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# *Effects of Perioperative Central Neuraxial Analgesia on Outcome after Coronary Artery Bypass Surgery*

## *A Meta-analysis*

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***Background:*** **Perioperative central neuraxial analgesia may improve outcome after coronary artery bypass surgery due to attenuation of stress response and superior analgesia.**

***Methods:*** **MEDLINE and other databases were searched for randomized controlled trials in patients undergoing coronary artery bypass surgery with cardiopulmonary bypass who were randomized to either general anesthesia (GA) *versus* general anesthesia–thoracic epidural analgesia (TEA) or general anesthesia–intrathecal analgesia (IT).**

***Results:*** **Fifteen trials enrolling 1,178 patients were included for TEA analysis. TEA did not affect incidences of mortality (0.7% TEA *vs.* 0.3% GA) or myocardial infarction (2.3% TEA *vs.* 3.4% GA). TEA significantly reduced the risk of dysrhythmias with an odds ratio of 0.52, pulmonary complications with an odds ratio of 0.41, and time to tracheal extubation by 4.5 h and reduced analog pain scores at rest by 7.8 mm and with activity by 11.6 mm. Seventeen trials enrolling 668 patients were included for IT analysis. IT had no significant effect on incidences of mortality (0.3% IT *vs.* 0.6% GA), myocardial infarction (3.9% IT *vs.* 5.7% GA), dysrhythmias (24.8% *vs.* 29.1%), nausea/vomiting (31.3% *vs.* 28.5%), or time to tracheal extubation (10.4 h IT *vs.* 10.9 h GA). IT modestly decreased systemic morphine use by 11 mg and decreased pain scores by 16 mm. IT significantly increased the incidence of pruritus (10% *vs.* 2.5%).**

***Conclusions:*** **There were no differences in the rates of mortality or myocardial infarction after coronary artery bypass grafting with central neuraxial analgesia. There were associated improvements in faster time until tracheal extubation, decreased pulmonary complications and cardiac dysrhythmias, and reduced pain scores.**

MORE than 800,000 patients annually undergo coronary artery bypass grafting (CABG) worldwide.[1] The most recent report from the Society of Thoracic Surgeons National Database lists more than 322,000 CABGs performed in the United States alone in January 2002 through June 2003.§ Perioperative central neuraxial analgesia offers potential benefits for these patients. Thoracic epidural analgesia (TEA) may reduce mortality and cardiac morbidity by improving myocardial oxygen balance, reducing myocardial infarction size, and reducing perioperative stress response.[2–4] Superior postoperative analgesia with TEA may reduce systemic opioid consumption, time to tracheal extubation, and pulmonary morbidity.[3–5] All of these potential benefits are specific for TEA but not lumbar epidural analgesia because of enhanced potential for hypotension, profound bradycardia, and less segmental matching of analgesia with lumbar epidurals.[6] Intrathecal opioids offer fewer potential mechanisms for improved outcomes than TEA because of lack of effects on myocardial metabolism, lesser reduction of stress response, and lesser duration of analgesia.[3] However, improved analgesia and reduction in stress response from intrathecal analgesia (IT) may reduce mortality and hasten the time to tracheal extubation.[7] A recent observational meta-analysis of 176 studies enrolling more than 205,000 subjects undergoing CABG surgery from 1990 to 2001 determined that mortality (1.7%) and morbidity (incidence of myocardial infarction 2.4%) are relatively infrequent.[1] Such incidences would require approximately 4,600 patients in a single randomized controlled clinical trial (RCT) to have 80% power ($P = 0.05$) to detect a reduction in incidences from 2% to 1%. No such RCT currently exists to definitively determine whether the potential benefits of central neuraxial analgesia outweigh the risks of side effects and potentially increased risk for spinal hematoma.[8] Therefore, we performed this meta-analysis to determine whether there is currently evidence for improved outcomes with central neuraxial analgesia in CABG patients.

This article is featured in "This Month in Anesthesiology." Please see this issue of ANESTHESIOLOGY, page 5A.

