan 2006; Moore 1995; Scott 2001; Svircevic 2011; Tenling 1999) and high (Bach 2002; Bakhtiary 2007; Brix-Christensen 1998; de Vries 2002; El-Baz 1987; Fillinger 2002; Kendall 2004; Kirno 1994; Liem 1992; Lundstrom 2005; Nygard 2004; Onan 2011; Rein 1989; Royse 2003; Sharma 2010; Stenseth 1994; Stenseth 1996) risk of bias groups was not significantly different between the patients receiving TEA compared with patients receiving GA alone (OR 0.83; 95% CI 0.25 to 2.70 and OR 0.85; 95% CI 0.19 to 3.79, respectively). The explanatory subgroup analysis, which included trials with two different methods of general anaesthesia, the fast-track protocol (short-acting opioids) versus regular GA, was not feasible due to lack of data.

Sensitivity analysis (**Analysis 6.1**) showed that the risk of mortality within two weeks after surgery in low risk of bias studies was not different between the groups (OR 0.83; 95% CI 0.25 to 2.70).

Myocardial infarction

Seventeen studies reported on acute myocardial infarction (AMI). Fifteen studies (Bakhtiary 2007; Barrington 2005; Caputo 2009; Caputo 2011; de Vries 2002; Fillinger 2002; Hansdottir 2006; Heijmans 2007; Kendall 2004; Liem 1992; Onan 2011; Scott 2001; Stenseth 1994; Stenseth 1996; Svircevic 2011), which included 2127 patients, reported AMI after two weeks of follow-up (**Analysis 2.1**). There was no difference in the rate of AMI between groups of patients receiving TEA compared with patients receiving GA alone (OR 0.76; 95% CI 0.49 to1.19; I^2 = 0%). Three out

of the 15 included studies did not provide an estimate, resulting in the overall OR being based on 12 studies. The meta-analysis of studies that evaluated AMI six months after surgery included two studies (Loick 1999; Priestley 2002) with 170 patients (I^2 = 0%) and yielded an RR of 0.41 (95% CI 0.06 to 3.03) (Analysis 2.2).

Respiratory events

A total of 14 studies presented data on the number of patients who had respiratory complication within two weeks of surgery. Pooled analysis of data from 2011 patients (Barrington 2005; Berendes 2003; Caputo 2011; de Vries 2002; El-Baz 1987; Fillinger 2002; Hansdottir 2006; Liem 1992; Lundstrom 2005; Royse 2003; Scott 2001; Svircevic 2011; Tenling 1999) showed a lower risk of respiratory events for patient receiving TEA during surgery compared with those receiving GA alone (RR 0.68; 95% CI 0.54 to 0.86). The heterogeneity of these data was high (I^2 = 42%) (**Analysis 3.1**). With the use of a random-effects model the RR for respiratory events within two weeks was RR 0.66 (95% CI 0.45 to 0.98). One study (Priestley 2002) had a six-month follow-up of respiratory events (RR 3.00; 95% CI 0.13 to 71.92); this study was not included in the meta-analysis.

Supraventricular tachyarrhythmias

Thirteen studies (Bakhtiary 2007; Barrington 2005; Caputo 2009; Caputo 2011; de Vries 2002; Fillinger 2002; Hansdottir 2006; Liem 1992; Kilickan 2006; Nygard 2004; Royse 2003; Scott 2001; Svircevic 2011) that included 2250 patients reported on supraventricular tachyarrhythmias (SVT) within the two weeks after surgery. The use of TEA was associated with a lower risk of SVT compared with GA alone (RR 0.65 95% CI 0.50 to 0.86) (**Analysis 4.1**). However, heterogeneity between the studies was high (I^2 = 69%). With the use of a random-effects model the RR for SVT within two weeks was RR 0.65 (95% CI 0.50 to 0.86). After six-months follow-up, the beneficial effect of TEA on SVT was not statistically significant, but was only reported by two trials (Loick 1999; Priestley 2002) (RR 0.76; 95% CI 0.39 to 1.51) (**Analysis 4.2**).

Neurologic complications

Ten trials reported on stroke. One study (Priestley 2002) had a six-month follow-up (RR of 3.00, 95% CI: 0.13 to 71.92) and nine (Barrington 2005; Caputo 2009; Caputo 2011; Fillinger 2002; Hansdottir 2006; Heijmans 2007; Royse 2003; Scott 2001; Svircevic 2011) had a two-week follow-up. The frequency of neurological complications was lower in patients receiving TEA compared with those receiving GA alone. Pooled analysis of these 1791 patients, showed that there was not significant difference in the risk of neurological complications (OR 0.50; 95% CI 0.21 to 1.18; $I^2 = 0\%$) (**Analysis 5.1**). Two of the nine included studies did not provide an estimate, resulting in the overall OR being based on seven studies.

There were no reported episodes of epidural haematoma in any of the included studies.

Discussion

We conducted a meta-analysis of clinical trials comparing the effects of cardiac surgery with or without TEA on mortality and cardiac, respiratory and neurological complications. Our meta-analysis showed statistically significant reductions in the risk of supraventricular tachyarrhythmias and respiratory complications. The differences for risk of mortality, myocardial infarction and stroke after TEA were not statistically significant. In order to overcome lack of statistical power due to the small sample sizes of individual clinical studies, we were able to pool a large number of available clinical studies. These studies were performed over a 30-year time span, however, possibly reducing control of variability in the protocols for patient selection, treatment and outcome measurement.

The potential of TEA for decreasing tachyarrhythmias has been reported before (Royse 2003; Scott 2001) and was confirmed in this meta-analysis. However, the included studies were heterogeneous and the confidence intervals were wide. The large study by Scott et al (Scott 2001) contributes the most to this result. In this study, B-blockers were discontinued five days perioperatively, which may explain the large benefit of TEA on supraventricular arrhythmias. Repeating the meta-analysis without the data from the study by Scott results in similar

findings. While the Scott study was encouraging, most studies published since then have been unable to repeat its results. A recent, well designed study by Hansdottir (Hansdottir 2006) revealed no reduction in the incidence of adverse events. Recent studies have shown that postoperative supraventricular tachyarrhythmias can also be reduced with clearly less invasive treatments such as B-blockers and amiodarone (Burgess 2006; Kerstein 2004; Nygard 2004). The majority of the studies included in this meta-analysis did not report on whether the patients also used drugs to prevent postoperative arrhythmias. It is, therefore, unclear whether TEA has an additional preventive effect in patients who are also administered prophylactic antiarrhythmic drugs after their operation.

Our meta-analysis showed that TEA results in a statistically significant reduction in postoperative respiratory complications, which is consistent with previous meta-analyses (Ballentyne 1998; Chaney 2006). This may be explained by the superior analgesia after TEA, which facilitates earlier spontaneous respiration in the intensive care unit and faster tracheal extubation. It has been shown that other strategies to allow earlier tracheal extubation can also reduce respiratory complications (Silbert 1998).

There are several limitations in the quality of the included randomized studies that warrant caution in the interpretation of the results of this meta-analysis. First, the time period in which these studies were undertaken spanned over 30 years. The quality of anaesthesiological and intensive care has clearly improved over these years. It is possible that some beneficial effects of TEA, such as earlier extubation, are currently also achieved with modern general anaesthetics. Secondly, the allocation concealment was unclear and blinding information absent in the majority of the trials (**Figure 2; Figure 3**), and most of the included studies were designed to evaluate the effect of TEA on intermediate or surrogate outcome measures instead of clinical endpoints. The non-standardized coverage of clinical outcomes in most studies carried a high risk of observer bias, in particular when the endpoint adjudication was not blinded. Finally, as in any meta-analysis, our results may be subject to publication bias.

As sympathicolysis and enhanced coronary perfusion can be achieved with TEA, which could result in an improved myocardial oxygen balance (Priestley 2002; Scott 2001), we were interested in a possible difference in risk of myocardial

infarction. Our findings are largely comparable to those of the previous two meta-analyses (Ballentyne 1998; Liu 2004). However, it should be noted that the risk of overall bias in this and previous meta-analyses is probably high as the allocation and blinding were unclear in most of the trials. Since we were able to include 27 studies involving 2077 patients, which is substantially more patients than the earlier two previous meta-analyses, the confidence intervals are narrower resulting in more precise effect estimates. Still, for our meta-analysis the statistical power remains too low to reach statistical significance for the beneficial effect estimates for TEA on the risk of mortality, myocardial infarction and stroke. It should be noted that in order to demonstrate statistical significance for a difference in the risk of myocardial infarction from 3.8% after GA to 2.8% after TEA (as found in this meta-analysis), it would require a sample size of at least 10,000 patients.

This meta-analysis shows that the use of TEA in patients undergoing cardiac surgery reduces the risk of postoperative supraventricular arrhythmias and respiratory complications (Summary of findings **table 1**). The scarcity of events precludes conclusions about mortality, myocardial infarction and stroke, but the estimates suggest a reduced risk after TEA. The risk of side effects of TEA, including epidural haematoma (Bang 2011; Ho 2000; Ho 2006; Rosen 2004), could not be assessed with the current meta-analysis.

Summary of main results

This meta-analysis shows that the use of TEA in patients undergoing cardiac surgery reduces the risk of postoperative supraventricular arrhythmias and respiratory complications (Summary of findings **table 1**).

Overall completeness and applicability of evidence

The scarcity of events precludes statistically significant conclusions about mortality, myocardial infarction and stroke. The risk of side effects of TEA was not reported in any of the included studies and therefore could not be assessed with the current meta-analysis. In order to find the true risk of side effects, such as neurological complications, an updated review should consider including non-randomized controlled trials in the review.

Quality of the evidence

We identified 11 low risk of bias studies (Barrington 2005; Berendes 2003; Caputo 2009; Caputo 2011; Hansdottir 2006; Kilickan 2006; Moore 1995; Priestley 2002; Scott 2001; Svircevic 2011; Tenling 1999), 18 high risk of bias studies (Bach 2002; Bakhtiary 2007; Brix-Christensen 1998; de Vries 2002; El-Baz 1987; Fillinger 2002; Kendall 2004; Kirno 1994; Liem 1992; Loick 1999; Lundstrom 2005; Nygard 2004; Onan 2011, Rein 1989; Royse 2003; Sharma 2010; Stenseth 1994; Stenseth 1996) and two studies with unclear risk of bias (Heijmans 2007; Lagunilla 2006).

Potential biases in the review process

The risk of overall bias in this and previous meta-analyses is probably high as the allocation and blinding were unclear in most of the trials.

Agreements and disagreements with other studies or reviews

Our findings are largely comparable to those of the previous two meta-analyses (Ballentyne 1998; Liu 2004).

Authors' conclusions

Implications for practice

This meta-analysis showed that the use of TEA in cardiac surgery may reduce the risk of postoperative supraventricular arrhythmias, respiratory complications and neurological complications, but has no effect on the risk of mortality and myocardial infarction.

Implications for research

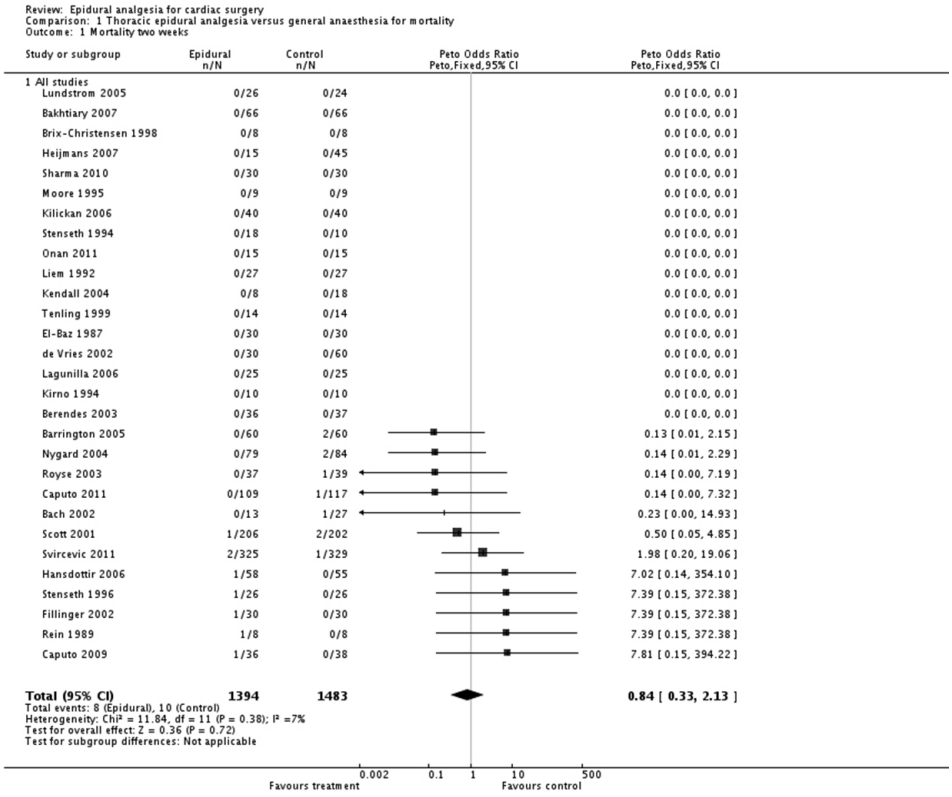
In view of inconsistent results for different outcomes and the long time period over which the included studies were undertaken, it would be interesting to focus future research on potential benefits of TEA compared to contemporary anaesthesia methods.

Declarations of interest

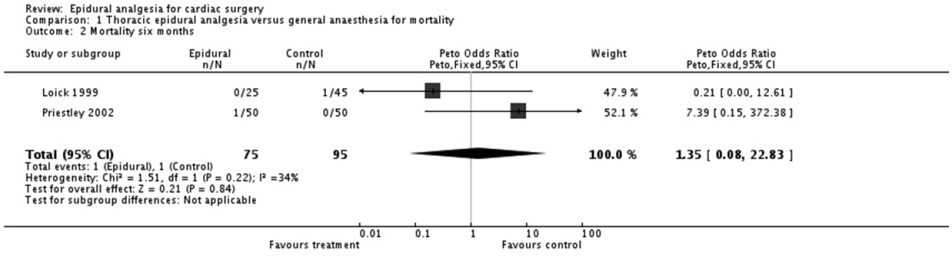
None known

Data and Analyses

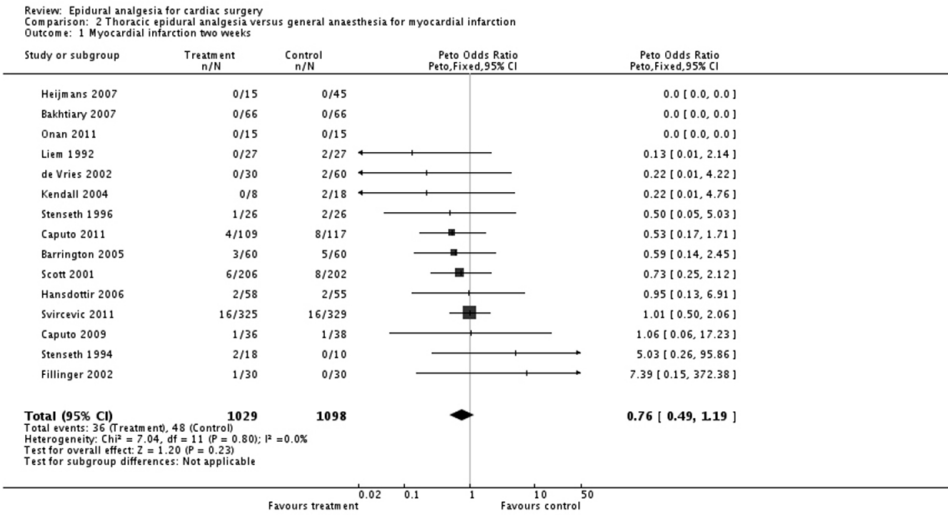
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
Mortality two weeks	29	2877	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.84 [0.33, 2.13]
Mortality six months	2	170	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.35 [0.08, 22.83]
Myocardial infarction two weeks	15	2127	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.49, 1.19]
Myocardial infarction six months	2	170	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.41 [0.06, 3.03]
Resp. complications two weeks	13	2011	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.45, 0.98]
SVTs two weeks	13	2250	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.50, 0.86]
SVTs six months	2	170	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.76 [0.39, 1.51]
Stroke two weeks	9	1791	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.50 [0.21, 1.18]
Low risk of bias studies	10	1794	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.83 [0.25, 2.70]



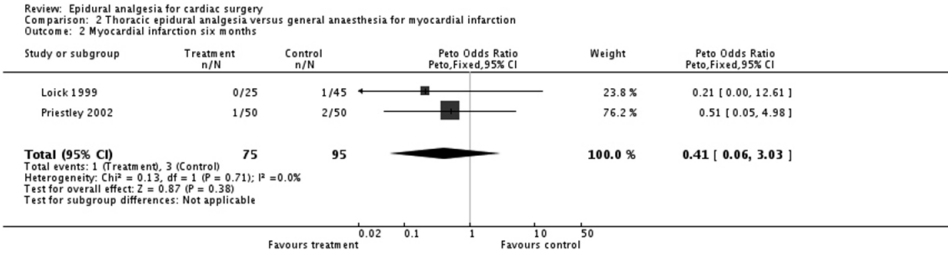
Analysis 1.1 *Two week mortality*



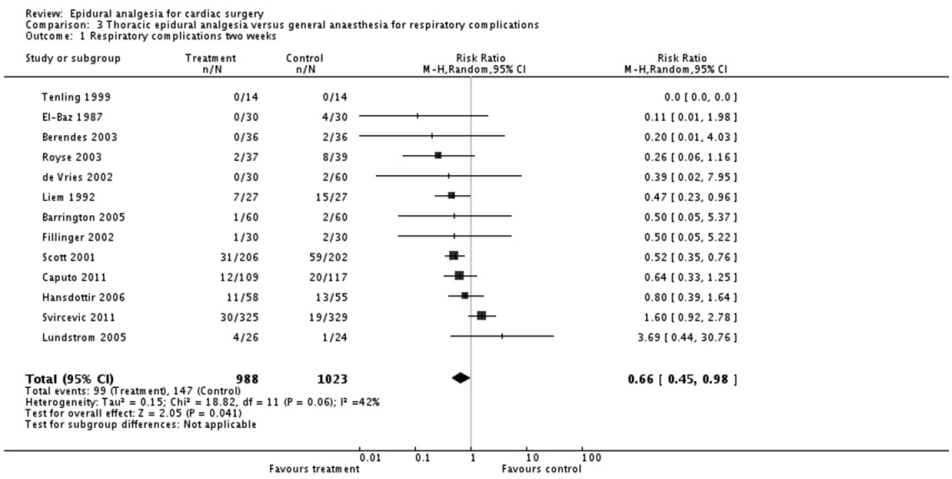
Analysis 1.2 *Six month mortality*



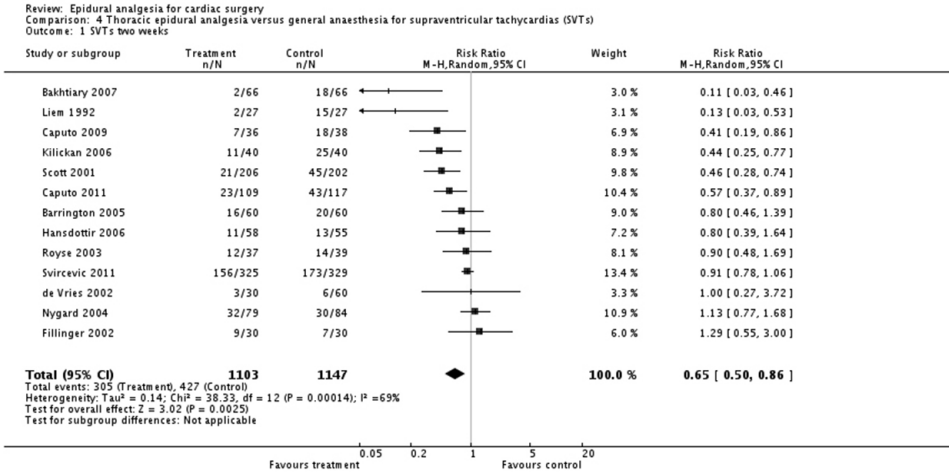
Analysis 2.1 *Two week Myocardial infarction*



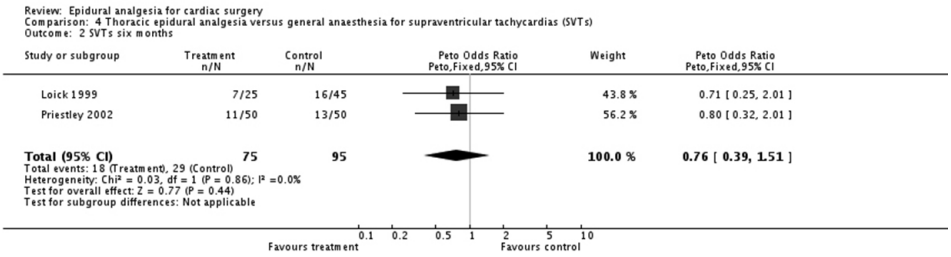
Analysis 2.2 *Six month Myocardial infarction*



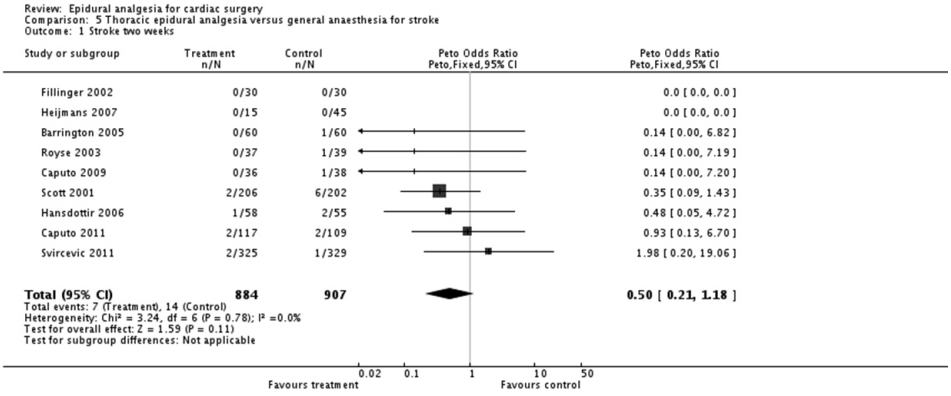
Analysis 3.1 *Two week Respiratory complications*



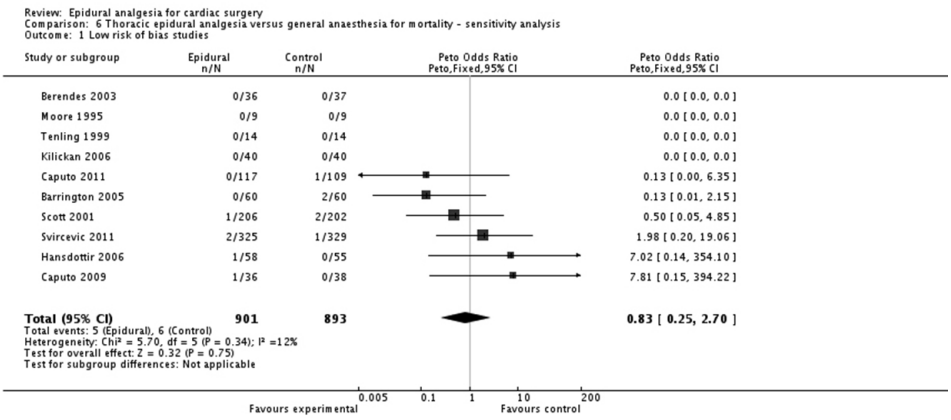
Analysis 4.1 *Two week Supraventricular tachyarrhythmias*



Analysis 4.2 *Six month Supraventricular tachyarrhythmias*



Analysis 5.1 *Two week Stroke*



Analysis 6.1 *sensitivity analysis, Low risk of bias studies*

Summary of findings for the main comparison. Epidural analgesia for cardiac surgery

Studies: randomized clinical trials

Patient or population: adult patients undergoing cardiac surgery

Intervention: thoracic epidural anaesthesia

Comparison: general anaesthesia

Outcomes	Illustrative comparative risks*		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Assumed risk GA	Corresponding risk TEA			
respiratory complications	144 per 1000 (79 to 141)	100 per 1000	0.66 (0.45, 0.98)	2011 (14)	++OO[1]
supraventricular arrhythmias	372 per 1000 (186 to 208)	242 per 1000	0.65 (0.50, 0.86)	2250 (15)	++OO[2]
mortality	7 per 1000 (2 to 16)	6 per 1000	0.84 (0.33, 2.13)	2877 (31)	+++O[3]
myocardial infarction	44 per 1000 (22 to 52)	33 per 1000	0.76 (0.49, 1.19)	2127 (17)	+OOO[4]
stroke	15 per 1000 (3 to 18)	8 per 1000	0.50 (0.21, 1.18)	1791 (10)	+OOO[5]

*The basis for the assumed risk (e.g. the mean control group risk) is provided in footnotes. The corresponding risk is based on the assumed risk in the comparison group and the effect estimate of the intervention.
CI: Confidence interval;
GRADE Working Group grades of evidence
High quality (++++): Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality (+++O): Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality (++OO): Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality (+OOO): We are very uncertain about the estimate.Footnotes
[1] Narrow confidence intervals, however high variability in effect estimates (I2 = 42%) and the definition of this endpoint was variable among the studies, for this reason the quality of evidence was down graded
[2] There was substantial variability in effect estimates (I2 = 67%)
[3] Large number of participants with narrow confidence intervals and small variability in effect estimates (I2 = 0%)
[4] Large number of participants and small variability in effect estimates, but with wide confidence intervals indicating imprecision in results
[5] The wide confidence intervals indicate imprecision in results

Characteristics of included studies

Bach 2002

Methods	Randomized controlled trial
Participants	40 patients scheduled for elective coronary artery bypass grafting surgery. Exclusion criteria were impaired coagulation, allergies to local anaesthetics, corticoid medication, preoperative signs of infection, renal or liver failure, diabetes mellitus and an impaired left ventricular function (ejection fraction 50%)
Interventions	Continuous epidural infusion of bupivacaine 0.25% versus general anaesthesia group The 13 patients received an epidural bolus of 10ml of bupivacaine 0.25% through the catheter followed by a continuous epidural infusion of bupivacaine 0.25% (Bupivacain 0.25%, Curasan Pharma AG, Kleinostheim, Germany) adjusted to body height for the whole observation period until 18h after surgery. The control group consists of 13 patients who received an intravenous dopexamine infusion beside general anaesthesia and 14 patients with general anaesthesia alone who received equal volumes of NaCl 0.9% intravenously as placebo in a time-matched fashion.
Outcomes	Inflammatory response Mortality

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	One day before surgery and after written informed consent was obtained, patients were randomly assigned to the study groups by drawing lots
Allocation concealment (selection bias)	Unclear Risk	Drawing lots
Blinding (performance bias and detection bias)	High Risk	

Incomplete outcome data (attrition bias)	High Risk	One patient of the control group was excluded during the study. He died 8h after surgery as a result of a non-occlusive ischaemia of the small intestine. All other patients who were initially included terminated the study.
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias

Bakhtiary 2007

Methods Randomized controlled trial

Participants 132 patients with symptomatic coronary artery disease were prospective enrolled in this study. All patients underwent elective OPCAB surgery and were randomized to receive either GA or combined GATEA. Patients with a history of atrial arrhythmias, those undergoing emergency operations, and patients requiring intraoperative inotropic support were excluded from this study.

Interventions General anaesthesia only or combined general anaesthesia with high thoracic epidural analgesia (66 patients in each group)
TEA: a continuous epidural infusion with ropivacaine 0.16% and sufentanil 1 g/mL at an hourly rate of 2 to 5 mL was started after a bolus dose of 6 mL to provide intraoperative analgesia. GA: propofol (1.5 mg/kg) and remifentanil (1 ug/kg) administered over 120 seconds. After loss of eyelash reflex, 0.1 mg/kg of cisatracurium was administered to facilitate tracheal intubation. Anaesthesia was maintained with continuous infusion of propofol (50-100 ug/kg/min) and remifentanil (0.1-0.3 ug/kg/min). Patients undergoing GA without TEA received intravenous metamizole (Novalgin; Aventis Pharma, Bad Soden, Germany), a peripheral analgesic derived from pyrazolone acid, 15 mg/kg, before skin incision. Intravenous piritramide, a-receptor agonist with a potency of 0.7 compared with morphine, 0.1 mg/kg, was

	administered after completion of coronary anastomosis and repeated during wound closure.
Outcomes	Mortality Myocardial infarction Supraventricular tachyarrhythmias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	Patients were randomized to receive either GA or combined GATEA
Allocation concealment (selection bias)	Unclear Risk	Not stated
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	All pre-specified outcomes reported
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation not stated

Barrington 2005

Methods	Randomized controlled trial
Participants	120 patients scheduled for elective coronary artery bypass grafting surgery All patients scheduled for elective CABG surgery (using cardiopulmonary bypass (CPB)) were eligible. Exclusion criteria were emergency or repeat CABG surgery, combined valve and CABG surgery, aspirin ingestion within 6 days of surgery, a platelet count $150x10^9$/L, an international normalized ratio 1.1, active neurological disease, and cutaneous disorders at the epidural insertion site.
Interventions	General anaesthesia only or combined general anaesthesia with high thoracic epidural analgesia (ropivacaine 1%; 60 patients in each group)

	epidural block was established with 5 mL of ropivacaine 1% and fentanyl 50 ug. If required, the block was extended with 2 mL of ropivacaine 1%. GA was induced with midazolam (0.05 - 0.1 mg/kg), fentanyl (7-15 ug/kg for the GA group and 5-7 ug/kg for the HTEA group), propofol (20 mg increments as required), and rocuronium (0.6 mg/kg). GA was maintained with propofol 3-6 mg/kg/hr. Further doses of rocuronium 10 mg were given only for overt patient movement, with no additional rocuronium given after CPB.
Outcomes	Mortality Myocardial infarction Supraventricular tachyarrhythmias Stroke Respiratory complications

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	Patients were randomized the day be fore surgery to two groups. The random allocation sequence was computer-generated in permuted blocks of four and enclosed in sequentially numbered opaque sealed envelopes.
Allocation concealment (selection bias)	Low Risk	Opaque sealed envelopes
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	All patients were included in the intention to treat analysis; all prespecified outcomes reported
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. A formal sample size determination was not possible because primary endpoint data were not avail-

able at the time of study inception. The confidence intervals between groups were calculated post hoc to assess the precision of the data and the adequacy of sample size

Berendes 2003

Methods	Randomized controlled trial
Participants	73 patients scheduled for coronary artery bypass who had left ventricular ejection fraction of 50% or more Eligible patients had coronary artery disease with a left ventricular function of 50% or more and were scheduled for elective CABG. Exclusion criteria were any pre-existing endocrinological diseases, renal insufficiency, coagulation disorders or right and/or left ventricular dysfunction, concomitant disorders of heart valves, having undergone cardiac surgical procedures, acute myocardial infarction and heart failure.
Interventions	General anaesthesia only (37 patients) or combined general anaesthesia with high thoracic epidural analgesia (36 patients) (bupivacaine and sufentanil) correct position of the epidural was tested by 2 ml of bupivacaine 0.5% with epinephrine. Before induction high TEA was initiated by 6-12 mL of bupivacaine 0.5% and 15-25 ug sufentanil. General anaesthesia was induced in all patients with midazolam 0.1 mg/kg IV and pancuronium 0.1 mg/kg. The GA group received propofol 1.5-3 mg/kg/hr and sufentanil 1-2 ug/kg/hr. In the TEA group they received propofol 1.5-3 mg/kg/hr supported by repetitive injections of sufentanil 0.2-1 ug/kg.
Outcomes	Mortality Respiratory complications Left ventricular function Postoperative complications

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Computer-generated block randomization
Allocation concealment (selection bias)	Low Risk	Administered through a sequential opaque envelope technique
Blinding (performance bias and detection bias)	Unclear Risk	Participants, staff and research personnel unblinded to the intervention. The investigator collected data, but was not involved in patient care or management
Incomplete outcome data (attrition bias)	Low Risk	All pre-specified outcomes reported
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias

Brix-Christensen 1998

Methods	Randomized controlled trial
Participants	16 patients scheduled for elective coronary artery bypass grafting surgery Patients with diabetes mellitus or cancer were excluded
Interventions	Low dose opioid anaesthesia (epidural: bupivacaine 2 mg/mL and fentanyl 5 ug/mL at 5 ml/hr)) and general inhalational anaesthesia with fentanyl (8 patients in each group) In the TEA group 8 mL of bupivacaine 0.5 % was injected 30 mins before surgery. Peroperative a continuous epidural infusion was given with bupivacaine 2 mg/ ml and fentanyl 5ug/mL at 5 mL/hr. General anaesthesia was induced with midazolam 0.15 mg/kg and fentanyl 5ug/kg. Muscle relaxation was achieved with pancuronium 0.1mg/kg. Anaesthesia was maintained with enflurane 0.4-0.8%. In the high dose fentanyl group anaesthesia was induced with midazolam 0.15 mg/kg and fentanyl 50 ug/kg. Anaesthesia was maintained with enflurane, midazolam and sufentanil.

Outcomes	Mortality Cytokine response

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	Patients were randomly allocated into two groups
Allocation concealment (selection bias)	Unclear Risk	Not stated
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	The peri- and postoperative courses were uneventful for all patients. All data addressed
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias

Caputo 2009

Methods	Randomized controlled trial
Participants	74 patients undergoing off-pump coronary artery bypass surgery
Interventions	The anaesthetic technique consisted of premedication with benzodiazepines, and induction with intravenous infusion of propofol at 3 mg/kg/hr combined with fentanyl (10 to 20 g/kg). Neuromuscular blockade was achieved with 0.1 to 0.15 mg/kg pancuronium bromide or vecuronium. Intervention (36 patients): bilateral neuraxial block was established from T1 to T10 with an initial bolus of 5 mL bupivacaine 0.5% followed by another 5-mL bolus after 10 minutes. After induction of GA and when central haemodynamic status was stable, a continuous infusion of 0.125% bupivacaine and 0.0003% clonidine (150 g in 500 mL) was commenced at an initial rate of 10 mL/h Control (38 patients): In the GA group, a patient-controlled analgesia intravenous morphine pump was started in the intensive

	care unit for 48 hours by using a 1 mg bolus dosing with a 5-minute lockout period
Outcomes	Mortality Stroke Myocardial infarction Supraventricular arrhythmias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	Patients were randomly assigned to receive either general anaesthesia only or general anaesthesia plus epidural. Random treatment allocations were generated by computer in advance of starting the study, using block randomization with varying block sizes. Allocation details were concealed in sequentially numbered opaque sealed envelopes.
Allocation concealment (selection bias)	Low Risk	Opaque sealed envelopes
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	All patients received the treatment allocated, all pre-specified outcomes reported
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation stated

Caputo 2011

Methods	Two-centre, open, parallel-group, randomized controlled trial
Participants	226 adults undergoing primary OPCAB surgery without the use of CPB and cardioplegic arrest
Interventions	In both groups the induction with propofol at 0.5–1 mg/kg combined

with fentanyl (10 –20g/kg). Neuromuscular blockade was achieved with 0.1–0.15 mg/kg pancuronium bromide or vecuronium. Anesthesia was maintained with either isoflurane at 0.8 –1.0 minimal anaesthetic concentration or intravenous propofol 3– 4 mg/kg/hr, at the discretion of the consultant anaesthetist. Patients in the GAE group had a thoracic epidural catheter sited in the operating theatre immediately before surgery at the T2–3 or T3–4 intervertebral space. Bilateral neuraxial block was established from T1 to T10 with an initial bolus of 5 mL bupivacaine, 0.5%, followed by another 5 mL bolus after 10 min. Determination of the spread of block was performed with ethyl chloride spray. After induction of GA and when central hemodynamic status was stable, a continuous infusion of 0.125% bupivacaine and 0.0003% clonidine (150 g in 500 mL) was commenced at an initial rate of 10 ml/hr.

Outcomes Mortality
Myocardial infarction
Chest infections
Pain scores
Length of hospital stay
Arrhythmias
Stroke

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	Randomized treatment allocations were generated using Stata version 8. They were stratified by consultant team with a 1:1 allocation using blocks of varying sizes.
Allocation concealment (selection bias)	Low Risk	Allocation details were concealed in sequentially numbered, opaque sealed envelopes. These were prepared by the clinical trials and evaluation unit

Blinding (performance bias and detection bias)	High Risk	Not blinded
Incomplete outcome data (attrition bias)	Low Risk	There were 18 protocol violations in patients allocated to GAE who received GA because the epidural could not be inserted
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation stated

de Vries 2002

Methods Randomized controlled trial

Participants 90 patients scheduled for elective minimally invasive direct coronary artery bypass surgery

Interventions 30 patients had general anaesthesia and were extubated immediately after surgery (extubated group), 30 patients had a thoracic epidural (bupivacaine and sufentanil) and general anaesthesia and were extubated immediately after surgery (epidural group), and 30 patients had general anaesthesia and were ventilated after surgery (intubated group)

In the extubated group, at induction the patients received midazolam, 0.1 mg/kg, and sufentanil, 0.5 to 1 ug/kg. Anaesthesia was maintained with either isoflurane (0.5% to 0.8%) or propofol (3 to 5 mg/kg/hr) with incremental supplements of sufentanil (25 to 50 g) when the mean arterial pressure (MAP) exceeded baseline values by 20%.