## Materials and Methods

### *Literature Review*

This meta-analysis was performed with a prospective protocol (outlined below) using recommended literature search strategies incorporating multiple search terms.[9] The National Library of Medicine's MEDLINE database, the American College of Physicians Journal Club, the Cochrane Central Register of Controlled Trials, the Cochrane Database of Systematic Reviews, and the Database of Abstracts of Reviews of Effects were searched for

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§ The Society of Thoracic Surgeons: STS National Database Executive summary. Fall 2003. Available at: www.sts.org. Last updated December 23, 2003.

the time period 1966 to January 1, 2004. No language restrictions were used. For the epidural analgesia portion of the meta-analysis, MESH term *Anesthesia, Epidural* and text word *Epidural anesthesia* were used and combined with *OR* (n = 9514). MESH term *Analgesia, Epidural* and the word *epidural analgesia* were used and combined with the term *OR* (n = 5,646). Text words *peridural* (n = 1,461) and *extradural* (n = 3,312) were used for a search, and the two searches were combined with *OR* (n = 16,893). MESH terms *coronary artery bypass* (n = 26,473) and *cardiac surgical procedures* (n = 18,978) were used to search the database and combined with the term *OR* (44,530). This search was combined with the epidural analgesia search terms with the term *AND* and limited by *Human* and *Clinical trials* (n = 40).

For the spinal analgesia portion of the meta-analysis, MESH term *Anesthesia, Spinal* and text word *Spinal Anesthesia* were used and combined with *OR* (n = 6,649). MESH term *Injection, Spinal* (n = 7085) was used and combined with the previous search with *OR* (13,346). Text words *intrathecal* (n = 9,260) and *subarachnoid* (n = 14,132) were used for a search, and the two searches were combined with *OR* (n = 22,829). MESH terms *coronary artery bypass* and *cardiac surgical procedures* were used to search the database and combined with the term *OR*. This search was combined with the spinal anesthesia search terms with the term *AND* and limited by *Human* and *Clinical trials* (n = 18). Each of the 58 abstracts was then reviewed by one of the authors for inclusion in the meta-analysis.

**Inclusion Criteria.** Only studies that compared perioperative TEA or IT *versus* parenteral opioid analgesia in a randomized clinical trial were included. Cardiac surgical procedures were limited to CABG with cardiopulmonary bypass. Studies were included if the patient sample included a minority of non-CABG patients undergoing cardiac surgery with cardiopulmonary bypass. The study period had to extend to at least the morning of postoperative day 1. *Thoracic epidural analgesia* was defined as medicine delivered into the thoracic epidural space by infusion, patient-controlled analgesic device, or repeated bolus dosing. Studies that gave only a single epidural dose at the time of surgery (single shot) were not included. *Intrathecal analgesia* was defined as morphine with or without adjuncts delivered into the intrathecal space. *Parenteral analgesia* was defined as opioid drugs given by bolus dosing, infusion, or patient-controlled analgesic device *via* the intravenous, subcutaneous, or intramuscular route. No minimum sample sizes were invoked for inclusion of studies in the analysis. Only randomized studies in adults (aged $\geq$ 18 yr) were included. Because the use of summary scores to identify trials of high quality may be problematic,[10] we explicitly chose not create a quality score for weighting purposes. Instead, we attempted to include only good-quality studies (prospective, randomized, and controlled) and weight them only by sample size. Any disputes were resolved by agreement of at least two reviewers. After selecting the initial articles, the reference list of each of the analyzed articles was checked for any additional studies, as were the author's personal files for additional references that met all inclusion criteria.