In the epidural group, a thoracic epidural catheter was inserted at the T3-4 level before induction of anaesthesia. Anaesthesia was induced with midazolam, 0.1 mg/kg, and sufentanil, 0.5 to 1 g/kg. Through the epidural catheter, 8 to 10 mL of bupivacaine 0.25% with sufentanil, 25 ug/10 mL, were given 10 minutes before the start of surgery. Anaesthesia was maintained as in the extubated group. In the intubated group, induction of anaesthesia was

	performed with midazolam and sufentanil as previously reported.15 Briefly, midazolam, 0.1 mg/kg, and sufentanil, 1.5 ug/kg, were slowly infused over 5 minutes. Anaesthesia was maintained with continuous infusions of midazolam and sufentanil at a rate of 2 ug/kg/min for midazolam and 1 ug/kg/hr for sufentanil. In all groups, pancuronium, 0.1 mg/kg, was administered to facilitate endotracheal intubation. In the extubated group and in the intubated group, postoperative analgesia was given on patient request with piritramide, 0.2 mg/kg intramuscularly. In the epidural group, a continuous infusion of bupivacaine 0.125% and sufentanil, 25 ug/50 mL, was given at 8 to 10 mL/hr. All groups received additional paracetamol suppositories, 1g 4 times daily.
Outcomes	Mortality Myocardial infarction or ischaemia (ST segment analysis) Haemodynamics: MAP and heart rate Pain scores Length of hospital stay
Notes	MIDCAB surgery

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	"90 patients were randomly divided into 3 groups"
Allocation concealment (selection bias)	Unclear Risk	Not stated
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	Five patients were excluded from analysis: three because of surgical reasons and in two patients the epidural technique failed
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation stated

El-Baz 1987

Methods	Randomized controlled trial
Participants	60 patients, aged 34 to 76 years, after coronary artery bypass surgery (one to four grafts)
Interventions	IV opioids or low dose continuous opioid epidural analgesia (morphine 0.1 mg/mL at 1 mL/hr) with 30 patients in each group. General anaesthesia was induced with pentothal 3-4 mg/kg followed by succinylcholine 1-2 mg/kg. Anaesthesia was maintained with a nitrous-oxide-oxygen-halothane gas mixture. Pancuronium 0.1-0.2 mg/kg was used for muscle relaxation to facilitate control of ventilation. The control group received morphine 2 mg/2 hr and as needed. The epidural group received a continuous epidural infusion of 0.1 mg morphine/hr, this was supplemented by 2 mg IV as needed.
Outcomes	Mortality Respiratory function Cardiovascular parameters Pain relief

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	"Patients were randomly divided into two equal groups of 30 patients"
Allocation concealment (selection bias)	Unclear Risk	Not stated
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	Appears have no incomplete outcome data
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias

Fillinger 2002

Methods	Randomized controlled trial
Participants	60 patients scheduled for elective coronary artery bypass Patients scheduled for elective CABG surgery were considered eligible for inclusion in the study in the absence of any specific contraindication to the use of EAA (heparin or warfarin (Coumadin (Endo Laboratories Inc, Wilmington, DE)) anticoagulation, pre-existing coagulopathy, infection at insertion site, or septicaemia).
Interventions	General anaesthesia with IV morphine or combined general anaesthesia with high thoracic epidural analgesia (bupivacaine 0.5% at 4-10 mL/hr) with 30 patients in each group. On arrival in the operating room, intravenous sedation was initiated with incremental doses of fentanyl ≤2 ug/kg, and midazolam, 0≤.05 mg/kg. GA was induced in all patients with intravenous fentanyl (5 to 20 g/kg total), midazolam (0.1 mg/kg), thiopental (1 to 2 mg/kg), and pancuronium or vecuronium for muscle relaxation and tracheal intubation. Inhaled isoflurane was used for anaesthesia maintenance. Muscle relaxation was reversed at the end of the operation with neostigmine and glycopyrrolate. For participants randomized to receive TEAA, a thoracic epidural catheter was inserted after vascular catheter placements and before induction of GA. After a negative epidural test dose of 3 mL of 1.5% lidocaine with 1:200,000 epinephrine, the epidural catheter was injected with preservative-free morphine, 20 ug/kg, and 0.5% bupivacaine, in 5 mg increments, to a total loading dose of 25 to 35 mg of bupivacaine. Then the epidural catheters were continuously infused with 0.5% bupivacaine with morphine, 25 ug/mL, at 4 to 10 mL/hr beginning after the induction of GA. Clinical signs of inadequate epidural analgesia (haemodynamic response to surgical stimulation) during surgery were managed with a 3 mL bolus of the infusion solution followed by an increase in the infusion rate of 1 mL/hr (to a maximum of 10 mL/hr). After surgery: patients in the GA group received intravenous

	morphine for postoperative analgesia according to a standard CTICU protocol, whereas patients in the TEAA group received an epidural infusion of 0.125% bupivacaine with morphine, 25 ug/mL, at 4 to 10 mL/h.
Outcomes	Mortality Myocardial infarction Supraventricular tachyarrhythmias Stroke Respiratory (time to tracheal extubation) Pain control Duration of hospital stay

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	Computerized randomization
Allocation concealment (selection bias)	Unclear Risk	Not stated
Blinding (performance bias and detection bias)	High Risk	Participants, staff and research personnel unblinded to the intervention
Incomplete outcome data (attrition bias)	Low Risk	All pre-specified outcomes reported
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias

Hansdottir 2006

Methods	Randomized controlled trial
Participants	113 patients undergoing elective cardiac surgery (CABG, cardiac valve procedures, combined CABG and valve procedures or the Maze procedure, with or without CABG), absence of contraindications to epidural anaesthesia, abnormal coagulation tests (i.e., partial thromboplastin time 45 sec or prothrombin time (international normalized ratio) 1.5 or a platelet count 80,000), or recent (1 week) treatment with thrombolytic or potent antiplatelet

drugs (streptokinase, alteplase, clopidogrel, abciximab, tirofiban, integrelin). Aspirin treatment was not considered a contraindication to the placement of a thoracic epidural catheter.

Interventions General anaesthesia with postsurgical PCA with morphine or combined general anaesthesia with high thoracic epidural analgesia (bupivacaine 5 mg/mL at 0.05 mL/kg/hr)

All patients (58 patients in epidural group and 55 in the control group) received infusions of propofol and remifentanil to a target anaesthetic depth of 15-25 AAI using an auditory evoked response monitor. Tracheal intubation was facilitated with 0.5 mg/kg atracurium. After induction of anaesthesia and insertion of monitoring devices, patients in the PCTEA group received an epidural 0.1 mL/kg bolus dose followed by a continuous 0.05 mL/kg/hr infusion with bupivacaine (5 mg/mL). In the PCTEA group, postoperative pain treatment was achieved by epidural bolus doses of 2 mL of the mixture 1 mg/mL bupivacaine plus 2 g/mL fentanyl plus 2 g/mL adrenaline, a lockout interval of 20 min, and a background epidural infusion of 0.1 mL/kg/hr. An epidural 0.1 ml/kg loading dose of this mixture was given at the end of surgery. In the PCA group, postoperative pain treatment was achieved by intravenous PCA morphine with bolus doses of 0.01 mg/kg and a lockout interval of 6 min with no background infusion. A loading dose of 0.1 mg/kg morphine was given in the operating room when remifentanil infusion was stopped.

Outcomes Myocardial infarction
Supraventricular tachyarrhythmias
Stroke
Respiratory (lung volumes)
Pain and sedation scores
Length of hospital stay

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Patients were randomly assigned the day before surgery to one of two regimens
Allocation concealment (selection bias)	Low Risk	Sealed envelopes
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	113 patients were randomized, 110 patients received allocated treatment, and 97 patients were eventually analysed
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation stated

Heijmans 2007

Methods Randomized controlled trial

Participants 60 patients undergoing elective cardiac surgery

Exclusion criteria included left ventricular ejection fraction of less than 25%, hypothermic circulatory arrest, recent myocardial infarction, preoperative inotropic or intra-aortic balloon pump metabolic, or neurologic diseases. All patients were receiving chronic B-adrenoceptor blocking drugs

Interventions Alfentanil or low dose remifentanil or high dose remifentanil or epidural (15 patients in the epidural and 45 patients in the control group)

A test dose of 2 mL of lidocaine 2% was given to test for the correct position of the catheter. A loading dose of 10 mL of bupivacaine 0.25% with 2.5 mg of morphine was infused over 1 hour.

In the present study, 4 groups of patients were compared as follows: group 1 (AG): a loading dose of alfentanil, 50 ug/kg, was infused over 4 minutes, and, thereafter, alfentanil was infused at a

maintenance rate of 1 ug/kg/min throughout surgery; group 2 (HDRG): a loading dose of remifentanil, 2.5 ug/kg, was infused over 4 minutes, and, thereafter, remifentanil was infused at a maintenance rate of 0.5 ug/kg/min throughout surgery; group 3 (LDRG): a loading dose of remifentanil, 2.5 ug/kg, was infused over 4 minutes, and, thereafter, remifentanil was infused at a maintenance rate of 0.25 ug/kg/min; and group 4 (TEG): a loading dose of remifentanil, 2.5 ug/kg, was infused over 4 minutes, and, thereafter, remifentanil was infused at a maintenance rate of 0.125 ug/kg/min and via thoracic epidural infusion bupivacaine 0.375% plus morphine 0.2 mg/mL were administered at a rate of 1.5 mL/hr throughout surgery. The initial infusion setting for propofol on the Diprifusor was a plasma concentration of 2 ug/mL to be reached in 4 minutes.

At arrival in the ICU, a sedative-analgesic infusion of propofol, 0.5 mg/kg/hr, together with alfentanil, 0.1 ug/kg/min, in group 1 and remifentanil, 0.025 g/kg/ min, in groups 2, 3, and 4, were started for 4 hours. If necessary, propofol was increased to achieve the desired level of sedation (Ramsay sedation score 3, 4, or 5). Additionally, acetaminophen, 1 g, 4 times daily, was started as a basic analgesic. In the TEG group, the catheter was left in position 48 hours postoperatively and bupivacaine 0.125% and morphine, 0.2 mg/mL, were infused at a rate of 1.5 mL/hr. Fifteen minutes before cessation of the sedative analgesic infusion, pirinitramide, a synthetic morphine derivative (analgesic potency in comparison with morphine [1] is 0.7) 0.15 mg/kg, intravenously, was administered in the remifentanil groups 2 and 3, and placebo was administered to the AG in a blinded fashion.

Outcomes

Infectious parameters (CRP, IL-6)

Mortality

Supraventricular tachyarrhythmias

Stroke

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	"60 patients scheduled to undergo coronary artery bypass surgery were randomized"
Allocation concealment (selection bias)	Unclear Risk	Not stated
Blinding (performance bias and detection bias)	Low Risk	The study was blinded for the opioid infusion, except in the thoracic epidural group
Incomplete outcome data (attrition bias)	Unclear Risk	Not stated
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation not stated

Kendall 2004

Methods Randomized controlled trial

Participants 26 patients undergoing off pump coronary artery bypass grafting
Patients undergoing emergency surgery and those with unstable angina were excluded from the study. Patients with plasma creatinine values greater than 160 mmol/L were also excluded from the study. Patients taking anticoagulant therapy and those with any other contraindication to the insertion of a thoracic epidural were also excluded.

Interventions General anaesthesia: propofol or isoflurane or epidural: isoflurane with bupivacaine
In the propofol group (9 patients), anaesthesia was induced with fentanyl 10-15 ug/kg and propofol delivered by a DiprifusorTM pump (AstraZeneca, London, England), aiming for a target blood concentration in the range 4-8 ug/mL
In the isoflurane group (9 patients), anaesthesia was induced with etomidate 0.2 mg/kg and fentanyl 10-15 ug/kg. Anaesthesia was maintained with isoflurane in oxygen and air at an end-tidal con-

	centration of 1%. This was discontinued at the end of the procedure, and a propofol infusion was started to provide sedation if required until the criteria for tracheal extubation were met In the epidural group (8 patients), anaesthesia was as for the isoflurane group, with the exception that fentanyl was given in a dose of 1.5 ug/kg epidural: bupivacaine 0.1% with fentanyl 5 ug/ml was given, followed by an infusion of 0.1 ml/kg/hr, adjusted according to haemodynamic values
Outcomes	Mortality Myocardial infarction (troponin levels, new Q waves, loss of R progression) Prolonged intensive care stay (GT; 24 hr) Duration of tracheal intubation Return to operating room Intraoperative haemodynamic parameters
Notes	Surgery with the octopus

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	Patients were randomly allocated to one of three groups using a shuffled, sealed envelope technique
Allocation concealment (selection bias)	Low Risk	Sealed envelopes
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Unclear Risk	"Three patients were excluded from the study and further analysis. Their treatment was re-randomized and re-allocated, providing 30 complete data sets for analysis"
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation not stated

Kilickan 2006

Methods	Randomized controlled trial
Participants	80 patients scheduled for elective coronary artery bypass grafting Exclusion criteria: contraindications for the epidural technique, contraindications to any of the intended drugs in the treatment protocol, alcohol abuse, cognitive impairment
Interventions	General anaesthesia alone or general anaesthesia in combination with high thoracic epidural analgesia (40 patients in each group). Anaesthesia was induced in all groups by 0.2 mg/kg midazolam, 10-15 ug/kg fentanyl and 0.1 mg/kg vecuronium. Anaesthesia was maintained with propofol 2-6 mg/kg/hr and 2 ug/kg fentanyl intermittently. In the TEA group, 1 hr before surgery a bolus of 20 mg of bupivacaine was administered and a continuous infusion was started (bupivacaine 0.25 % at 8 ml/hr). Postoperatively, in the TEA group received an epidural infusion of bupivacaine 0.125%, 4-10 ml/hr. The control group received a standard analgesia protocol (morphine PCA)
Outcomes	Mortality Bcl-2 immunoreactivity (rate of apoptosis) Haemodynamic parameters (CI) Reperfusion ventricular fibrillation

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	80 patients scheduled for elective CABG were randomized in two groups
Allocation concealment (selection bias)	Low Risk	Sealed envelopes
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	All pre-specified outcomes reported
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation not stated

Kirno 1994

Methods	Randomized controlled trial
Participants	20 patients undergoing coronary artery bypass grafting All patients had a history of stable ischaemic heart disease with 2 or 3 vessel coronary artery disease and an ejection fraction of > 50%. Patients with co-existing valvular anomaly, arrhythmias or diabetes mellitus were not included.
Interventions	General anaesthesia (fentanyl nitrous oxide) and general anaesthesia and epidural analgesia with 10 patients in each group. Anaesthesia was induced with thiopental 3-5 mg/kg, followed by pancuronium 0.1 mg/kg IV. Fentanyl was given in incremental doses up to a total amount of 10-15 ug/kg before sternotomy. The patients were ventilated with 70% nitrous oxide in oxygen. In the TEA group 3-3.5 mL mepivacaine was given epidurally after induction.
Outcomes	Mortality MAP Regional myocardial oxygen consumption Myocardial ischaemia Haemodynamic parameters Noradrenaline spillover (sympathetic nervous system activation)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	The patients were randomized into two groups
Allocation concealment (selection bias)	Unclear Risk	Not stated
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	All pre-specified outcomes reported
Selective reporting (reporting bias)	Unclear Risk	Not stated

Lagunilla 2006

Methods Randomized controlled trial

Participants 50 patients submitted for scheduled coronary revascularization of, at least, the left anterior descending (LAD) coronary artery were enrolled in the study.

The exclusion criteria were as follows: patient refusal, urgent or emergency procedure, unstable haemodynamic status (myocardial infarction less than 2 weeks prior to surgery, requirement for inotropic drugs or for intra-aortic balloon contrapulsation), absence of normal sinus rhythm, neurologic or neuromuscular disorders, previous thoracic or cervical spine surgery or trauma, significant left main coronary artery stenosis, anticoagulation, haematologic disorders and infection at the puncture site.

Interventions General anaesthesia with a thoracic epidural with either ropivacaine or a saline solution with 25 patients in each group.

Thereafter, general anaesthesia was induced with midazolam 1 mg, remifentanil at 0.7 mg/kg/min, cisatracurium in a single bolus of 0.2 mg/kg and 2-3% inhaled sevoflurane in oxygen. All patients received the corresponding volume of plain saline or 0.3% ropivacaine, in a blind manner, accordingly to the group to which they had been randomized. Then, an epidural infusion of 0.3% ropivacaine at 5-7 ml/hr (reduced to 2-3 mL/h during grafting) was started in all patients. In the postoperative period, 0.2% ropivacaine with 5 mg/mL fentanyl was used for analgesia in all patients, employing a patient controlled system.

Outcomes Mortality

Haemodynamic parameters

Intramyocardial oxygen partial pressure

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	Patients enrolled in the study were randomly assigned, randomization was performed using a computer-

		generated random sequence
Allocation concealment (selection bias)	Unclear Risk	Computer-generated random sequence
Blinding (performance bias and detection bias)	Low Risk	Patients enrolled in the study were randomly assigned to receive either epidural saline or epidural 0.3% ropivacaine
Incomplete outcome data (attrition bias)	Low Risk	One patient was excluded in the ropivacaine group due to a wet tap (no catheter placement). One patient in the saline group became unstable after anaesthesia induction and required inotropic support; this patient was subsequently withdrawn from the study.
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation stated

Liem 1992

Methods	Randomized controlled trial
Participants	54 patients scheduled for elective coronary artery bypass surgery To be admitted to the study they were required to have normal or only moderately impaired left ventricular (LV) function (ejection fraction greater than 40%) as assessed by preoperative LV cineangiography and a LV end-diastolic pressure of less than 18 mmHg. Patients who had a myocardial infarction in the 7 days preceding surgery. Pre-existing haemorrhagic diathesis, or valvular heart disease were excluded from the study.
Interventions	High thoracic epidural with bupivacaine 0.375% plus sufentanil 5 ug/mL in combination with general anaesthesia midazolam/N_2O and general anaesthesia with midazolam/fentanyl (27 patients in each group).

	IV anaesthesia in the GA group was induced over a period of 10 minutes with midazolam, 0.1 mg/kg, sufentanil, 5 ug/kg, and pancuronium, 0.1 mg/kg. Anaesthesia was maintained with an infusion of midazolam, 0.1 mg/kg/hr, and sufentanil, 2.5 ug/kg/hr. Pancuronium, 0.025 mg/kg, was administered every hour. Epidural analgesia in the TEA group was induced, over a period of 10 minutes, with a mixture of 0.375% bupivacaine plus sufentanil, 1:200,000 (i.e., 5 ug/mL) in a dose of 0.05 mL/cm body length. Continuous epidural analgesia was then started with 0.125% bupivacaine plus sufentanil, 1:1,000,000 (i.e., 1 ug/mL) at an infusion rate of 0.05 mL/cm body length/hour. Just before induction of GA, measurements were taken (point 2). IV anaesthesia was induced with etomidate, 0.2 mg/kg, midazolam, 0.1 mg/kg, and pancuronium, 0.1 mg/kg. IV anaesthesia was maintained with an infusion of midazolam, 0.1 mg/kg/hr, and after the establishment of cardiopulmonary bypass (CPB), a bolus of midazolam, 0.05 mg/kg, was administered IV; pancuronium, 0.025 mg/kg, was administered every hour.
Outcomes	Mortality Myocardial infarction Haemodynamic parameters Respiratory complications VAS scores Time to awakening Arrythmias (tachycardia) Adrenergic responses
Notes	All three articles

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	On the day before surgery, the patients were assigned randomly to either a TEA or a GA group
Allocation concealment (selection bias)	Unclear Risk	Not stated

Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	Re-sternotomy was necessary in two patients (1 in each group). In one TEA group patient, the epidural catheter was dislocated. These patients were excluded from the study
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias

Loick 1999

Methods Randomized controlled trial

Participants 70 patients scheduled for elective coronary artery bypass grafting
Seventy-two patients scheduled for elective CABG fulfilled the study criteria and were selected for the investigation. Disorders of the intestine and liver, gastritis, ulcera ventriculi and duodeni, autonomic neuropathy, and diabetes mellitus (patients receiving insulin or oral hypoglycaemic drugs) were exclusion criteria

Interventions General anaesthesia with clonidine IV or general anaesthesia with thoracic epidural analgesia with 25 patients in epidural group and 45 in the control group (with and without clonidine).
Anaesthesia was induced with sufentanil (1-2 mg/kg) and propofol (1-2 mg/kg). Pancuronium (0.1 mg/kg) was used to facilitate tracheal intubation. Anaesthesia was maintained by a continuous infusion of sufentanil (1-2 ug/kg/hr) and propofol (1-3 mg/kg/hr) throughout the surgical procedure. On the day of surgery, after insertion of the invasive catheters, the patients received 8-12 mL of bupivacaine 0.375% and 16-24 ug of sufentanil into the epidural space. In the clonidine group, patients received a standardized opioid-based general anaesthesia supplemented with IV clonidine. In the control group, patients received a standardized opioid-based general anaesthesia without any supplement. Postoperative pain management consisted of an IV

application of 1 g of paracetamol four times daily. Additionally, patients in the clonidine and control groups were allowed to administer a bolus of 2 mg of piritramide IV on demand by a patient-controlled analgesia device with a lockout time of 20 min. Patients in the TEA group received a continuous infusion of 2-3 mL of bupivacaine 0.75% via the epidural catheter. If the patient was < 65 yr of age, the bupivacaine solution contained 1 ug/mL sufentanil, but this drug was not given to older patients. If pain relief was not sufficient, patients administered an additional 2 mL of bupivacaine with a lockout interval of 20 min. IV piritramide was supplemented for additional pain relief.

Outcomes Mortality
Myocardial infarction and ischaemia
Haemodynamics, lactate, cortisol plasma levels, and cardiac enzymes

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	"The patients were randomly allocated to one of the following three study groups"
Allocation concealment (selection bias)	Unclear Risk	Not stated
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Unclear Risk	Not stated
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias

Lundstrom 2005

Methods	Randomized controlled trial
Participants	A total of 50 patients undergoing elective coronary artery bypass grafting The criteria for inclusion in the study were age greater than 18 years, sinus rhythm on the ECG preoperatively, and written and oral informed consent. The criteria for exclusion from the study were oral anticoagulation and coagulopathy
Interventions	Conventional IV anaesthesia (24 patients) or general anaesthesia combined with thoracic epidural anaesthesia followed by postoperative epidural analgesia (26 patients) with bupivacaine Epidural analgesia was induced with 8 to 10 mL of bupivacaine, 5 mg/mL. Anaesthesia was induced with IV midazolam, 3 to 5 mg, fentanyl, 0.3 mg, and a dose of pancuronium, 0.1 mg/kg. Anaesthesia was maintained with isoflurane and a continuous epidural infusion of bupivacaine, 1.25 mg/mL, with morphine, 25 ug/mL and 5 mL/h. Top-up bolus doses of 4 mL of bupivacaine, 5 mg/mL, were administered hourly during the operation. The administration of fentanyl was restricted to the dose given at the induction of general anaesthesia. Postoperatively, the epidural infusion continued, and bolus doses of 4 mL of 0.25% bupivacaine were administered as needed Anaesthesia was induced with midazolam, 3 to 5 mg, fentanyl, 15 to 30 ug/kg, and pancuronium, 0.1 mg/kg, which were administered at induction only and not repeated. Anaesthesia was maintained with isoflurane. Analgesia in the CON group was provided with intermittent IV morphine boluses (2.5 to 5 mg) until the morning of the first postoperative day when morphine, 5 to 10 mg, orally were given as needed. Postoperatively, all patients received oral paracetamol, 1 g every 6 h.
Outcomes	Mortality Respiratory complications: episodic hypoxaemia

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	"Patients were randomly assigned to receive either conventional IV anaesthesia (CON) or general anaesthesia combined with TEA. The randomization list was generated from a table of random numbers."
Allocation concealment (selection bias)	Unclear Risk	Not stated
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	All pre-specified outcomes reported
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation stated

Moore 1995

Methods	Randomized controlled trial
Participants	18 patients undergoing elective coronary artery bypass grafting They had no history of metabolic or endocrine disease and had a normal bleeding time
Interventions	General anaesthesia alone or combined with thoracic epidural analgesia with 9 patients in each group Bupivacaine 0.5% was given in 2 mL increments to achieve a adequate block, followed by an infusion of 0.375% bupivacaine at 5-8 mL/hr. General anaesthesia was induced by all patients with sufentanil 10 ug/kg, followed by a sleep-dose of thiopentone. Pancuronium 0.1 mg/kg was given and ventilation was with nitrous oxide in 50% oxygen. Post-OK analgesia was with 0.25 % bupivacaine at 5-8 mL/hr, increments of 2.5 mg papaveretum IV was given in the control group.

Outcomes	Mortality Plasma catacholamines Plasma cortisol Serum insulin and growth hormone Haemodynamic parameters

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	Patients were allocated by selection of a sealed envelope
Allocation concealment (selection bias)	Low Risk	Sealed envelopes
Blinding (performance bias and detection bias)	Unclear Risk	Not stated
Incomplete outcome data (attrition bias)	Unclear Risk	One patient had a severe haemorrhage and data from this patient were not presented
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation not stated

Nygard 2004

Methods	Randomized controlled trial
Participants	163 patients scheduled for elective coronary artery bypass grafting Patients scheduled for elective CABG were screened for participation in the study. Inclusion criterion was sinus rhythm. Exclusion criteria were off-pump surgery; implanted pacemaker; use of amiodarone within 4 months of enrolment; a history of amiodarone toxicity; known thyroid disease, liver disease, or uncontrolled heart failure; a resting heart rate of less than 50 beats/min in the absence of medical therapy known to slow the heart rate; anticoagulant medication with warfarin; coagulopathy; pregnancy; and use of antiarrhythmic drugs other than alfa1-receptor antagonists, calcium channel antagonists, and digoxin.

Interventions Group E (44 patients) had perioperative TEA, group E and A had TEA and amiodarone (35 patients), group A had amiodarone (36 patients), and group C served as control (48 patients).
On arrival in the operating room, epidural analgesia was induced with 8 to 10 mL of bupivacaine, 5 mg/mL. Anaesthesia was induced with intravenous (IV) midazolam, 3 to 5 mg, fentanyl, 0.3 mg, and pancuronium, 0.1 mg/kg. Anaesthesia was maintained with isoflurane in oxygen and a continuous epidural infusion of bupivacaine, 1.25 mg/mL, with morphine, 25 ug/mL, 5 mL/h. Additional bolus doses of 4 mL of bupivacaine, 5 mg/mL, were given hourly during the operation. Fentanyl was restricted to the dose given at induction of anaesthesia. Postoperatively, the epidural infusion was continued for 4 days. In groups A and C, anaesthesia was induced with midazolam, 3 to 5 mg, fentanyl, 15 to 30 ug/kg, and pancuronium, 0.1 mg/kg. Anaesthesia was maintained with isoflurane in oxygen. Postoperative analgesia in the non-TEA groups was provided with intermittent IV morphine boluses (2.5 to 5 mg) until the morning of the first postoperative day when 5 to 10 mg of oral morphine was given as needed.

Outcomes Mortality
Supraventricular tachyarrhythmias

Notes

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	Patients were randomly assigned to four groups; randomization was 1:1:1:1
Allocation concealment (selection bias)	Unclear Risk	The randomization list was generated from a computerized table of random numbers
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	Of the 196 patients included, 163 were evaluated: 18 patients had sur-

		gery cancelled, and 4 patients had a change in surgical procedure. One withdrew consent preoperatively, and 6 withdrew consent postoperatively. One patient had a stroke before surgery, and in 1 patient placement of the epidural catheter was unsuccessful. Two patients were excluded because of protocol violations.
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation stated

Onan 2011

Methods	A prospective randomized study
Participants	30 patients with documented 3-vessel coronary artery disease who were scheduled for elective coronary artery bypass graft surgery
Interventions	In both groups, anesthesia was induced with midazolam (0.1-0.2 mg/kg), fentanyl (7-10 g/kg), and rocuronium (0.6 mg/kg). The patients in the GA TEA group received a 20-mg bolus of 0.25% bupivacaine through the epidural catheters 1 hour before surgery. During the intraoperative period, 0.25% bupivacaine was infused at a rate of 20 mg/hr. The patients received a continuous epidural infusion of 0.125% bupivacaine, 4 to 10 mL/h, after surgery to attain sensory blockade.
Outcomes	Immunoreactivity (Mortality) (Myocardial infarction) Graft blood flow

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear Risk	"The patients were assigned randomly into 2 groups"

Allocation concealment (selection bias) Risk	Unclear	Not clear
Blinding (performance bias and detection bias)	High Risk	Not blinded
Incomplete outcome data (attrition bias)	Low Risk	Data appear to be completed
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation stated

Priestley 2002

Methods Randomized controlled trial

Participants 100 patients scheduled for elective coronary artery bypass grafting All patients presenting for elective CABG were eligible for inclusion unless they had one or more of the following exclusion criteria: contraindications to the epidural technique (e.g., pre-existing coagulopathy, anticoagulation (i.e., full therapeutic doses of standard or low-molecular-weight heparin, warfarin, thrombolytic drugs, or potent antiplatelet drugs), or systemic or local infection); arthritis of the thoracic or cervical spine with a history of associated neurologic deficit; coexisting surgery (e.g., valvular, carotid, or aortic surgery); contraindications to any of the intended drugs in the treatment protocol; significant alcohol or other substance abuse; cognitive impairment; or other reason for inability to comply with treatment as assessed by the investigators.

Interventions High (T1 to T4) thoracic epidural anaesthesia (TEA) with ropivacaine 1% (4 mL bolus, 3-5 mL/h infusion), with fentanyl (100 ug bolus, 15-25 ug/hr infusion) and a propofol infusion (6 mg/kg/hr) in 50 patients. Another 50 patients (the general anaesthesia group) received fentanyl 15 ug/kg and propofol (5 mg/kg/hr), followed by IV morphine patient-controlled analgesia. On the day of surgery, after monitoring devices were inserted, an epidural bolus of 4 mL ropivacaine 1% and fentanyl 100 ug was

	administered, with supplemental ropivacaine 1% given as necessary to obtain blockade. After the bolus, an epidural infusion was commenced with ropivacaine 1% and fentanyl 5 ug/mL, and this continued for 48 h at 3-5 mL/hr. General anaesthesia (GA) in the TEA group consisted of IV fentanyl 2 ug/kg plus propofol 15 mg/kg/hr until consciousness was lost, followed by a propofol infusion at 6 mg/kg/hr, which continued until wiring of the sternum was completed. The GA group received fentanyl 15 ug/kg in divided doses from the induction of anaesthesia to sternotomy, in addition to propofol 15 mg/kg/hr until loss of consciousness, followed by a propofol infusion of 5 mg/kg/h (the larger fentanyl dose allowed a slightly smaller propofol dose than in the TEA group) until sternal closure. During cardiopulmonary bypass (CPB), a morphine infusion was commenced at 40 ug/kg/hr. All patients received pancuronium 0.1 mg/kg for muscle relaxation
Outcomes	Mortality VAS pain score Stroke Respiratory parameters: spirometry results Time to extubation Length of hospital stay Mobilization goals

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	Block randomization using sealed envelopes was used; patients at high risk were randomized separately
Allocation concealment (selection bias)	Low Risk	Sealed envelopes
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Unclear Risk	Not stated

Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation stated

Rein 1989

Methods	Randomized controlled trial
Participants	16 male patients requiring aorta-coronary bypass with extra-corporal circulation
Interventions	General anaesthesia alone or general anaesthesia combined with thoracic epidural analgesia (8 patients in each group) All patients received morphine-scopolamine as premedication. General anaesthesia was obtained by the administration of thiopentone, pancuronium, nitrous oxide, diazepam and oxygen. The control group received fentanyl 54 ug/kg , the study group received fentanyl 14 ug/kg. TEA at T4-T5, initial dose of 50 mg bupivacaine, followed by 20 mg/hr during surgery. Postoperatively the control patients received morphine, the TEA patients were treated with epidural bupivacaine at 20 mg/hr.
Outcomes	Transcapillary fluid balance Postoperative haemodynamics (Mortality)

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	"16 male patients were allocated at random to two groups"
Allocation concealment (selection bias)	Unclear Risk	Not stated
Blinding (performance bias and detection bias)	Unclear Risk	Not stated
Incomplete outcome data (attrition bias)	Low Risk	One patient died 9 hr postoperatively and was excluded from the final analyses
Selective reporting (reporting bias)	Unclear Risk	Not stated

Royse 2003

Methods	Randomized controlled trial
Participants	76 patients receiving elective coronary artery bypass grafting with cardiopulmonary bypass
Interventions	High thoracic epidural analgesia with ropivacaine and fentanyl (37 patients) or IV morphine analgesia (39 patients) Acetaminophen, indomethacin, and tramadol were allowed as supplemental analgesia in both groups Epidural at T1-2 or T2-3. Eight mL of 0.5% ropivacaine with 20 ug of fentanyl was administered prior to induction of anaesthesia. Thereafter, ropivacaine 0.2% with fentanyl 2 ug/mL was infused at a rate of 5 to 14 mL per hour, adjusted to attain a sensory blockade of T1 to T10, and was ceased at 6:00 am on postoperative day 3. Anaesthesia consisted of midazolam (3 to 5 mg), fentanyl (200 ug), and a target-controlled infusion of propofol. For the control group anaesthesia consisted of midazolam (3 to 5 mg), propofol (2 to 4 g/mL), and a 2-stage target controlled alfentanil infusion (2 ug/mL, reduced to 0.05 ug/mL after cardiopulmonary bypass, and ceased after sternal wiring. Nurses were permitted to administer boluses of morphine in the intensive care unit until the patient was awake. This was followed by demand patient controlled intravenous morphine (1 mg bolus with 5 minute lockout period), which was continued until 6:00 am on postoperative day 3.
Outcomes	Pain Physiotherapy cooperation Depression and post-traumatic stress Somatosensory sensitization Lung function Intraoperative haemodynamics (Mortality) (Myocardial infarction)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low Risk	Eighty patients undergoing elective CABG were randomized
Allocation concealment (selection bias)	Unclear Risk	Not described
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	4 patients were withdrawn: 1 patient withdrew itself from the study after randomization, deciding not to participate in research, and 2 patients failed epidurals and 1 patient from the control group requested the epidural
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation not stated

Scott 2001

Methods	Randomized controlled trial
Participants	408 patients undergoing elective coronary artery bypass grafting with a normal coagulation screen and an ejection fraction of > 35%
Interventions	General anaesthesia alone (202 patients) or general anaesthesia combined with thoracic epidural analgesia (bupivacaine and clonidine) in 206 patients All patients received target-controlled infusions (TCIs) of propofol and alfentanil for anaesthesia and analgesia, respectively. In Group GA, TCI of alfentanil continued for 24 hr and was then converted to a patient-controlled analgesia (PCA) IV morphine pump for another 48 h by using 1 mg bolus dosing with a 3 min lockout period. Patients in Group TEA had a thoracic epidural catheter sited

	in the operating theatre immediately before surgery at the T2-3 or T3-4 interspace with an initial bolus of 5 mL bupivacaine 0.5% followed by another 5 mL bolus after 10 min. After induction of GA and when central haemodynamic status was stable, a continuous infusion of 0.125% bupivacaine and 0.0006% clonidine (300 ug in 500 mL) commenced at an initial rate of 10 mL/hr. In Group TEA, the epidural infusion continued for 96 hr. "Top-up" bolus doses up to a maximum of 4 mL of 0.25% bupivacaine were administered either when the patient complained of pain.
Outcomes	(Mortality) Myocardial infarction Supraventricular arrhythmias Stroke or cerebrovascular accident Pulmonary complications Acute confusion Significant bleeding Renal failure Incidence of major organ complications

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	"Patients were randomized to one of two regimens...by using cards drawn from a sealed envelope"
Allocation concealment (selection bias)	Low Risk	Sealed envelope
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	12 subjects had insufficient data
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation stated. Interim analysis performed and presented after 120 patients

Sharma 2010

Methods	Randomized controlled trial
Participants	Sixty patients scheduled for elective OPCAB
Interventions	Patients in both the groups received general anaesthesia as per hospital protocol. Intravenous propofol (1-1.5 mg/kg) for induction of anesthesia along with fentanyl citrate (2-3 μgm/kg), midazolam (0.04 mg/kg) and vecuronium bromide (0.1 mg/kg) while isoflurane (1- 2 MAC) in air and oxygen mixture was used for maintenance of anesthesia. An epidural catheter was placed at C7-T1 /T1 -T2 level. Intrathecal placement was ruled out by using 3 mL of 2% lignocaine as a test dose. Once on the operation table, the patient was administered a bolus dose of 8-10 mL of bupivacaine (0.25%), inducing sensory block till at least T4. After confirming the block by loss of sensation to cold and pin prick, general anesthesia was administered. Bupivacaine infusion (0.125%) with 1μg/mL fentanyl citrate) at the rate of 5 mL/hr was commenced and continued till 3rd postoperative day for providing intra- and postoperative analgesia.
Outcomes	Postoperative spirometric values Postoperative PaO_2/FiO_2 ratio and $PaCO_2$ values Painscores (Mortality)
Notes	Only obese patients (BMI > 30 kg/m^2) were included

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear Risk	"Patients were randomized into two groups of 30 each."
Allocation concealment (selection bias)	Unclear Risk	Not clear
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	Data appear to be completed

Selective reporting (reporting bias)	Unclear Risk	Appears to be free of other sources of bias. Sample size calculation not stated

Stenseth 1994

Methods	Randomized controlled trial
Participants	28 male patients < 65 years and with an ejection fraction of > 50% undergoing cardiac surgery. They were all ASA III with double or triple vessel disease
Interventions	General anaesthesia with high dose fentanyl (10 patients), general anaesthesia with low dose fentanyl and thoracic epidural analgesia (18 patients). Epidural at T4-5 or T5-6. 10 mL 0.5% bupivacaine, top up doses of 4 mL 0.5% bupivacaine during surgery. GA with thiopentone, pancuronium. High dose fentanyl was 20-30 ug/kg, low dose fentanyl was 5 ug/kg. HF received morphine IV on demand, both epidural groups received a continuous epidural infusion of bupivacaine 0.5 % at 3 mL/hr with additional top ups of 4 mL every hour.
Outcomes	(Mortality) (Myocardial infarction) Hypertension Tachycardia Other haemodynamic parameters Use of vasoactive drugs

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	30 male patients gave informed consent and were randomized into one of three groups
Allocation concealment (selection bias)	Unclear Risk	Not stated
Blinding (performance bias and detection bias)	High Risk	

Incomplete outcome data (attrition bias)	Low Risk	Two patients were excluded from the final analysis due to surgical problems
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation not stated

Stenseth 1996

Methods Randomized controlled trial

Participants 52 male patients age < 65 years and with an ejection fraction of > 50%. They were all in NYHA class III and presented with double- or triple-vessel disease

Interventions High dose fentanyl general anaesthesia and an epidural group receiving low dose fentanyl general anaesthesia + thoracic epidural analgesia with bupivacaine 0.5% (26 patients in each group)

Patients allocated to the epidural group had an epidural catheter inserted at level T4- T5 or T5-T6. Epidural group patients received an epidural injection of 10 mL of bupivacaine 5 mg/mL. Top up bolus doses of 4 mL bupivacaine 5 mg/mL were given hourly during the operation. General anaesthesia consisted of thiopentone, diazepam, nitrous oxide and pancuronium (with no difference between the groups) in addition to fentanyl. The control group patients received a total of 55 ug/kg of fentanyl, the epidural group a total of 15 ug/kg. Control group patients received morphine IV on demand for pain relief during the first 20 hr after surgery. During the next 2 days daily paracetamol 3.2 g and codeine 240 mg (Paralgin forte) were given rectally as basal analgesia, which was supplemented with morphine IV as needed. Epidural group patients received a continuous epidural infusion of bupivacaine 5 mg/ml, 3 ml/h with additional top up doses of 4 mL bupivacaine every 4 hr and supplementation with IV morphine when needed. They received morphine epidurally 4-6 mg 3-4

	times a day for the next 2 days, supplemented with bupivacaine 5 mg/mL and morphine IV when needed. For both groups, supplementation was most often needed in association with physiotherapy and mobilization. From the 3rd postoperative day all patients received only Paralgin forte on request
Outcomes	(Mortality) (Myocardial infarction) Extubation time Spirometry results after surgery

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	54 male patients were randomized into two groups
Allocation concealment (selection bias)	Unclear Risk	Not stated
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	Two patients were excluded from the analysis because of the suffered complications
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation not stated

Svircevic 2011

Methods	Two centre, randomized controlled trial
Participants	656 patients scheduled for elective cardiac surgery, including off-pump procedures
Interventions	Patients allocated to the epidural group received a thoracic epidural catheter at least 4 h before heparinization. The epidural catheter was inserted in the thoracic 2–3 or thoracic 3–4 intervertebral space. The location of the catheter was verified before induction of GA with a test dose of lidocaine (Xylocain 2%, 3 ml). Before the start of GA, an epidural injection of 0.1 ml/kg was administered of a solution of 0.08 mg/ml morphine and 0.125 mg/ml bupivacaine, followed by a continuous infusion of 4–8 ml/h of the same solution. The GA technique for both groups consisted of 0.1–0.3 mg/kg etomidate, 0.15 mg/kg pancuronium, and 100–200 µg remifentanil at induction, followed by a continuous infusion of 1–4 $mg \cdot kg^{-1} \cdot h^{-1}$ propofol or 1–1.5% sevoflurane, and 0.01 $mg \cdot kg^{-1} \cdot h^{-1}$ remifentanil. Hypnotic depth was monitored electroencephalographically with a bispectral index monitor.
Outcomes	Mortality Myocardial infarction Pulmonary complications Length of hospital stay Arrhythmias Stroke

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	The random allocation sequence was concealed and computer-generated in permuted unequal blocks, accessible through an Internet site
Allocation concealment (selection bias)	Low Risk	The random allocation sequence was concealed
Blinding (performance bias	High Risk	Not blinded

and detection bias)		
Incomplete outcome data (attrition bias)	Low Risk	One patient was excluded because his surgery was cancelled, and one patient withdrew his consent after randomization
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation stated

Tenling 1999

Methods Randomized controlled trial

Participants 28 patients scheduled for coronary artery bypass grafting. Inclusion criteria were stable angina pectoris with a left ventricular ejection fraction of more than 40%

Interventions Perioperative and postoperative TEA (bupivacaine) was added to general anaesthesia (GA) in 14 patients, and 14 patients receiving GA alone served as controls

Epidural at T3-4 or T4-5. Epidural analgesia was induced with 8 to 12 mL of bupivacaine, 5 mg/mL. The block was maintained with an infusion of bupivacaine, 5 mg/mL, 4 to 8 mL/hr, until the patient arrived at the intensive care unit. Anaesthesia was induced with fentanyl, 5 to 10 ug/kg; thiopental, 1.5 to 2.5 mg/kg; and pancuronium, 0.1 mg/kg. In the TEA group, fentanyl was restricted to the dose administered at induction. From then on, analgesia was achieved with TEA. The GA group was administered small doses of fentanyl as needed (1 to 2 mg total). In both groups, anaesthesia was maintained with inhaled isoflurane, 0.5 to 1.0 minimal alveolar concentration.