*Data Extraction and Analysis*

The methodology and results of each study were recorded. Data were extrapolated from figures as needed. Wherever possible, data were converted to incidence for dichotomous outcomes and to mean and SD (normal distribution was assumed) for continuous outcomes. Definition of outcomes was recorded as originally defined by the study. Specific outcomes that were abstracted included incidence of death during the immediate postoperative study period, incidence of myocardial infarction during the postoperative study period, incidence of dysrhythmias (atrial fibrillation and supraventricular tachycardia) during the postoperative study period, and incidence of pulmonary complications (atelectasis, pneumonia, or respiratory failure) during the postoperative study period. Myocardial infarction may be defined by several means, and in cases of discrepancy between electrocardiographic diagnosis *versus* enzyme diagnosis, the electrocardiogram-based incidence was used. In cases where troponin was used to define myocardial injury, a level greater than 3.9 ng/ml was used to define myocardial infarction after CABG surgery.[11] Time to extubation was abstracted and entered as mean and SD hours. Visual or verbal analog pain scores were converted to a 0–100 scale. Pain data were weighted by sample size, and if a given article measured pain at multiple time points, all measurements were averaged and included in the analysis. Thus, the n value reported is the total number of patients. Where possible, rest and incident pain were separated in the analysis. Incidences of nausea and vomiting and pruritus were abstracted, and consumption of systemic opioids was abstracted. Opioid consumption data were converted to morphine equivalents (mg/day) and were weighted by sample size. If a given article measured opioid consumption over multiple days, all measurements were included in the analysis. Thus, the n value reported is the total number of patient observations.

*Statistical Analysis*

A random effects model was used for all analyses. The level of significance for all tests was set at an $\alpha$ level of 0.05, and variances were not assumed to be equal. For dichotomous outcomes, study results were pooled, and odds ratios were calculated with the Mantel-Haenszel method. Thus, odds ratios with 95% confidence intervals are displayed for effect statistic. For continuous out-

**Table 1. Included Randomized Controlled Trials for Effects of Perioperative Thoracic Epidural Analgesia on Outcomes after Coronary Artery Bypass Surgery**

| Study | Participants | Interventions | Abstracted Outcomes |
|---|---|---|---|
| Berendes *et al.*[26] | 37 GA<br>36 TEA | GA: midazolam (0.1 mg/kg)–sufentanil (2–5 μg/kg)<br>Postoperative analgesia: not specified<br>TEA: GA with midazolam (0.1 mg/kg)/sufentanil (1–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$)/propofol (1.5–3 $mg \cdot kg^{-1} \cdot h^{-1}$)/C7–T1 epidural with 6–12 ml bupivacaine, 0.5%/12–25 μg sufentanil<br>Postoperative analgesia: 0.75% bupivacaine at 2 ml/h until POD 4 | Death<br>MI: Q wave<br>Time until extubation<br>Respiratory insufficiency |
| Brix-Christensen *et al.*[12] | 8 GA<br>8 TEA | GA: midazolam (0.15 mg/kg)/fentanyl (50 μg/kg)/enflurane<br>Postoperative analgesia: morphine and paracetamol intravenously as needed<br>TEA: GA with fentanyl (5 μg/kg)/T3–T4 epidural with 8 ml bupivacaine, 0.5%<br>Postoperative analgesia: 0.2% bupivacaine/fentanyl (5 μg/ml) at 5 ml/h until POD 2 | Death |
| El-Baz and Goldin[13] | 30 GA<br>30 TEA | GA: halothane<br>Postoperative analgesia: morphine 2 mg intravenously as needed<br>TEA: GA/T3–T4 epidural with morphine 0.1 mg/h until POD 2 | Death<br>Time until extubation<br>Pain scores |
| Fillinger *et al.*[14] | 30 GA<br>30 TEA | GA: fentanyl (5–20 μg/kg)/midazolam (≤0.1 mg/kg)/isoflurane<br>Postoperative analgesia: morphine intravenously as needed<br>TEA: GA/T3–T10 epidural with 25–35 mg bupivacaine/morphine 20 μg/kg then 4–10 ml/h with 0.5% bupivacaine/morphine (25 μg/ml)<br>Postoperative: 0.125% bupivacaine/morphine (25 μg/ml) at 4–10 ml/h until POD 1 | Death<br>MI: Q wave<br>Time until extubation<br>Pain scores<br>Pneumonia<br>Atrial fibrillation |
| Jideus *et al.*[15] | 80 GA<br>41 TEA | GA: fentanyl/isoflurane<br>Postoperative analgesia: ketobemodine intravenously as needed<br>TEA: GA/T2–T5 epidural with 8–14 ml bupivacaine, 0.5%<br>Postoperative analgesia: 0.2% bupivacaine/sufentanil (1 μg/ml) at 3–7 ml/h for 96 h | Death<br>MI undefined<br>Atrial fibrillation |
| Liem *et al.*[16] | 27 GA<br>27 TEA | GA: midazolam (0.1 mg/kg)/sufentanil (5 μg/kg)<br>Postoperative analgesia: 0.1 mg/kg nicomorphine every 6 h intravenously + as needed<br>TEA: GA/T1–T2 epidural with 0.375% bupivacaine/sufentanil 1:200,000, 0.05 ml/cm body length<br>Postoperative analgesia: 0.125% bupivacaine + sufentanil 1:1,000,000 at 0.05 $ml \cdot cm\ height^{-1} \cdot h^{-1} \times 72$ h | Death<br>MI: Q wave/enzyme<br>Pain scores<br>Atelectasis by radiograph<br>Supraventricular tachycardia |
| Loick *et al.*[17] | 45 GA | GA: sufentanil (1–2 μg/kg then 1–2 $\mu g \cdot kg^{-1} \cdot h^{-1}$)/propofol (1–3 $mg \cdot kg^{-1} \cdot h^{-1}$)/± 4 μg/kg clonidine<br>Postoperative analgesia: 1 g paracetamol 4 times a day 2 mg intravenous PCA piritramid every 20 min/± 0.2–0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ clonidine<br>TEA: GA/C7–T1 epidural with 8–12 ml bupivacaine, 0.375%/16–24 μg sufentanil<br>Postoperative analgesia: 0.75% bupivacaine ± sufentanil (1 μg/ml) at 2–3 ml/h until POD 2 | Death<br>MI: troponin T at 24 hrs<br>Time to extubation<br>Pain scores<br>Tachycardia |
| Moore *et al.*[18] | 10 GA<br>9 TEA | GA: sufentanil (20 μg/kg)<br>Postoperative analgesia: papaveretum intravenously as needed<br>TEA GA/T1–T5 epidural with 0.5% bupivacaine<br>Postoperative analgesia: 0.25% bupivacaine at 5–8 ml/h for 24 h | Death |
| Priestley *et al.*[19] | 50 GA<br>50 TEA | GA: fentanyl (15 μg/kg)/propofol (6 $mg \cdot kg^{-1} \cdot h^{-1}$)<br>Postoperative analgesia: Continuous infusion morphine then intravenous PCA on POD 1<br>TEA: GA/T1–T4 epidural with 10 ml ropivacaine, 1%<br>Postoperative analgesia: 1% ropivacaine/fentanyl (2 μg/ml) at 3–5 ml/h × 48 h | Death<br>MI: Q wave/troponin I<br>Time to extubation<br>Atrial fibrillation |

(*continues*)