In the GA group, postoperative analgesia was achieved with titrated doses of ketobemidone, 1 to 3 mg intravenously, according to standard procedures. The TEA group received a continuous infusion of bupivacaine, 2 mg/mL, and sufentanil, 1 ug/mL epidurally (3 to 7 mL/hr), from arrival at the ICU until the end of the study on the day after surgery.

Outcomes Mortality
Respiratory: ventilation/perfusion mismatch, atelectasis, time to extubation

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low Risk	"After giving their informed consent, 30 patients scheduled for CABG were randomized to receive either general anaesthesia (GA group) or GA with TEA (TEA group). Randomization was achieved with sealed envelopes"
Allocation concealment (selection bias)	Low Risk	Sealed envelopes
Blinding (performance bias and detection bias)	High Risk	
Incomplete outcome data (attrition bias)	Low Risk	Two patients were excluded from the analyses
Selective reporting (reporting bias)	Low Risk	Appears to be free of other sources of bias. Sample size calculation stated

Characteristics of excluded studies

	Reason for exclusion
Chae 1998	No adequate sequence generation
Dohle 2001	No adequate sequence generation and no allocation concealment
Fawcett 1997	No adequate sequence generation
Greisen 2012	Not randomized
Jakobsen 2012	No relevant outcomes reported
Jideus 2001	Not randomized
Kessler 2005	No adequate sequence generation
Liang 2012	Comparison between epidural anesthesia perioperatively and postoperatively
Liem 1992a	No relevant outcomes reported
Liem 1992b	No relevant outcomes reported
Mehta 1998	No adequate sequence generation and no allocation concealment
Olivier 2005	No comparison to general anaesthesia
Stenseth 1995	No relevant outcomes reported
Thorelius 1996	No adequate sequence generation

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Chapter 5

Meta-analysis of thoracic epidural anesthesia versus general anesthesia for cardiac surgery

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Abstract

Background

A combination of general anesthesia (GA) with thoracic epidural anesthesia (TEA) may have a beneficial effect on clinical outcomes after cardiac surgery. We have performed a meta-analysis to compare mortality and cardiac, respiratory, and neurologic complications in patients undergoing cardiac surgery with GA alone or a combination of GA with TEA.

Methods

Randomized studies comparing outcomes in patients undergoing cardiac surgery with either GA alone or GA in combination with TEA were retrieved from PubMed, Science Citation index, EMBASE, CINHAL, and Central Cochrane Controlled Trial Register databases.

Results

The search strategy yielded 1,390 studies; 28 studies that included 2,731 patients met the selection criteria. Compared with GA alone, the combined risk ratio for patients receiving GA with TEA was 0.81 (95% CI: 0.40–1.64) for mortality, 0.80 (95% CI: 0.52–1.24) for myocardial infarction, and 0.59 (95% CI: 0.24–1.46) for stroke. The risk ratios for the respiratory complications and supraventricular arrhythmias were 0.53 (95% CI: 0.40–0.69) and 0.68 (95% CI: 0.50–0.93), respectively.

Conclusions

This meta-analysis showed that the use of TEA in patients undergoing cardiac surgery reduces the risk of postoperative supraventricular arrhythmias and respiratory complications. The sparsity of events precludes conclusions about mortality, myocardial infarction, and stroke, but the estimates suggest a reduced risk after TEA. The risk of side effects of TEA, including epidural hematoma, could not be assessed with the current dataset, and therefore TEA should be used with caution until its benefit-harm profile is further elucidated.

Outcomes after cardiac surgery have been markedly improved over recent decades because of advances in anesthesiology, surgery, cardiopulmonary bypass, and postoperative care.[1,2] A combination of general anesthesia (GA) with thoracic epidural anesthesia (TEA) may have an additional beneficial effect on outcomes after cardiac surgery,[3–5] compared with GA alone. TEA may enhance coronary perfusion, improve myocardial oxygen balance, and reduce the incidence of tachyarrhythmias and perioperative myocardial ischemia through sympathycolysis.[6,7] The excellent analgesia that is associated with TEA facilitates early tracheal extubation and may prevent respiratory complications.[8,9]

TEA in cardiac surgery is controversial, considering possible complications of TEA, including spinal cord compression caused by a hematoma or abscess. Systematic anticoagulation needed during cardiopulmonary bypass could increase the incidence of epidural hematoma related to the use of an epidural catheter.[10] More commonly, the intense sympathycolysis may lead to systemic hypotension, which can be difficult to correct. The majority of studies comparing GA with the combination of GA and TEA were insufficiently powered to quantify the effect of TEA on clinical outcome measures. A previous meta-analysis by Liu et al.[11] was published in 2004 and included 1,178 patients. This meta-analysis found no difference in rates of mortality or myocardial infarction after cardiac surgery for patients receiving TEA versus GA alone. Since then, several new randomized studies evaluating TEA in cardiac surgery have been published.

The purpose of this study was to update the meta-analysis and explore reasons for discrepancies between the clinical trials that have evaluated the effects of TEA on mortality and cardiac, respiratory, or neurologic complications in patients undergoing cardiac surgery.

Materials and Methodes

Search Process

We combined various synonyms for cardiac surgical procedures and epidural anesthesia to retrieve studies comparing GA and TEA from CENTRAL, PubMed, EMBASE, CINAHL, and Web of Science (SCI/SSCI). For EMBASE and PubMed, we

combined our topical search filter with a sensitive evidence-based search query for effectiveness studies. Bibliographies and references of selected publications and systematic reviews and editorials on cardiac surgery and epidural anesthesia were screened using Web of Science (SCI/SSCI).[7,8,11] The complete search strategy is presented in **appendix 1**. The current study only used published literature data, and no institutional review board approval was required by our institute.

Only randomized clinical studies published before January 1, 2010, that included adult patients (i.e., 18 yr or older) undergoing cardiac surgery, comparing the outcomes of the patients undergoing cardiac surgery with GA or the combination of GA and TEA, were considered for inclusion in the review. We applied no restrictions with respect to language.

Risk of Bias Assessment

All publications found during the search were manually and independently reviewed by the same two authors (V. S. and M. P. P.), using the risk of bias assessment tool [12] (**appendix 2**). Criteria that were used for assessing the risk of bias of the included studies were: method of randomization; concealed treatment allocation; blinding during pre-, peri-, and postoperative care; blinded data collection and analysis; blinded adjudication of study endpoints; and completeness of (follow-up) data. The decision on the suitability of a study for our analysis was compared by two authors (V. S. and M. P. P.). Discrepancies were resolved by discussion, where necessary, with the help of a third reviewer (D. v. D.).

Data Extraction and Principal Endpoints

Data were extracted from the full-text article of each included study, using a standardized data-extraction form (**appendix 2**). The principal endpoints for the current analysis were mortality, acute myocardial infarction, supraventricular tachyarrhythmia, and respiratory or neurologic complications (e.g., stroke, epidural hematoma, or abscess). These endpoints were chosen because of their clinical importance and frequency of reporting. More recent studies have also assessed the lengths of stay in the intensive care unit and in the hospital, but not enough data were available to pool a reliable estimate. From all included studies, data on the number of events for the endpoints were extracted for both the TEA and the GA groups. Because the endpoints

were analyzed separately, it is possible that studies attributed information to one, two, or more endpoints. The definition of myocardial infarction and stroke were those used in each study, although a sensitivity analysis was performed with an endpoint combining the two. The endpoint respiratory complication was defined as respiratory insufficiency requiring reintubation, prolonged ventilation, or a ventilatory-associated pneumonia, according to the reported data in the studies.

Statistical Methods

Meta-analysis was performed with MIX 2.0 Pro (release 2.0.0.9; BiostatXL, Tokyo, Japan) and Stata (release 10.0; StataCorp., College Station, TX). Patients who only had GA were treated as control groups, and patients with TEA were treated as intervention groups. For each trial, we calculated the risk per treatment group by dividing the number of events by the number of patients randomized. Subsequently, risk ratio (RR) and the corresponding 95% CIs were calculated for each trial, where a risk ratio less than 1 indicates an effect in favor of TEA. For trials without events in the control group, the RR and its SE could not be calculated. To deal with this problem, it is common to add 0.5 or a smaller value to each cell in the contingency table of these trials. This is, nevertheless, known to cause bias [13] when treatment arm sizes are unequal, as was the case with a number of the included studies. We therefore used a treatment arm–dependent approach, in which the correction was proportional to the size of the relevant treatment arm.[14] Sensitivity analyses were planned to assess the impact of different continuity corrections and weighting methods. To provide readers with information about control (baseline) risks and experimental group risks, L'Abbe plots were created for each outcome.

The presence of heterogeneity of outcomes across trials was assessed using the I^2 measure and the DerSimonian–Laird two-step between-study variance estimate, t^2.[15] The dataset was graphically explored by forest, Galbraith, L'Abbe, and funnel plots. We intended to use random-effects models, while anticipating that they effectively become fixed-effect syntheses when the between-study variance t^2 is estimated as being 0. The Mantel–Haenszel method was used for the fixed-effect syntheses.

Although a complete synthesis of the dataset was planned, it was anticipated that time to extubation as well as other factors that vary over time could be varying between studies and causing heterogeneity in the estimates. A metaregression as

well as subgroup analyses based on year of publication and time to extubation were therefore planned a priori. In addition, the presence of small study effects, indicative of biases related to selective reporting and selective publication of studies, was assessed with plots and Peters regression test.[16]

Results

Results of our search strategy are shown in **figure 1**. We have identified 1,390 titles, of which 1,167 studies did not satisfy the selection criteria or were duplicate publications retrieved from the five different databases. Full review was performed on 223 studies, of which 28 publications met all inclusion criteria. These 28 publications reported on a total of 2,731 patients: 1,416 patients with GA and 1,315 patients with GA plus TEA. Characteristics of the included trials are presented in **table 1**.

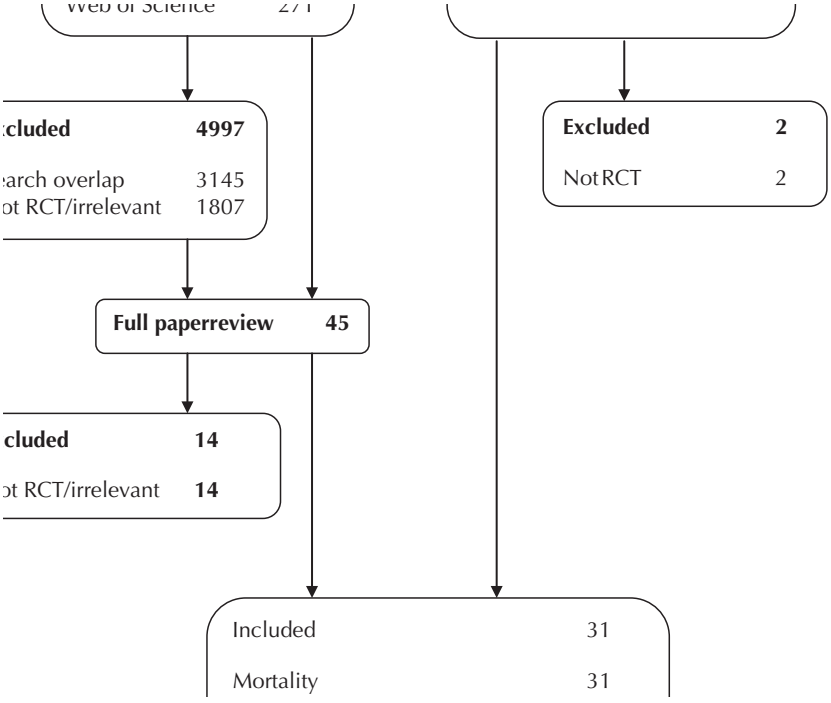

Figure 1. *Flowchart of the database search and selection process*

Mortality

All 28 studies reported mortality. None of the studies showed significant reduction in risk with TEA. The reported events were extremely sparse, with 25 studies reporting no events in either the TEA or the GA arms and 15 studies reporting no events at all. A total of 9 events were reported in the TEA arm, compared with 13 events in the GA arm. In the primary analysis, the 15 studies that did not report any events were excluded, resulting in 13 studies with a total number of 1,906 patients contributing to the dataset. The statistical heterogeneity was small (I^2: 0% [95% CI: 0–57%]; t^2 = 0). Combining the data from 13 studies yielded a fixed-effect estimate of the RR of 0.81 (95% CI: 0.40–1.64). Results of the primary meta-analysis for mortality are presented in **table 2** and **figure 2**. Different continuity corrections and weighting methods had little effect on the results and yielded in RRs ranging from 0.79 to 0.81. Using mortality and myocardial infarction as combined outcome (assuming independence of the events) led to an RR of 0.79 (95% CI: 0.54–1.16).

Table 2. *The effect of TEA versus GA on mortality, myocardial infarction, supraventricular tachyarrhythmia, respiratory complications and stroke.*

Outcome	studies	RR	95% CI		events		patients	
					TEA	GA	TEA	GA
Mortality	28	0.81	0.40	1.64	9	13	931	975
Myocardial infarction	13	0.80	0.52	1.24	33	43	899	950
Supraventricular tachyarrhythmias	14	0.68	0.50	0.93	300	410	1069	1125
Respiratory complications	12	0.53	0.40	0.69	67	128	915	943
Stroke	6	0.59	0.24	1.46	6	11	735	734

A risk ratio of >1.00 indicates an increased risk in the TEA group.

CI denotes confidence interval; GA denotes general anesthesia; RR denotes risk ratio;

TEA denotes thoracic epidural anesthesia.

Table 1. *Characteristics of the studies contributing data to this meta-analysis*

Author	Year of publication	Participants		Concealed allocation	Blinding
		TEA+GA	GA		
El Baz[29]	1987	30	30	+	-
Rein[30]	1989	8	8	+	?
Liem[31]	1992	27	27	+	+
Kirno[20]	1994	10	10	+	-
Stenseth[32]	1994	18	10	+	?
Moore[34]	1995	9	9	+	?
Stenseth[9]	1996	26	26	+	?
Brix-Christensen[35]	1998	8	8	+	+
Loick[36]	1999	25	25	+	-
Tenling[37]	1999	14	14	+	-
Scott[6]	2001	206	206	+	+

Lost to follow-up (n)	Reported outcome measures	Interventions (epidural medication)
0	mortality respiratory complications neurologic complications	morphine
0	mortality	bupivacaine (bolus plus infusion)
4	mortality myocardial infarction supraventricular tachycardia's respiratory complications neurologic complications	bupivacaine/sufentanil (bolus plus infusion)
0	mortality neurologic complications	mepivacaine (bolus)
2	mortality myocardial infarction neurologic complications	bupivacaine (bolus plus infusion)
	mortality	Bupivacaine (bolus plus infusion)
2	mortality myocardial infarction	bupivacaine (bolus plus infusion)
0	mortality	bupivacaine/sufentanil (bolus plus infusion)
2	mortality myocardial infarction supraventricular tachycardia's neurologic complications	bupivacaine/sufentanil (bolus plus infusion)
2	mortality respiratory complications	bupivacaine/sufentanil (bolus plus infusion)
12	mortality myocardial infarction supraventricular tachycardia's respiratory complications neurologic complications	bupivacaine (bolus plus infusion)

Table 1. *Continued*

Author	Year of publication	Participants		Concealed allocation	Blinding
		TEA+GA	GA		
Bach[38]	2002	13	13	+	+
Fillinger[39]	2002	30	30	+	+
Priestley[5]	2002	50	50	+	-
Vries[40]	2002	30	30	+	?
Berendes[41]	2003	36	36	+	+
Royse[17]	2003	37	37	+	?
Kendall[42]	2004	8	8	+	?
Nygard[6]	2004	79	79	+	_

Lost to follow-up (n)	Reported outcome measures	Interventions (epidural medication)
0	mortality	bupivacaine (bolus plus infusion)
0	mortality myocardial infarction supraventricular tachycardia's respiratory complications neurologic complications	bupivacaine/morphine (bolus plus infusion)
0	mortality myocardial infarction supraventricular tachycardia's respiratory complications neurologic complications	ropivacaine/fentanyl (bolus plus infusion)
5	mortality myocardial infarction supraventricular tachycardia's respiratory complications neurologic complications	bupivacaine.sufentanil (bolus plus infusion)
0	mortality respiratory complications neurologic complications	bupivacaine.sufentanil (bolus plus infusion)
4	mortality supraventricular tachycardia's respiratory complications neurologic complications	ropivacaine/fentanyl (bolus plus infusion)
3	mortality myocardial infarction neurologic complications	bupivacaine/fentanyl (bolus plus infusion)
0	mortality supraventricular tachycardia's	bupivacaine/morphine (bolus plus infusion)

Table 1. *Continued*

Author	Year of publication	Participants TEA+GA	Participants GA	Concealed allocation	Blinding
Barrington[43]	2005	60	60	+	+
Lundstrom[44]	2005	26	26	+	?
Hansdottir[20]	2006	58	58	+	+
Kilickan[18]	2006	40	40	+	-
Langunilla[45]	2006	25	25	+	?
Bakhtiary[46]	2007	66	66	+	+
Heijmans[47]	2007	15	15	+	+
Caputo[48]	2009	36	38	+	+
Svircevic[49]	2010	325	329	+	+
Total		1315	1416		

GA denotes general anesthesia; TEA denotes thoracic epidural anesthesia.

Lost to follow-up (n)	Reported outcome measures	Interventions (epidural medication)
0	mortality myocardial infarction supraventricular tachycardia's respiratory complications neurologic complications	ropivacaine/fentanyl (boluses)
4	mortality respiratory complications	bupivacaine/morphine (bolus plus infusion)
16	mortality myocardial infarction supraventricular tachycardia's respiratory complications neurologic complications	bupivacaine/fentanyl (bolus plus infusion)
0	mortality supraventricular tachycardia's	bupivacaine (bolus plus infusion)
2	mortality	ropivacaine/fentanyl (bolus plus infusion)
0	mortality myocardial infarction supraventricular tachycardia's neurologic complications	ropivacaine.sufentanil (bolus plus infusion)
0	mortality myocardial infarction neurologic complications	bupivacaine/morphine (bolus plus infusion)
0	mortality myocardial infarction supraventricular tachycardia's neurologic complications	
0	mortality myocardial infarction supraventricular tachycardia's respiratory complications neurologic complications	bupivacaine/morphine

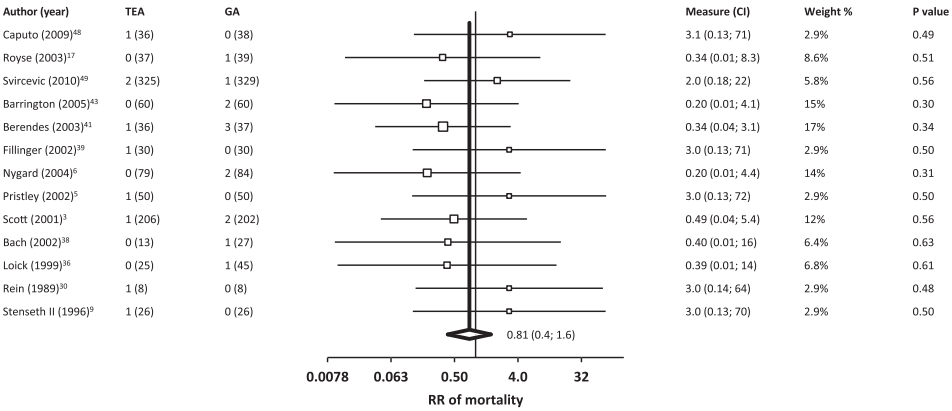

Figure 2. *Risk ratios and Forest plot for mortality in the first 2 weeks after surgery. GA = general anesthesia; RR = Risk ratio; TEA = thoracic epidural anesthesia.*

Myocardial Infarction

Fifteen studies with 2,041 patients reported on myocardial infarction. Of the 15 studies, two studies reported no events in both the TEA and the GA arms and they were excluded from the primary analysis. The analysis dataset contained 1,849 patients with 33 events in the TEA arm and 43 events in the GA arm. The I^2 statistic (I^2: 0%; 95% CI: 0–57%), as well as the t^2 statistic (t^2: 0), indicated that the statistical heterogeneity was low. Synthesis of the 13 studies showed no evidence for a difference in the risk of

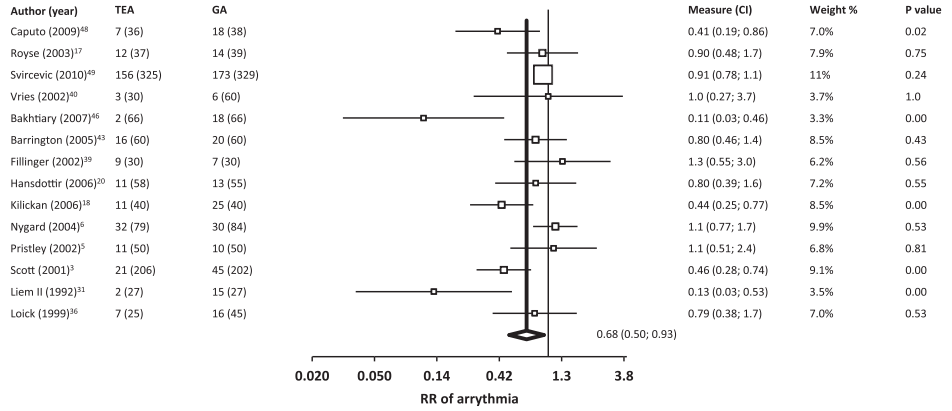

Figure 3. *Risk ratios and Forest plot for supraventricular tachyarrhythmias in the first 2 weeks after surgery. GA = general anesthesia; RR = Risk ratio; TEA = thoracic epidural anesthesia.*

acute myocardial infarction between groups of patients receiving TEA, compared with patients receiving GA alone (RR: 0.80; 95% CI: 0.52–1.24; see **table 2** and **fig. 3**). Sensitivity analyses with different continuity corrections and weighting methods had little effect on the results, with RRs ranging from 0.79 to 0.81.

Supraventricular Tachyarrhythmias

Fourteen studies with 2,194 patients reported on supraventricular tachyarrhythmias, with 300 events in the TEA and 410 events in the GA arms. There were no studies without events. Heterogeneity was substantial (I^2: 62% [95% CI: 33–79%]; $t^2 = 0.21$), and we applied a random-effects model for the synthesis. The resulting RR was 0.68 (95% CI: 0.50–0.93), showing that combining TEA with GA may be associated with a lower risk of supraventricular tachyarrhythmias than the use of GA alone. The 95% prediction interval ranges from 0.25 to 1.83. Meta-analysis results are shown in **table 2** and **figure 4**.

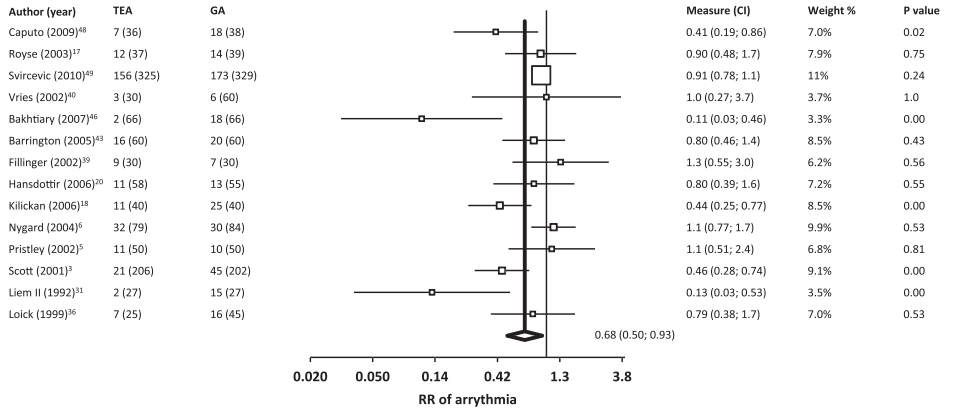

Figure 4. *Risk ratios and Forest plot for respiratory complications in the first 2 weeks after surgery. GA = general anesthesia; RR = Risk ratio; TEA = thoracic epidural anesthesia.*

Respiratory Complications

A total of 13 studies with 1,886 patients presented data on the number of patients who had had respiratory complications. The respiratory complications were rare, with five studies reporting no events in one of the treatment arms and one study reporting no events at all. The primary synthesis was performed on the 12 studies

that had one or more events in the study. There were 67 events in the TEA and 128 events in the GA arms. The I^2 statistic was low (I^2: 0%; 95% CI: 0–57%), and the t^2 statistic also showed no evidence of statistical heterogeneity (t^2: 0). Combined fixed-effect analysis of data from 1,858 patients of 12 studies showed a lower risk of respiratory complications for patients receiving TEA and GA during surgery, compared with those receiving GA alone (RR: 0.53; 95% CI: 0.40–0.69). Alternative continuity corrections and weighting models yielded RRs of 0.52–0.55.

Neurologic Complications

None of the trials reported events of epidural hematoma or abscess. Thirteen trials with 1,986 patients reported on stroke events. However, because of the extremely low event rate, seven studies reported no events at all, and only six studies with 1,469 patients were used for the primary analysis. There were 6 events in the TEA and 11 events in the GA arms. There was no evidence of statistical heterogeneity (I^2: 0%; 95% CI: 0–75%). Formal synthesis yielded an RR of 0.59 (95% CI: 0.24–1.46), indicating that the use of TEA was associated with a lower risk of stroke that may be substantial. However, the risk ratio estimate was not statistically significant and was based on a small number of events. Alternative weighting models had little impact on the results, but alternative continuity corrections that integrated the excluded studies yielded RRs from 0.52 to 0.77.

Additional Evaluations

Metaregression did not show likely associations between the study outcome and factors varying over the years of execution of the individual studies or risk of bias items for any of the outcomes. Neither graphical explorations nor formal regression tests showed evidence of small study effects due to selective dissemination of studies or study results for any of the above-mentioned endpoints. **Figure 5** contains risk-based L'Abbé plots, showing the per-study control group (baseline) risks, index group risks, and their relationship for all endpoints in a single graph.

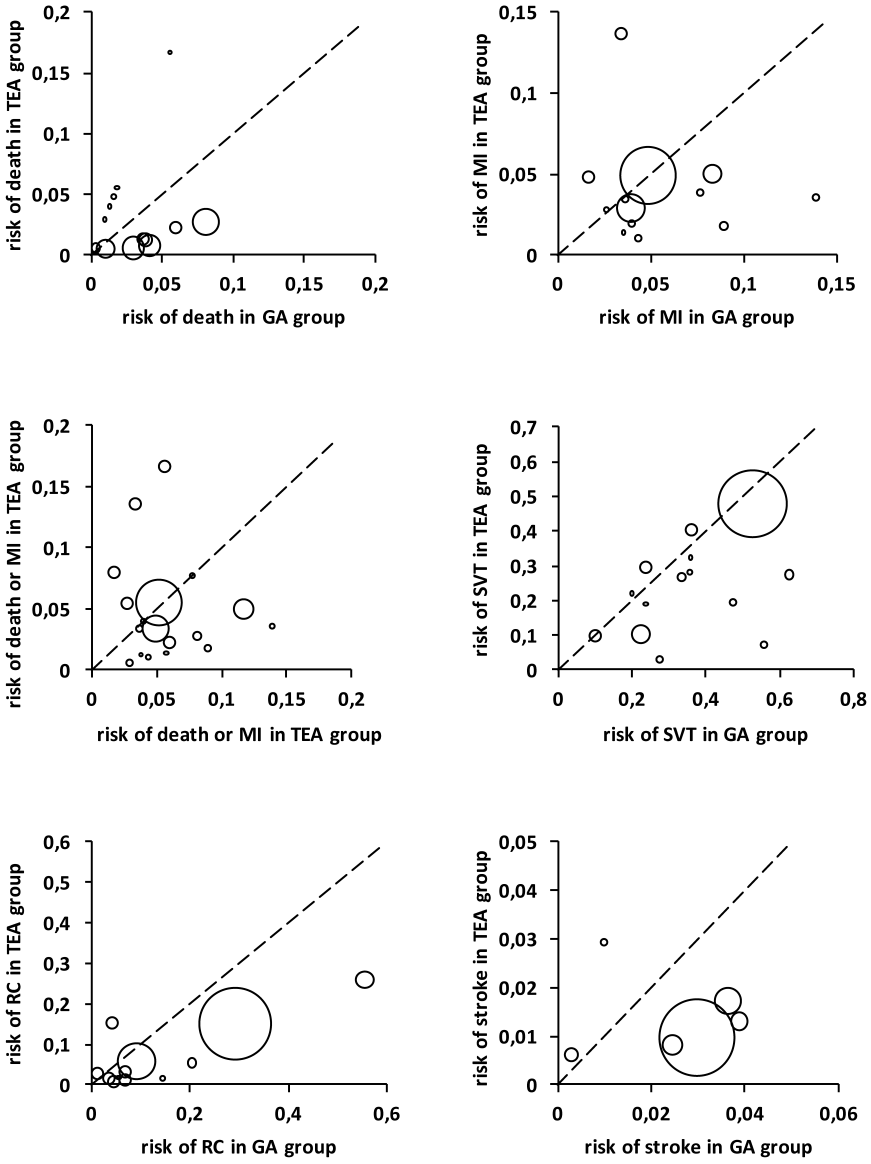

Figure 5. *Risk-based L'Abbé plots for baseline, index group risks, and relationship for endpoints. GA denotes general anesthesia; MI denotes myocardial infarction; RC denotes respiratory complications; SVT denotes supraventricular tachyarrhythmias; TEA denotes thoracic epidural anesthesia.*

Discussion

We have conducted a meta-analysis of clinical trials comparing the effects of cardiac surgery with and without TEA on mortality and cardiac, respiratory, and neurologic complications. Our meta-analysis showed statistically significant reductions in the incidence of supraventricular tachyarrhythmias and respiratory complications after TEA. There were no significant differences in the incidences of mortality, myocardial infarction, and stroke.

The potential of TEA for decreasing tachyarrhythmias has been reported before[3,17,18] and was confirmed in this meta-analysis. However, the included studies were heterogeneous, and the confidence intervals around the risk ratio estimates were wide. The study by Scott et al.[3] in 420 patients was contributing the most to this result. In this study, [beta]-blockers were discontinued 5 days perioperatively. Moreover, the patients randomized to TEA received the cardioprotective drug, clonidine, through their epidural catheter. This cardioprotective drug[19] was not administered to the control patients. The withdrawal of [beta]-blockers in all study patients and the selective use of clonidine in the patients randomized to TEA may explain the large benefit of TEA on supraventricular arrhythmias found in this trial. Although the Scott study was encouraging, most studies published since then were unable to repeat its results. A recent, well-designed study by Hansdottir[20] revealed no benefits of TEA on the incidence of tachyarrhythmias, plus a 17% failure of epidural catheter insertion. Recent studies showed that postoperative supraventricular tachyarrhythmias can also be reduced with less invasive treatments, such as [beta]-blockers and amiodarone.[6,21,22] The majority of the studies included in this meta-analysis did not report whether the patients also used drugs to prevent postoperative arrhythmias. It is therefore unclear whether TEA has an additional preventive effect in patients who are also administered prophylactic antiarrhythmic drugs after their operation.

Our meta-analysis also showed that TEA results in a statistically significant reduction in postoperative respiratory complications, which is consistent with previous meta-analyses.[8,11] This may be explained by the superior analgesia after TEA, which facilitates earlier spontaneous respiration in the intensive care unit and faster tracheal extubation. It has been shown, however, that other strategies that

allow earlier tracheal extubation can also reduce respiratory complications.[23–25] A previous meta-analysis by Liu[11] showed that pulmonary complications after cardiac surgery can also be reduced with spinal anesthesia. Interestingly, this benefit was not explained by a shorter time to extubation. As the risk of an epidural hematoma is considerably lower after a single spinal injection than after insertion of an epidural catheter, spinal anesthesia might be a viable option for cardiac surgical patients with a high risk of pulmonary complications.

There are several limitations associated with the included randomized studies that warrant caution in the interpretation of the results of this meta-analysis. First, the time period in which the studies were undertaken spanned 30 yr. The quality of anesthesiological and intensive care has clearly improved over these years. It is possible that some beneficial effects of TEA, such as earlier extubation, are currently also achieved with modern general anesthetics. Second, most of the included studies were designed to evaluate the effect of TEA on intermediate or surrogate outcome measures, instead of clinical endpoints. Third, the nonstandardized coverage of clinical outcomes in most studies carries a high risk of observer bias, in particular when the endpoint adjudication was not blinded.

Our findings are largely comparable with those of the two previous meta-analyses.[8,11] Because we were able to include 28 studies including 2,731 patients, which is substantially more patients than in the two previous meta-analyses, the effect estimates are more precise with narrower confidence intervals. Although the number of patients in the current meta-analysis is more than twice the number of patients in previous meta-analyses, the events were extremely sparse, and the current meta-analysis is still not sufficiently powered to detect small beneficial or harmful effects of TEA on mortality, myocardial infarction, paraplegia, and stroke. To demonstrate statistical significance for the reduction in the incidence of myocardial infarction from 3.8% after GA to 2.8% after TEA (as found in this meta-analysis), a sample size of at least 10,000 patients is required. It is obvious that such a large trial would be extremely difficult to perform.

Despite the benefit of TEA on supraventricular tachyarrhythmias and respiratory complications, our findings must be viewed with caution. Thoracic epidural anesthesia in cardiac surgery remains controversial in the absence of a sufficiently large, statistically significant effect on mortality, stroke, or myocardial infarction

while possible hazardous complications of TEA, such as epidural hematoma or abscess, must be taken into account. Systematic anticoagulation needed during cardiopulmonary bypass could increase the incidence of epidural hematoma related to the use of an epidural catheter.[10] More commonly, the intense sympathycolysis may lead to systemic hypotension, which can be difficult to correct.

In the included studies, no cases of epidural hematoma were reported, but this devastating complication is too rare to evaluate in randomized studies. There are a few reports[26,27] on neuraxial hematoma in cardiac surgery, of which some have directly been linked to TEA.[28] The benefit-harm trade-off could not be explored in the current framework of meta-analysis of randomized trials. However, given the severity of this complication and the lack of a clear beneficial effect on mortality, stroke, or myocardial infarction, the potential benefits of TEA in cardiac surgery may not be worth the potential risks.

In conclusion, this meta-analysis showed that the use of TEA in patients undergoing cardiac surgery reduces the risk of postoperative supraventricular arrhythmias and respiratory complications. The sparsity of events precludes conclusions about mortality, myocardial infarction, and stroke, but the estimates suggest a reduced risk after TEA. The risk of side effects of TEA, including epidural hematoma, could not be assessed with the current dataset, and therefore TEA should be used with caution until its benefit-harm profile is further elucidated.

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Database:
EMBASE (1989 to 2010)
Searchfilter:
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Database:
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Database:

Cochrane Anaesthesia Review Group trials register and CENTRAL (the current issue of The Cochrane Library).

Searchfilter:

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#11. (#7 or #8 or #10)
#12. (#11 and #6)

Appendix 2 Processing-form:
Epidural versus non-epidural anaesthesia in cardiac surgery

Article nr:
Date: //.
Name reviewer: Svircevic Passier van Dijk
First authors name .....
Year of publication .....

Study Quality

1 Group size				
Neuraxial	N=			
Control	N=			
2 Randomized allocation		Yes	No	Method unclear
3 Concealed allocation		Yes	No	Method unclear
4 Number Crossovers				
Neuraxial	N=			
Control	N=			
5 Maximum number dropouts				
Neuraxial	N=			
Control	N=			
6 Maximum number Loss-to-follow-up				
Neuraxial	N=			
Control	N=			
7 Intention to treat analyses		Yes	No	unclear
8 Blinded analyses		Yes	No	unclear
9 Blinding pre- and post surgery care		Yes	No	unclear
10 Standardized pre- and post surgery care		Yes	No	unclear
11 Blinding end points		Yes	No	unclear
12 Standardization endpoints		Yes	No	unclear

Preoperative data

13 Age

Neuraxial Mean= Sd=

Control Mean= Sd=

14 Males

Neuraxial N=

Control N=

15 Prior vascular surgery:

Neuraxial N=

Control N=

16 Diabetic status: Type 1 2 dialysis

Neuraxial N= N= N=

Control N= N= N=

17 Preoperative risk score: French score Parsonnet score Euro score

Neuraxial Mean= SD=

Control Mean= SD=

18 Type(s) of surgery .....

19 Type of neuraxial anaesthesia: Intrathecal epidural

20 Outcome measures

Primary endpoint .....

Secondary endpoints .....

21 Time to follow-up .....

22 Main outcomes of this study (give absolute numbers, no percentages)

Outcome	**Neuraxial group**	**Control group**	**p**
Mortality			
MI			
SVT			
Respiratory complications			

Other important outcomes:

.....

.....

main conclusion(s) (see last paragraph discussion):

.....

.....

Remarks:

.....

.....

.....

Chapter 6

Decrease in Quality of Life 1 Year after Cardiac Surgery

V. Svircevic, D. van Dijk, G.A. Ettema, A.P. Nierich,
C.J. Kalkman, K.G.M. Moons, L.M. Peelen

Abstract

Objective:

To investigate changes in health-related quality of life after elective cardiac surgery, and to identify predictors for a decreased HRQoL one year after elective cardiac surgery.

Design:

Cohort study

Setting:

Cardiac surgery hospital in the Netherlands

Patients:

Adult patients undergoing elective cardiac surgical procedures

Measurements:

HRQoL was measured in 2709 patients at baseline, 30 days and one year after surgery using the ShortForm 36 and EuroQoL questionnaires. Subsequently we identified perioperative factors related to a decrease in HRQoL one year after surgery.

Main Results:

Health related quality of life decreased in 16.2% of the patients after cardiac surgery. For the mental component summary score (MCS) of the SF-36 one year post-surgery, the independent predictors were age, female gender and MCS at baseline. For the physical component summary score (PCS) of the SF-36 and EuroQol additional independent factors were BMI, lung disease, diabetes mellitus, peripheral vascular disease, renal failure, poor left ventricle function and length of cardiopulmonary bypass. Prolonged ICU was an additional independent predictor for the both PCS and EuroQol, and prolonged hospital stay only for the PCS.

Conclusions

In about 1 out of 6 patients undergoing cardiac surgery quality of life has decreased at one year after surgery. Overall risk indicators for a decrease in HRQoL are age,

female gender and quality of life at baseline, and for an important part prolonged ICU and hospital stay, reflecting perioperative complications. Therefore, patients identified as 'high-risk' should be, carefully evaluated and treated, possibly requiring a dedicated 'high-risk patient perioperative process'.

Introduction

Over the last decades advances in surgical techniques, anesthesia and critical care medicine have reduced the risk of perioperative complications after cardiac surgery. Therefore there is now an increasing interest in health-related quality of life (HRQoL) endpoints[6-8] to better define the health benefits and risks associated with cardiac operations, especially in the elderly population with cardiac disease.[9] Previous studies have shown that, overall, quality of life improves after cardiac surgery.[2,6,7] However, not all patients benefit from cardiac surgery, and in some patients quality of life is even reduced after surgery.[10] Such suboptimal patient outcomes could be related to preoperative comorbidity, or result from perioperative complications.[11,12] Better insight in pre- and perioperative indicators for a reduced postoperative quality of life may influence postoperative care for patients at increased risk and perhaps even preoperative decision making.