**Table 1. (continued)**

| Study | Participants | Interventions | Abstracted Outcomes |
|---|---|---|---|
| Rein *et al.*[25] | 8 GA<br>8 TEA | GA: fentanyl (54 μg/kg)/nitrous oxide<br>Postoperative analgesia: unspecified<br>TEA: GA with fentanyl (14 μg/kg)/T4–T5 epidural with 10 ml bupivacaine, 0.5%<br>Postoperative analgesia: 20 mg/h bupivacaine × 24 h | Death<br>MI: undefined |
| Royse *et al.*[20] | 39 GA<br>37 TEA | GA: midazolam/propofol/alfentanil with targeted continuous infusion<br>Postoperative analgesia: intravenous PCA morphine × POD 3<br>TEA: GA/T1–T3 epidural with 8 ml ropivacaine, 0.5% + 20 μg fentanyl<br>Postoperative analgesia: 0.2% ropivacaine/fentanyl (2 μg/ml) at 5–14 ml/h until POD 3 | Death<br>MI undefined<br>Pain scores<br>Atrial fibrillation |
| Scott *et al.*[5] | 202 GA<br>206 TEA | GA: propofol/alfentanil with targeted continuous infusion<br>Postoperative analgesia: TCI alfentanil × 24 h and then intravenous PCA morphine<br>TEA: GA/T2–T4 epidural with 10 ml bupivacaine, 0.5%<br>Postoperative analgesia: 0.125% bupivacaine/0.0006% clonidine at 10 ml/h for 96 h | Death<br>MI: Q wave/enzyme<br>Pulmonary infection<br>Supraventricular tachycardia<br>Time to extubation<br>Renal dysfunction |
| Stenseth *et al.*[21] | 10 GA<br>28 TEA | GA: fentanyl (50 μg/kg)<br>Postoperative analgesia: morphine intravenously as needed<br>TEA: GA/T4–T6 epidural with 10 ml bupivacaine, 0.5%<br>Postoperative analgesia: 0.5% bupivacaine at 3 ml/h | Death<br>Tachycardia |
| Stenseth *et al.*[22] | 26 GA<br>26 TEA | GA: fentanyl (55 μg/kg)<br>Postoperative analgesia: morphine intravenously as needed<br>TEA: GA/T4–T6 epidural with 10 ml bupivacaine, 0.5%<br>Postoperative analgesia: 0.5% bupivacaine at 3 ml/h with 4 ml every 4 h and 4–6 mg epidural morphine 3–4 times/day until POD 3 | Death<br>MI undefined<br>Time to extubation |
| Tenling *et al.*[23] | 14 GA<br>14 TEA | GA: fentanyl (5–10 μg/kg)/isoflurane<br>Postoperative: ketobemidone intravenously as needed<br>TEA: GA/T3–T5 with 8–12 ml bupivacaine, 0.5%<br>Postoperative analgesia: 0.2% bupivacaine/sufentanil (1 μg/ml) at 3–7 ml/h until POD 1 | Death<br>Time to extubation<br>Atelectasis with computed tomography scan |

GA = general anesthesia; MI = myocardial infarction; PCA = patient-controlled analgesia; POD = postoperative day; TCI = targeted continuous infusion; TEA = general anesthesia with perioperative thoracic epidural analgesia.

comes, study results were pooled, and means and SDs were calculated with the inverse variance method. Thus, weighted mean differences and 95% confidence intervals are displayed for effect statistic. All statistical analyses were performed with Review Manager 4.2 (The Cochrane Collaboration's Information Management System; Nordic Cochrane Centre Rigshospitalet, Copenhagen, Denmark).

## Results

### *Thoracic Epidural Analgesia*

Fifteen RCTs enrolling a total of 1,178 patients met all inclusion criteria. All of these studies enrolled only CABG patients (table 1).[5,12–26] TEA did not significantly affect incidences of mortality or myocardial infarction (table 2). TEA significantly reduced dysrhythmias, pulmonary complications, time to tracheal extubation, and pain scores (table 2).

### *Intrathecal Analgesia*

Seventeen RCTs enrolling a total of 668 patients met inclusion criteria (table 3),[24,27–38] and 4 enrolled mixed CABG–valve patients (primarily CABG).[7,38–41] IT had no significant effect on incidences of mortality, myocardial infarction, dysrhythmias, nausea/vomiting, or time to tracheal extubation (table 2). A subset of patients receiving smaller doses of IT (≤ 500 μg or 7 μg/kg morphine) demonstrated a slightly faster time until tracheal extubation (table 2). IT modestly decreased systemic morphine use and decreased global pain scores (table 2). IT also significantly increased the incidence of pruritus (table 2).