The aim of our study was to describe changes in health-related quality of life after elective cardiac surgery, and to identify perioperative factors that are associated with a decreased HRQoL one year after elective cardiac surgery.

Materials and Methods

Study Population

This single-site cohort study included all adult, consecutive patients who underwent elective cardiac surgery in the period of January 2008 until March of 2010 at the Isala Clinics, Zwolle, The Netherlands. All patients consented to participate in our local cardiac surgery outcomes registry which contains data from the pre-, intra- and postoperative period on clinical condition and quality of life. Types of surgery varied

from coronary artery bypass grafting, valve surgery, maze procedures, redo cardiac surgery and combined procedures.

Outcome: HRQoL

HRQoL was measured at baseline, 30 day and 12 months postoperatively using Medical Outcomes Study 36-item Short Form Health Survey, version 2 (SF-36) and EuroQol (EQ5D).[13-16] Results of the SF-36 can be summarized according to the eight subscales that measure physical functioning, role limitations due to physical problems, social role functioning, role limitation due to emotional problems, bodily pain as well as sense of vitality, general health, and change in health. Scores of each subscale can be normalized to a scale ranging from 0 to 100, with lower scores representing a lower HRQoL. These eight subscales were further comprised to 2 scales according to existing algorithms:[13-14] a physical component summary (PCS) and a mental component summary (MCS) scale, each ranging from 0 to 100. The EuroQol instrument has been designed for self-completion by the respondent to report their health state on 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It can be comprised to one value ranging from 0 to 1, with 1 representing the highest possible HRQoL. Furthermore, it includes a visual analog scale (VAS) by which the patient marks his/her own health state on a thermometer calibrated from 0 (worst imaginable health state) to 100 (best imaginable health state).

Candidate predictors for decreased HRQoL

We a priori selected a total of fourteen candidate risk factors for mortality one year after cardiac surgery procedure based on existing literature,[17-19] and assumed that these are associated with quality of life after one year as well. These factors included the patients' gender, age, body mass index, presence of co-morbidities (hypertension, renal failure, chronic obstructive pulmonary disease, peripheral vascular disease, neurological disease and left ventricular ejection fraction), intra-operative data (kind of surgery, number of coronary artery bypass grafts and duration of cardiopulmonary bypass) and prolonged ICU and hospital stay. Prolonged ICU and hospital stay were defined as more than twice the median duration of either ICU or hospital stay respectively in our study population.

Statistical Analysis

For each HRQoL outcome (i.e. SF36 and EQ5D) we first analyzed differences between HRQoL measures at one year after the cardiac surgical procedure and the baseline HRQoL measures, using the paired Student's test. Clinically relevant differences were assessed by Cohen's effect size computed by dividing the mean difference between a post- and pre-intervention HRQoL scores by the pre-intervention standard deviation. An effect size of <0.20 can be considered as clinically irrelevant, 0.21-0.49 as small, 0.50-0.79 as moderate and >0.80 as large.[20] Furthermore, we analyzed the proportion of patients experiencing at least the minimally detectable differences (MDD) in HRQoL at one year. MDD is an arbitrary cut-off point at half a standard deviation higher than the quality of life before cardiac surgery.[21]

We used multivariable linear regression modeling to assess which factors were associated with a decrease in the HRQoL from baseline to one year after surgery. Continuous predictors were analyzed as linear terms as there were no indications of non-linearity based on cubic spline analysis. We developed separate models for MCS, PCS, and EQ5D as outcomes. For each of these outcomes we first analyzed a model containing preoperative and intraoperative risk factors. Subsequently, the variables prolonged ICU stay and prolonged hospital stay were added to the model, to investigate their independent predictive value.

Missing data were imputed by multiple imputation using the MICE algohritm in R. Sensitivity analysis was performed with the imputed data. Statistical analysis was performed using SPSS software version 15 (SPSS Inc.,Chicago, IL) and R version 2.14.1 (R, Auckland, New Zealand).

Results

2709 patients underwent elective cardiac surgery at from January 2008 until March of 2010. The median age at the date of cardiac surgery was 69.2 (53.6-79.8) years and the median EuroSCORE was 5 (1-10). Other baseline and intra-operative

characteristics of the patients are shown in **table 1**. The median duration of ICU and hospital admission were one (interquartile range 0-3.75) and nine days (interquartile range 6-22). 465 (17.2%) patients had a prolonged ICU stay and a total of 619 (22.8%) patients had a prolonged hospital admission. 95 (3.5%) of all patients died during their hospital stay. The 30 day follow-up could be completed in 93.4% (2530/2709) and one-year follow-up in 94.6% of the cases (2562/2709).

Table 1. *Baseline characteristics and intra-operative data*

	N=2709	Missing data (n)
Age (years)	69.2 (53.6-79.8)	0
Gender male	69.4	0
Euroscore	5 (1-10)	0
Weight (kg)	82 (65-100)	0
COPD	14.4	0
Hypertension	48.2	0
Diabetes mellitus	77.7	1
Peripheral vascular disease	10.2	0
Renal failure	8.1	0
Neurological disease	4.8	0
LVEF <30%	8.2	0
Type of surgery		0
CABG	70.3	
CABG off pump	4.6	
Aortic valve replacement	24.7	
Mitral valve replacement	18.3	
Other cardiac surgical procedure	4.0	
Number of anastomoses (CABG)	4 (2-5)	0
CPB time (min)	109 (62-219)	0
Aortic cross clamp time (min)	69 (37-136)	0

Data are % or median (interquartile range).
CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease. Neurological disease = history of stroke or other neurological dysfunction severely affecting ambulation or day-to-day functioning;
CPB = cardiopulmonary bypass; LVEF = left ventricular ejection fraction;

Both questionnaires and its summary scales indicated a slight decrease in HRQoL one month after cardiac surgery. The mean differences in HRQoL according to the different questionnaires are presented in table 2. One year postoperatively there was an overall moderate improvement in HRQoL as expressed by the physical component summary scale and the EuroQol score. These findings correspond with higher percentages of patients who have experienced a minimal detectable difference on these scales (last column of **table 2**). Health related quality of life decreased in 16.2% (439/2709) of the patients one year after cardiac surgery.

Results of the multivariable linear regression analysis are given in table 3 for the two summarized SF-36 scales and the EuroQol scale. Age, female gender, BMI, lung disease, diabetes mellitus, peripheral vascular disease, renal failure, poor left ventricle function, length of cardiopulmonary bypass and PCS at baseline were significantly associated with the physical component summary scale of SF-36 one year after surgery. For the mental component summary score at one year post-surgery, only age, female gender and MCS at baseline were independent predictors. Age, female gender, BMI, lung disease, diabetes mellitus, peripheral vascular disease, renal failure, poor left ventricle function, length of cardiopulmonary bypass and EuroQol at baseline were independent predictors of the EuroQol score at one year. Prolonged ICU stay was a strong independent predictor for decreased quality of life for the PCS of the SF-36 and EuroQol scale when added to these models, but not for the MCS scale one year post-surgery. Prolonged hospital stay was a strong independent predictor for decreased quality of life for the PCS of the SF-36 when added to the models, but not for the MCS scale and EuroQol, one year post-surgery. The results remained unchanged when the analyses were repeated with imputed data.

Table 2. *Changes in HRQoL between baseline, 30 days and one year after surgery across the different HRQoL questionnaires*

Endpoint	Baseline	30 day	Change	95% CI	Cohen's effect size[1]
PCS	33.9	32.7	-1.16	(-1.68 to -0.64)	0.09
MCS	44.2	43.5	-0.78	(-1.52 to -0.01)	0.05
EuroQol	0.74	0.71	-0.03	(-0.04 to -0.01)	0.11

[1] An effect size of <0.20 can be considered as clinically irrelevant, 0.20-0.49* as small, 0.50-0.79† as moderate and >0.80 as large
PCS = physical component summary; MCS = mental component summary;
CI = confidence interval; MDD = minimally detectable difference

Table 3. *HRQoL risk factors analysis*

	PCS								MCS			
	model 1				model 2				model 1			
	Beta	95%CI		P value	Beta	95%CI		P value	Beta	95%CI		P value
Age (years)	-0,12	-0,17	-0,08	,000	-0,11	-0,16	-0,07	,000	-0,08	-0,14	-0,02	0,01
Gender	-3,56	-4,61	-2,51	,000	-3,31	-4,36	-2,27	,000	-3,79	-5,11	-2,46	,000
BMI	-0,33	-0,44	-0,22	,000	-0,33	-0,44	-0,22	,000	0,04	-0,10	0,19	0,55
COPD	-1,68	-3,00	-0,35	0,013	-1,57	-2,88	-0,25	0,02	0,31	-1,38	2,00	0,72
Hypertension	-0,07	-0,86	1,00	0,888	0,01	-0,92	0,92	0,99	-0,62	-1,81	0,56	0,30
Diabetes mellitus	-1,76	-2,89	-0,63	0,002	-1,75	-2,86	-0,63	0,01	-1,19	-2,63	0,26	0,11
Peripheral vascular disease	-2,38	-3,92	-0,83	0,003	-2,40	-3,92	-0,87	0,01	-0,97	-2,93	0,99	0,33
Renal failure	-4,78	-6,54	-3,01	0,000	-3,84	-5,60	-2,01	,000	-1,83	-4,06	0,41	0,11
Neurological disease	-1,28	-3,49	0,92	0,254	-0,80	-2,98	1,38	0,47	-1,70	-4,45	1,09	0,23
LVEF <30%	-2,93	-4,73	-1,14	0,001	-2,37	-4,16	-0,58	0,01	-1,54	-3,81	0,73	0,18
CABG	1,36	0,08	2,63	0,037	1,24	-0,03	2,45	0,06	0,01	-1,62	1,63	0,99
Number of anastomoses	0,30	-0,07	0,67	0,111	0,26	-0,10	0,63	0,16	-0,4	-0,51	0,44	0,89
valve	1,04	-0,26	2,34	0,118	1,07	-0,22	2,36	0,11	-0,31	-1,97	1,34	0,71
CPB time (min)	-0,02	-0,03	-0,01	,000	-0,01	-0,02	0,01	0,06	-0,01	-0,02	0,00	0,12
PCS/MCS/EuroQol at baseline	0,32	0,28	0,36	,000	0,32	0,28	0,35	,000	0,21	0,17	0,24	,000
Prolonged ICU stay	-	-	-	-	-2,20	-3,65	-0,74	0,01	-	-	-	-
Prolonged hospital stay	-	-	-	-	-3,86	-5,10	-2,61	,000	-	-	-	-

PCS = physical component summary, MCS = mental component summary, 95%CI = confidence interval, BMI = body mass index;
COPD = chronic obstructive pulmonary disease. CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass;
LVEF = left ventricular ejection fraction; ICU = intensive care unit

1 year	Change	95% CI	Cohen's effect size[1]	% of patients reaching MDD after 1 year
41.6	7.65	(7.10 to 8.20)	0.53†	49.0
46.2	2.06	(1.45 to 2.88)	0.11	27.2
0.83	0.10	(0.09 to 0.11)	0.39*	37.3

MCS				EuroQol							
model 2				model 1				model 2			
Beta	95%CI		P value	Beta	95%CI		P value	Beta	95%CI		P value
-0,08	-0,14	-0,02	0,01	-0,01	-0,02	0,00	0,03	-0,01	-0,001	0,00	0,05
-3,80	-5,14	-2,47	,000	-0,50	-0,07	-0,03	,000	-0,05	-0,06	-0,03	,000
0,04	-0,10	0,18	0,57	-0,004	-0,006	-0,002	,000	-0,001	-0,006	-0,002	,000
0,25	-1,45	1,94	0,78	-0,03	-0,05	-0,01	0,01	-0,03	-0,05	-0,01	0,01
-0,62	-1,80	0,57	0,31	-0,01	-0,02	0,01	0,56	-0,01	-0,02	0,01	0,51
-1,18	-2,63	0,26	0,11	-0,04	-0,06	-0,02	,000	-0,04	-0,06	-0,02	,000
-0,94	-2,90	1,02	0,35	-0,04	-0,07	-0,02	0,01	-0,04	-0,07	-0,02	0,01
-2,05	-4,31	0,20	0,08	-0,05	-0,08	-0,02	,000	-0,04	-0,07	-0,01	0,01
-1.82	-4,62	0,98	0,20	-0,03	-0,07	0,01	0,09	-0,03	-0,06	0,01	0,14
-1,56	-3,85	0,72	0,18	-0,04	-0,07	-0,01	0,01	-0,04	-0,07	-0,01	,000
0,06	-1,57	1,69	0,94	0,01	-0,01	0,03	0,45	0,01	-0,01	0,03	0,14
-0,03	-0,50	0,44	0,90	0,01	-0,003	0,01	0,26	0,01	-0,01	0,02	0,45
-0,39	-2,05	1,27	0,65	0,02	-0,01	0,04	0,09	0,02	-0,01	0,04	0,12
-0,01	-0,02	0,01	0,07	0,01	-0,01	0,03	0,51	0,01	-0,01	0,03	0,53
0,21	0,17	0,24	,000	0,25	0,22	0,28	,000	0,24	0,21	0,28	,000
-0,26	-2,12	1,61	0,79	-	-	-	-	-0,04	-0,07	-0,02	,000
1,54	-0,06	3,13	0,06	-	-	-	-	-0,02	-0,04	0,001	0,06

Discussion

We reported health-related quality of life of patients after 2,709 elective cardiac surgery procedures and evaluated predictive indicators for a poor health related quality of at one-year follow-up. At one month after surgery quality of life after cardiac surgery was lower than before the procedure, whereas on average HrQOL one year after surgery had increased considerably. For all three outcome measures we have identified age, female gender and quality of life at baseline as predictors for a reduced HrQOL after cardiac surgery at one year after surgery. Additionally age, female gender, BMI, lung disease, diabetes mellitus, peripheral vascular disease, renal failure, poor left ventricle function, length of cardiopulmonary bypass, PCS and EuroQol at baseline and prolonged ICU, were significantly associated with a lower score on the physical component summary scale of SF-36 and EuroQOL score one year after the procedure. Prolonged hospital stay was also significantly associated with a lower score on the physical component summary scale of SF-36.

A reduction in quality of life (with respect to baseline) shortly after cardiac surgery (30 days QoL) is most likely explained by a yet incomplete recovery from cardiac surgery, since full recovery has been shown to take approximately eight weeks in the majority of the patients.[22,23] The significant increase in health related quality of life in the majority of patients observed one year after cardiac surgery is in line with previous findings.[24,25] However, in the current study we found that one out of six patients undergoing cardiac surgery still have a reduced quality of life one year after surgery.

Several studies have examined factors that are predictive for mortality after cardiac surgery.[17-19] These risk factors appear to be similar to the risk factors responsible for a decrease in HRQoL[26] , as also evident from our results. Also, in our study prolonged ICU and hospital stay, indicating a complicated early recovery phase, were significantly associated with the physical component of quality of life. We identified different predictive factors for the mental and physical scores for HRQoL, which can be explained by several reasons. Mental scores were already relatively good at baseline, suggesting that the burden of cardiac disease is mainly in reduced physical functioning. Consequently there was less room for improvement on the mental domain. Age was an independent factor for PCS, but not for MCS.

This might be explained by the fact that older cardiac surgery patients tend to be more satisfied with their quality of life in general than younger patients.[27]

A prolonged ICU and hospital stay after cardiac surgery are known to be associated with increased mortality.[11] And even if patients do survive, severe postoperative complications, perhaps resulting in physical and mental limitations, may permanently impair their quality of life.[28,29] Therefore, in addition to long-term survival, quality of life after cardiac surgery has become a matter of growing interest, especially with regard to the increasing numbers of older patients referred for cardiac surgery.[10-12] Perhaps one's physical and mental abilities may more accurately define our well-being than survival alone. A detailed characterization of the high risk patient, identified through quantitative risk factor analysis, may possibly contribute to perioperative individualized decision making and thereby improve both survival as well as quality of life. This would perhaps contribute to more efficient use of intensive care and hospital resources in the future. Our findings have shown which pre- and perioperative characteristics should be taken into account when such decisions are being made. Altogether, our findings may add to perioperative patient care by extending the current knowledge about future quality of life when facing severe postoperative complications.

This study on health related quality of life in cardiac surgery has its strengths and weaknesses. Strengths include the relatively large sample of patients, the completeness of the data, and the high response rate on the quality of life questionnaires. Limitations include the retrospective design and the fact that it is a single-center study, which may limit the generalizability of our findings.

In conclusion, health related quality of life generally improves at one-year follow-up after cardiac surgery. However, in about 1 out of 6 patients undergoing cardiac surgery quality of life has decreased at one year after surgery. Overall risk indicators for a decrease in HRQoL are age, female gender and quality of life at baseline, and for an important part prolonged ICU and hospital stay, reflecting perioperative complications. Therefore, patients identified as 'high-risk' should be, carefully evaluated and treated, possibly requiring a dedicated 'high-risk patient perioperative process'.

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Chapter 7

General Discussion

Worldwide, 1.5 million patients undergo cardiac surgery each year, with approximately 18.500 procedures annually in the Netherlands.[1,2] Since the 1950s, cardiac anesthesia has evolved from a high risk intervention to a safe procedure creating optimal surgical conditions, yet allowing quick recovery of the patient after the surgery. In this thesis, we have evaluated several components of anesthetic techniques that may contribute to even safer, more comfortable, or faster recovery after cardiac surgery.

Fast Track Cardiac Anesthesia

Prolonged postoperative sedation and ventilatory support of cardiac surgery patients has been the standard practice until the early 1990s.[3-5] Anesthesia for cardiac surgery mainly consisted of high-dose opioids which was associated with minimal impairment of cardiac function and maintenance of perioperative hemodynamic stability.[3-5] This high-dose, long-acting narcotic technique made prolonged postoperative ventilatory support of heart surgery patients necessary; the time of extubation was already determined intraoperatively, when the opioids were administered to the patient.[3-5] Ventilatory support was maintained until the morning of the first postoperative day and until the hemodynamic, respiratory and coagulation systems had stabilized completely. Particularly the first few hours after cardiac surgical interventions were regarded as a critical period for the occurrence of myocardial ischemia,[6-8] triggered by the hypothermia and hemodilution resulting from the use of extracorporeal circulation and the consecutive activation of the sympathetic nervous system.[8,9] Moreover, the extracorporeal circulation itself was thought to cause transient functional and metabolic damage to the myocardium, making it more more susceptible to new ischemia.[8,10] Because prolonged postoperative sedation may reduce complications, such as uncontrollable hypertension, arrhythmias and postoperative hemorrhage, it was perceived as a convenient side effect of the high doses of opioids administered during the operation. Interest in fast track protocols emerged because of a growing pressure on the health systems due to rapidly growing patient numbers, ageing patient population, more severe comorbidities and scarce resources. The idea was to optimize the use of

available intensive care capacity by having several patients on one intensive care bed daily. This required efficient surgical planning, as well as a cautious preoperative assessment of patients.[6-9,11-20] Beside shortening intensive care occupancy time, which is frequently a limiting factor in the number of heart surgery patients that can be operated per day, it was assumed that the rising costs could also be contained by shortening the overall hospitalization period.[14,17,18]

New surgical techniques, improved myocardial protection, improvements in anesthesia techniques, and management of perioperative coagulopathy have all supported the development of fast-track techniques.[4,9,15] Fast-track cardiac anesthesia (FTCA) is not a concept with a set, clear definition, but rather a combination of strategies resulting in shortening of recovery time. The introduction of the FTCA concept was based on the assumption that both immobilization and prolonged suppression of autonomous functions contribute to perioperative morbidity. Therefore, a principal component of fast-track cardiac anesthesia is a reduction of postoperative ventilatory support to less than 6 hours, or even immediate postoperative extubation in the operating room. Avoiding high-dose, long-acting narcotics is the most important step in achieving early exubation. The introduction of short-acting sedatives and opioids such as propofol and remifentanil as well as inhalation anesthetics such as sevoflurane has contributed decisively to changing anesthesia practice in cardiac surgery. However, the choice of the anesthetic agents is probably not as important as the dosage and the time of discontinuation of the drugs.[3,12,21]

After introduction of fast track cardiac anesthesia protocols an increase in patient flow of about 15% in the intensive care was observed without a negative impact on the quality of patient care, expressed as the incidence of postoperative morbidity or mortality.[19] The number of postponed or cancelled operations appeared to decrease due to the better use of limited intensive care (ICU) capacity. A meta-analysis found that cost savings are possible in high volume centers with flexible nurse staffing and flexible cardiac operating room scheduling.[22] The practice of early tracheal extubation allows a shift from the high costs of the ICU to the lower costs of the ward. This is mainly achieved by reducing the intensity of nursing care, by decreasing the length of stay in the intensive care, and by early mobilization in the ICU and on the ward, eventually leading to earlier hospital discharge.[21] Even a long term reduction of costs of as much as 50% was reported one year after implementing a FTCA protocol.[23]

Realizing fast-track cardiac anesthesia protocols in the everyday cardiac surgery practice is therefore an obvious priority. Recently the data from Eindhoven hospital were analyzed and published, showing that the local fast-track protocol is not only safe for the management of selected patients undergoing cardiac surgery, but is very efficient as well. Almost 40% of the cardiac surgery patients is discharged from the ICU on the day of surgery and this helped the number of cardiac procedures grow from 1200 to 1500 a year.[24]

Thoracic Epidural Anesthesia

Without calling it fast-track cardiac anesthesia, it was Yeager et al. in 1987 who published a trial that found a reduction of mortality and morbidity by using perioperative epidural analgesia for cardiac surgery.[25] Although it is surprising to detect mortality difference in a trial only of 53 patients - most likely this was a play of chance - it was the first of many trials in which researchers attempted to demonstrate benefits of thoracic epidural anesthesia in cardiac surgery. The interest in the use of thoracic epidural anesthesia in cardiac surgery is also the resulted from experimental[26-30] and clinical[31-48] studies indicating that central neuroaxial blockade, which has reversible sympathicolytic effects, attenuates the response to surgical stress and improves myocardial oxygen balance. The excellent analgesia that can be achieved with thoracic epidural anesthesia has proved to enable earlier extubation and a smoother postoperative course, comparable to a fast-track cardiac anesthesia protocol.

Despite these advantages, thoracic epidural anesthesia has never gained widespread acceptance in cardiac surgery, mainly because of concerns regarding the potential development of spinal cord injury, due to epidural hematoma, from hypotension secondary to sympathicolysis induced by anesthetic blockade and the risks of epidural infection.[49-55] Systematic anticoagulation needed during cardiopulmonary bypass may increase the incidence of epidural hematoma related to the use of an epidural catheter.[52] There are a few reports[52,56,57] on epidural hematoma in cardiac surgery of which some have directly been linked to thoracic epidural anesthesia.[58,59] Various aspects of the hazard of epidural hematoma have

been investigated, and the risk of this complication has long been held to be negligible. It has also been assumed that infection may always be avoided by the strict use of aseptic techniques and hypotension prevented with medication or intravenous fluid management.[54,55]

However, the benefit-harm trade-off could not be explored in the current framework of literature. Twenty-five years later, we continue to try and show that regional anesthesia and analgesia can significantly alter surgical outcomes, but still without real success. Despite its substantial sample size, the trial reported in this thesis appeared to be just another study failing to show an effect on major complications by using epidural anesthesia for cardiac surgery. Perhaps it is not realistic for an anesthetic intervention to have a large effect on surgical morbidity or mortality, particularly in major operations where there are so many other factors, including surgical technique, patient comorbidities, and postoperative care standards, that determine patient outcome. Given the severity of neuraxial complications and the lack of a clear beneficial effect on mortality and major morbidity, the potential benefits of thoracic epidural anesthesia in cardiac surgery may not be worth the potential risks. Conceivably, beneficial effects of thoracic epidural anesthesia are just the consequences of administrating less long-acting opioids and this is something that the fast track cardiac anesthesia protocols without epidural technique accomplish as well.[56-58] Furthermore, the perceived benefit of the sympathicolytic effect of thoracic epidural anesthesia is questionable when most patients are on a perioperative beta blocker and when we have access to several less invasive anti-arrhythmic drugs. The use of epidural catheters can result in excellent postoperative analgesia. However pain after cardiac surgery can also very well be managed with more straightforward intravenous methods.[47, chapter 3]

We therefore argue that thoracic epidural anesthesia for cardiac surgery is a potentially dangerous mode of fast-track cardiac anesthesia that does not offer any substantial benefits over fast-track cardiac anesthesia protocols without epidural technique and therefore should not be practiced.

Health related Quality of Life

Mortality and morbidity are traditionally examined outcomes after cardiac surgery.[60-63] Advances in anesthesia and surgery techniques and postoperative care have resulted in a reduced risk of perioperative complications and have thus resulted in a shift of interest towards health-related quality of life endpoints.[64,65]

These endpoints can help to better define the benefits and risks associated with cardiac operations.[66] Overall improved quality of life from before to after cardiac surgery has been previously reported. Poor quality of life after cardiac surgery is often the result of complications and prolonged intensive care admission.[67,68] Identification of risk factors for a prolonged ICU stay and complications could help may also be helpful to predict long-term poor quality of life.

Health related quality of life relates to more than just the presence of symptoms of disease or the side effects of surgery. It is based on how patients perceive and experience these manifestations in their daily life and covers a broad range of experiences related to overall well-being. This means that the health related quality of life is based on subjective functioning in relation to personal expectations and is defined by subjective experiences and perceptions.

Perhaps it is time to move away from trying to prove that a single anesthetic intervention can reduce major morbidity or mortality, and to focus on other, smaller benefits to patients or their families. Postoperative quality of recovery is a new horizon in anesthetic research with outcomes primarily focused on patient well-being, rather than on doctor, hospital, or funding agency outcomes. Aspects of quality of recovery that could be evaluated in future research may include softer endpoints like safety parameters, pain and nausea, emotional well-being, return to activities of daily living, patient satisfaction, and cognitive recovery.

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SUMMARY

Summary

Fundamental principles of anesthesia for cardiac surgery include maintaining hemodynamic stability and minimizing myocardial ischemia. Traditionally, anesthetic techniques aimed to decrease cardiovascular stress during cardiac surgery and to provide hemodynamic stability without myocardial depression in patients with compromised cardiac function. These anesthetic techniques consisted of the administration of high-dose opioids and long-acting muscle relaxants resulting in prolonged controlled mechanical ventilation for twelve to twenty-four hours postoperatively. The concept of fast-track cardiac anesthesia (FTCA) emerged in the 1990s and has since then become a widespread technique. FTCA can be defined as a management protocol involving the perioperative care of patients with the goal of allowing a more rapid recovery following cardiac surgery. The necessary elements of the fast-track program are: Choice and titration of short-acting anesthetic drugs, standardized surgical procedures, early extubation, postoperative normothermia and pain control, early ambulation and discharge.

A retrospective cohort study of 7989 patients is presented in **Chapter 2** comparing the incidence of mortality and major morbidity between cardiac surgical patients undergoing FTCA and historical controls undergoing high-dose opioids anesthesia. The duration of mechanical ventilation and length of hospitalization in the intensive care unit and postoperative ward are compared as well. There is no difference in the incidence of in-hospital mortality and major morbidity between the two groups. The duration of mechanical ventilation in the FTCA group is significantly shorter compared with the high-dose opioid group. In conclusion, this retrospective study of 7989 cardiac surgical patients shows no evidence of an increased risk of adverse outcomes in patients undergoing FTCA.

Pain is a well-known cause of adrenergic response that increases both myocardial and global oxygen consumption. The excellent analgesia that is associated with high thoracic epidural anaesthesia (TEA) is thought to prevent respiratory complications by facilitating early tracheal extubation. Through sympathicolysis, TEA may enhance coronary perfusion, improve myocardial oxygen balance and reduce the incidence of tachyarrhythmias and perioperative myocardial ischemia. Along with these potential benefits, TEA in cardiac surgery, however, is

controversial because the insertion of an epidural catheter in patients requiring full heparinization for cardiopulmonary bypass may lead to an epidural hematoma.
In **Chapter 3** clinical effects of fast-track general anesthesia (GA) plus TEA were compared with those of fast-track GA alone in a randomized clinical trial including 654 patients. The primary endpoint was 30-day survival free from myocardial infarction, pulmonary complications, renal failure, and stroke. Secondary outcome measures were the combined endpoint at 1 yr and the occurrence of each component of the primary endpoint separately at 1 and 12 months. We also compared postoperative cardiac arrhythmias, resternotomy, transient ischemic attack, postoperative cardiac enzyme release, duration of mechanical ventilation, length of stay in the intensive care unit (ICU), and total length of stay in the hospital. This study was unable to demonstrate a clinically relevant benefit of TEA on the frequency of major complications after elective cardiac surgery, compared with fast-track cardiac anesthesia without epidural anesthesia. Given the potentially devastating complications of an epidural hematoma after insertion of an epidural catheter, it is questionable whether this procedure should be applied routinely in cardiac surgical patients who require full heparinization.

The objective of **Chapter 4** was to determine the impact of perioperative epidural analgesia in cardiac surgery on perioperative mortality and cardiac, pulmonary or neurological morbidity. We have performed a meta-analysis to compare the risk of adverse events and mortality in patients undergoing cardiac surgery under general anaesthesia with and without epidural analgesia. Through our literature search we have identified 5035 titles, of which 31 publications met our inclusion criteria and we reported on a total of 3047 patients. The following meta-analysis of studies shows that the use of TEA in patients undergoing cardiac surgery may reduce the risk of postoperative supraventricular arrhythmias and respiratory complications. There are no effects of TEA with GA on the risk of mortality, myocardial infarction or neurological complications compared with GA alone.

Chapter 5 focuses on a subgroup analysis , based on year of publication and time to extubation within the meta-analysis comparing mortality and morbidity in patients undergoing cardiac surgery with GA alone or a combination of GA with TEA. Metaregression did not show likely associations between the study outcome and factors varying over the years of execution of the individual studies or risk of

bias items for any of the outcomes. Neither graphical explorations nor formal regression tests showed evidence of small study effects due to selective dissemination of studies or study results for any of the endpoints. The meta-analysis shows that the use of TEA in patients undergoing cardiac surgery reduces the risk of postoperative supraventricular arrhythmias and respiratory complications. The sparsity of events precludes conclusions about mortality, myocardial infarction, and stroke, but the estimates suggest a reduced risk after TEA. The risk of side effects of TEA, including epidural hematoma, could not be assessed with this study.

Patient outcomes after cardiac surgery are affected by many factors including co morbidity, disease severity, effectiveness of treatment, and chance. Risk-prediction models play an important role in current cardiac surgical practice as they may be used for patient counseling and treatment selection, to examine medical provider quality, and to serve as the fundament for continuous quality improvement.

Advances in anesthesiological and surgical techniques and critical care medicine have resulted in reduced risks of perioperative complications over the last decades resulting in a shift of interest towards health-related quality of life endpoints.

The topic of **Chapter 6** is the investigation of changes in health-related quality of life (HRQoL) after elective cardiac surgery, and identifying predictors for a decreased HRQoL one year after elective cardiac surgery. HRQoL was measured in 2709 patients at baseline, 30 days and one year after surgery using the ShortForm 36 and EuroQoL questionnaires. Subsequently we identified perioperative factors related to a decrease in HRQoL one year after surgery. In about 1 out of 6 patients undergoing cardiac surgery quality of life has decreased at one year after surgery. Overall risk indicators for a decrease in HRQoL are age, female gender and quality of life at baseline, and for an important part prolonged ICU and hospital stay, reflecting perioperative complications. Therefore, patients identified as 'high-risk' should be, carefully evaluated and treated, possibly requiring a dedicated 'high-risk patient perioperative process'.

Samenvatting in het Nederlands

Basisprincipes van cardioanesthesie zijn onder andere: Het handhaven van hemodynamische stabiliteit en het minimaliseren van myocardischaemie. Van oudsher waren de anesthesietechnieken er in het bijzonder op gericht om cardiovasculaire stress gedurende de chirurgie te verminderen en om bij deze patiëntengroep met een verminderde hartfunctie myocarddepressie tegen te gaan met behoud van hemodynamische stabiliteit.

De technieken bestonden uit de toediening van hoge doses opiaten, en langwerkende spierverslappers, met als gevolg een verlengde beademingsduur van 12 tot soms 24 uur postoperatief. Het concept van Fast-track Cardioanesthesie (FTCA) werd vanaf de negentiger jaren van de vorige eeuw geleidelijk toegepast en is sindsdien breed geaccepteerd. FTCA moet beschouwd worden als een compleet behandelprotocol voor de gehele perioperatieve periode met als doel een versneld herstel na hartchirurgie. Elementen van een FTCA protocol zijn: keuze en titratie van kortwerkende anesthesiemiddelen, een gestandaardiseerd chirurgisch protocol, vroege detubatie, postoperatieve normothermie en goede analgesie, resulterend in een protocollaire vroege mobilisatie en sneller ontslag.

In **hoofdstuk 2** wordt een retrospectieve cohortstudie gepresenteerd van 7989 patiënten, waarbij de morbiditeit en ernstige morbiditeit wordt vergeleken tussen patiënten die met een fast-track protocol behandeld werden, vergeleken met een historische controlegroep die hooggedoseerde opiaten protocol kregen. Tevens wordt gekeken naar de beademingsduur en de duur van het IC-verblijf en op de verpleegafdeling. Er wordt geen verschil gevonden in mortaliteit en ernstige morbiditeit tussen deze twee groepen. Er is een significant kortere beademingsduur in de FTCA groep. We concluderen dat er geen bewijs is voor een toegenomen risico op ongewenste uitkomsten in de FTCA groep.

Pijn is een bekende oorzaak voor een adrenerge reactie die de algemene maar ook de myocard zuurstofbehoefte doet toenemen. Hoog thoracale epidurale anesthesie (TEA) kan een uitstekende analgesie geven, en de gedachte is dat mede hierdoor vroege detubatie mogelijk gemaakt kan worden, met als gevolg minder respiratoire complicaties. Via sympathicolyse zou TEA tevens een verbeterde coronairperfusie kunnen geven, evenals een verbetering van zuustofbalans in de

hartspier, en een verminderd voorkomen van tachycardieën, met als gevolg minder myocardischaemie. TEA is echter controversieel in hartchirurgie, omdat het plaatsen en verwijderen van een epidurale catheter een groter risico met zich mee zou kunnen brengen op epidurale bloedingsproblemen, bij deze patiëntencategorie die vanwege de toepassing van de hart-longmachine volledig gehepariniseerd moet worden.

In **hoofdstuk 3** worden de klinische effecten van FTCA + TEA vergeleken met FTCA zonder TEA in een gerandomiseerde studie met 654 patiënten. Het primaire eindpunt is: 30 dagen overleving zonder hartinfarct, longcomplicaties, nierfalen en hersenberoerte. Secondaire eindpunten zijn: Het gecombineerde eindpunt na een jaar en het optreden van een van de eindpunten na 1 en 12 maanden. Hiernaast kijken we naar postoperatieve hartritmestoornissen, re-operatie, TIA, postoperatieve hartenzymwaarden, beademingsduur, duur van het IC-verblijf en de totale opnameduur. De studie heeft geen klinisch relevant effect laten zien van de toevoeging van TEA aan fast-track anesthesie op het voorkomen van belangrijke complicaties na electieve hartchirurgie. Gezien de potentieel zeer ernstige complicaties zoals een epiduraal hematoom na plaatsing van een epidurale catheter, is het maar de vraag of deze routinematig dient te worden toegepast bij deze patiëntencategorie.

Het doel van **hoofdstuk** 4 is om de impact van perioperatieve epidurale anesthesie te bepalen op perioperatieve mortaliteit, en cardiale, pulmonale of neurologische complicaties. We hebben hiertoe een meta-analyse verricht om het risico op complicaties te vergelijken tussen patiënten die hartchirurgie ondergingen onder algehele anesthesie met of zonder epidurale analgesie. We hebben 5035 artikelen geïdentificeerd, waarvan 31 voldeden aan onze inclusiecriteria. Uiteindelijk hebben we kunnen rapporteren over 3047 patiënten. De uitkomst is dat de toevoeging van TEA aan de algehele anesthesie mogelijk een vermindering geeft van supraventriculaire ritmestoornissen en respiratoire complicaties. Er is geen verschil in mortaliteit, of in het optreden van een hartinfarct of neurologische symptomen, vergeleken met alleen algehele anesthesie.

Hoofdstuk 5 richt zich op een subgroepanalyse, gebaseerd op publicatiejaar en tijd tot detubatie binnen de meta-analyse. Hierbij wordt gekeken naar het verschil in morbiditeit en mortaliteit tussen algehele anesthesie alleen en algehele anesthesie met toevoeging van TEA. Metaregressie liet geen duidelijk verband zien tussen de

studie-uitkomsten en mogelijke verandering in behandelstrategieën over de jaren heen, waardoor er geen verhoogd risico op bias is voor de uitkomsten. Noch het bestuderen van de grafieken, noch formele regressie tests toonden een effect van kleine studieaantallen op de resultaten, die mogelijk veroorzaakt zouden kunnen worden door selectieve verspreiding van de studies of de studieresultaten, voor alle eindpunten. De meta-analyse laat zien dat het toevoegen van TEA aan algehele anesthesie een verminderd risico geeft op respiratoire complicaties of ritmestoornissen. Helaas kunnen door het zeer beperkt aantal gerapporteerde events geen conclusies getrokken worden over mortaliteit, hartinfarcten of hersenberoertes, maar schattingen suggereren een iets verminderd risico na toevoeging van thoracale epidurale analgesie. Het risico op specifieke procedure gerelateerde complicaties van TEA, zoals het optreden van een epiduraal hematoom, kon in deze studie niet worden vastgesteld.

De uiteindelijke uitkomsten voor de patiënt na hartchirurgie worden door vele factoren bepaald: Co-morbiditeit, ernst van de aandoeningen, effectiviteit van behandeling, en zelfs toeval. Risico-voorspellende modellen zijn belangrijk in de huidige cardiochirurgische praktijk, omdat ze gebruikt kunnen worden voor patiëntvoorlichting, selectie van behandeling, beoordelen van de kwaliteit van zorg in een instelling, en om te dienen als basis voor het continue proces van kwaliteitsverbetering.

Verbeteringen in anesthesiologische en chirurgische technieken, maar ook verbetering van intensive care behandelingen hebben de laatste tientallen jaren geleid tot een vermindering in risico's op perioperatieve complicaties. Hierdoor verschuift de aandacht tegenwoordig meer naar gezondheid gerelateerde kwaliteit-van-leven uitkomsten.

Het onderwerp van **hoofdstuk 6** is een onderzoek naar veranderingen in gezondheidsaspecten van kwaliteit van leven (HRQoL) een jaar na electieve cardiochirurgie. HRQoL werd gemeten bij 2709 patiënten voor de operatie, 30 dagen en één jaar postoperatief, waarbij ShortForm 36 en EuroQOL gevalideerde vragenlijsten werden gebruikt. Bij 1 op de 6 patiënten was er een vermindering van kwaliteit van leven na 1 jaar. Overall waren leeftijd, vrouwelijk geslacht en de kwaliteit van leven bij de uitgangswaarden voorspellende factoren voor een verminderde kwaliteit van leven na 1 jaar. Het belangrijkste was echter een verlengd

IC-verblijf en opnameduur, omdat in deze groep meer perioperatieve complicaties voorkwamen. Om deze reden moeten patiënten die als hoog risico patiënt worden geïdentificeerd zorgvuldig geëvalueerd en behandeld worden, mogelijk zelfs binnen een toegewijd 'hoog risico patiënt perioperatief proces'.

Dankwoord

Dankwoord

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