## Discussion

### *Thoracic Epidural Analgesia*

We were unable to identify beneficial effects of TEA on risk of mortality or myocardial infarction. Potential mechanisms for TEA to favorably influence mortality and

**Table 2. Outcomes for TEA and IT *vs.* GA for Cardiac Surgery**

| Outcome | No. | TEA | GA | OR or WMD (95% Confidence Interval) | *P* Value |
|---|---|---|---|---|---|
| Death | 1,178 | 0.7% | 0.3% | 1.56 (0.35–6.91) | 0.56 |
| Myocardial infarction | 1,026 | 2.3% | 3.4% | 0.74 (0.34–1.59) | 0.44 |
| Dysryhthmias | 913 | 17.8% | 30% | 0.52 (0.29–0.93) | 0.03 |
| Pulmonary complications | 644 | 17.2% | 30.3% | 0.41 (0.27–0.60) | < 0.00001 |
| Time to tracheal extubation, h | 905 | 6.9* | 10.4* | −4.5 (−7 to −2) | 0.0005 |
| VAS pain score at rest, mm | 392 | 12.4* | 19.6* | −7.8 (−15 to −0.6) | 0.03 |
| VAS pain score with activity, mm | 222 | 14* | 27.6* | −11.6 (−19.7 to −3.5) | 0.005 |
| Death | 668 | 0.3% | 0.6% | 0.88 (0.13–5.72) | 0.89 |
| Myocardial infarction | 290 | 3.9% | 5.7% | 0.75 (0.24–2.31) | 0.61 |
| Dysryhthmias | 204 | 24.8% | 29.1% | 0.81 (0.42–1.53) | 0.51 |
| Time to tracheal extubation, h | 588 | 10.4* | 10.9* | −0.85 (−1.83 to 0.12) | 0.09 |
| Time to tracheal extubation for small-dose IT, h | 189 | 7.1* | 9.3* | −1.2 (−1.8 to −0.7) | < 0.0001 |
| Morphine use per day, mg | 816 | 14* | 22* | −11 (−15 to −7) | < 0.00001 |
| VAS pain score, mm | 315 | 13.4* | 23.4* | −16 (−27 to −4.9) | 0.005 |
| Pruritus | 506 | 10.1% | 2.5% | 2.9 (1.2–6.7) | 0.01 |
| Nausea/vomiting | 490 | 31.3% | 28.5% | 1.27 (0.81–2.0) | 0.3 |

Random effects model used for all analyses.

* Weighted by number of subjects.

GA = general anesthesia; IT = intrathecal analgesia; OR = odds ratio; TEA = thoracic epidural analgesia; VAS = visual analog scale; WMD = weighted mean difference (inverse variance method).

myocardial infarction after CABG surgery include segmental sympathetic block and analgesia. Use of local anesthetics in TEA had been reported to reduce myocardial oxygen demand by decreasing heart rate, inotropy, and systemic vascular resistance.[2] At the same time, TEA has been reported to improve myocardial oxygen supply by dilating stenotic coronary arteries.[6] This improvement in myocardial oxygen balance has been demonstrated in humans to relieve angina[2] and in laboratory studies to reduce the size of myocardial infarction and to hasten recovery from myocardial stunning after ischemia.[6] It is likely that this meta-analysis lacks sufficient statistical power to determine whether these potential benefits affect risk of mortality and myocardial infarction. Almost all of the included RCTs were small, and even pooling the subjects resulted in numbers far short of the required subject size (4,600 patients) estimated by previous observational meta-analysis.[1] Although the pooled incidence for myocardial infarction (3.2%) from the RCTs in this meta-analysis is similar to that from the observational meta-analysis (2.4%),[1] the pooled mortality rate (0.5%) from our RCTs was smaller than that predicted from observational studies (1.7%). This may reflect enrollment of low-risk subjects or a Hawthorne-type effect and would further increase the subjects needed to approximately 30,000 to detect a 50% reduction in mortality (power = 0.8, $P = 0.05$). More large-scale RCTs are required to completely assess the potential benefits of TEA for reduction in mortality and myocardial infarction after CABG.

Dysrhythmias are common after CABG surgery, and TEA was associated with decreased risk of postoperative dysrhythmias (atrial fibrillation and tachycardia). TEA with local anesthetics reduces overall sympathetic tone, blocks cardiac accelerator fibers, and reduces stress response from cardiac surgery and cardiopulmonary bypass.[3,6] All of these effects would be expected to contribute to reduction in risk of dysrhythmias. The magnitude of reduction with TEA (30% *vs.* 17.8%) compares favorably with results from placebo-controlled RCTs examining efficacy of $\beta$ blockers (31% *vs.* 39%)[42] and amiodarone (12% *vs.* 25%)[43] for reduction of dysrhythmias after cardiac surgery.

Thoracic epidural analgesia significantly hastened the time until tracheal extubation. The ability to extubate the trachea after cardiac surgery is dependent on a number of factors, including analgesia and avoidance of respiratory depressant drugs. The significantly lower pain scores with TEA and the minimized use of systemic opioids likely contributed to the faster time until tracheal extubation with TEA. However, the clinical impact of the 4.5 h faster extubation with TEA may be uncertain with changing cardiac anesthesia practice. Fast-track cardiac anesthesia has focused on use of short-acting general anesthesia agents to allow early extubation of the trachea. A recent systematic review indicates that this practice is as safe[44] as the conventional cardiac anesthesia techniques used in the majority of our RCTs and results in comparable times until tracheal extubation (approximately 4.5 h) as use of TEA (6.9 h).[45]

Thoracic epidural analgesia was associated with reduced risk of pulmonary complications (pneumonia and atelectasis), which is consistent with previous meta-analyses in noncardiac surgery demonstrating that epidural anesthesia and analgesia decrease the overall incidence of pulmonary complications.[46,47] This finding may be explained by the faster time until tracheal extubation and reduced dynamic pain scores observed with TEA in

**Table 3. Included Randomized Controlled Trials for Effects of Perioperative Intrathecal Analgesia on Outcomes after Primarily Coronary Artery Bypass Surgery**

| Study | Participants | Interventions | Abstracted Outcomes |
|---|---|---|---|
| Alhashemi *et al.*[27] | 19 GA<br>31 IT | GA: fentanyl (7–10 μg/kg)/isoflurane<br>IT: GA/250 or 500 μg IT morphine<br>Postoperative analgesia: morphine intravenously as needed | Death<br>Time to extubation<br>Morphine use<br>N/V<br>Pruritus |
| Aun *et al.*[28] | 20 GA<br>40 IT | GA: 1,000 μg fentanyl nitrous oxide<br>IT: GA/intrathecal morphine 2 (n = 20) or 4 mg (n = 20)<br>Postoperative analgesia: papaveretum intravenously as needed | Death<br>Time to extubation<br>Morphine use<br>N/V<br>Pruritus |
| Bettex *et al.*[7]<br>Mixed CABG/valve | 13 GA<br>11 IT | GA: propofol target-controlled infusion/1.8 $\mu g \cdot kg^{-1} \cdot h^{-1}$ sufentanil<br>IT: GA/50 μg IT sufentanil/500 μg morphine<br>Postoperative analgesia: intravenous PCA nicomorphine | Death<br>Time to extubation<br>Morphine use<br>Pain scores<br>N/V<br>Pruritus |
| Boulanger *et al.*[39]<br>Mixed CABG/valve | 44 GA<br>20 IT | GA: sufentanil (3 μg/kg), midazolam (0.1 mg/kg), isoflurane<br>IT: GA/0.02 mg/kg IT morphine up to 1 mg<br>Postoperative analgesia: morphine intravenous PCA or subcutaneously as needed | Death<br>Time to extubation<br>Morphine use<br>Pain scores<br>N/V<br>Pruritus |
| Bowler *et al.*[29] | 12 GA<br>12 IT | GA: fentanyl (12 μg/kg), isoflurane<br>IT: GA with remifentanil (1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) instead of fentanyl/IT morphine 2 mg<br>Postoperative analgesia: 2 mg morphine intravenously as needed | Death<br>MI undefined<br>Time to extubation<br>Morphine use<br>Pain scores<br>N/V<br>Pruritus<br>Atrial fibrillation |
| Casey *et al.*[24] | 21 GA<br>19 IT | GA: fentanyl (40 μg/kg)<br>IT: GA/IT morphine (0.02 mg/kg)<br>Postoperative analgesia: morphine intravenously as needed | Death<br>Time to extubation<br>Morphine use<br>N/V<br>Pruritus |
| Chaney *et al.*[30] | 30 GA<br>30 IT | GA: Fentanyl (50 μg/kg), 10 mg midazolam<br>IT: GA/4 mg IT morphine<br>Postoperative analgesia: morphine intravenous PCA | Death<br>MI: Q wave/enzyme<br>Morphine use<br>N/V<br>Pruritus<br>Atrial fibrillation/ventricular tachycardia |
| Chaney *et al.*[31] | 21 GA<br>19 IT | GA: fentanyl (20 μg/kg), 10 mg midazolam<br>IT: GA/10 μg/kg morphine IT<br>Postoperative analgesia: morphine intravenous PCA | Death<br>MI: Q wave/enzyme<br>Morphine use<br>N/V<br>Pruritus<br>Atrial fibrillation/ventricular tachycardia |
| Chaney *et al.*[32] | 20 GA<br>20 IT | GA: fentanyl (10 μg/kg), midazolam (0.2 mg/kg)<br>IT: GA/IT morphine 10 μg/kg<br>Postoperative analgesia: morphine intravenous PCA | Death<br>MI: Q wave/enzyme<br>Morphine use<br>N/V<br>Pruritus<br>Atrial fibrillation/ventricular tachycardia |
| Fitzpatrick and Moriarty[40]<br>Mixed CABG/valve | 14 GA<br>30 IT | GA: 250 μg fentanyl/volatile agent<br>IT: GA/1 (n = 15) or 2 (n = 15) mg IT morphine<br>Postoperative analgesia: morphine intravenously as needed | Death<br>Time until extubation<br>Morphine use<br>Pain scores<br>N/V<br>Pruritus |

(*continues*)

**Table 3. (continued)**

| Study | Participants | Interventions | Abstracted Outcomes |
|---|---|---|---|
| Hall *et al.*[33] | 12 GA | GA: Fentanyl (10–15 $\mu$g/kg), propofol (50–200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) | Death<br>Pain scores |
| | 13 IT | IT: GA/IT morphine 1 mg > 60 yr, 1.5 mg < 60 yr<br>Postoperative analgesia: morphine intravenously as needed | |
| Latham *et al.*[38] | 20 GA | GA: sufentanil (0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$)/desflurane | Death |
| Mixed CABG/valve | 20 IT | IT: remifentanil (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$)/desflurane/8 $\mu$g/kg IT morphine | MI: Q wave<br>Time to extubation<br>Pulmonary complications |
| | | Postoperative analgesia: hydromorphone intravenously as needed | N/V<br>Pruritus<br>Atrial fibrillation and flutter/ventricular tachycardia and fibrillation |
| Lena *et al.*[34] | 16 GA | GA: sufentanil (< 3.5 $\mu$g/kg), 100 $\mu g \cdot kg^{-1} \cdot min^{-1}$ propofol, isoflurane | Death |
| | 29 IT | IT: GA/4 $\mu$g/kg IT morphine (n = 14) or 4 $\mu$g/kg morphine + 1 $\mu$g/kg clonidine (n = 15) | Time to extubation<br>Morphine use<br>Pain scores |
| | | Postoperative analgesia: intravenous PCA morphine | |
| Sebel *et al.*[35] | 10 GA | GA: fentanyl, nitrous oxide | Death |
| | 10 IT | IT: GA/4 mg morphine<br>Postoperative analgesia: papaveretum intravenously as needed | Morphine use |
| Shroff *et al.*[36] | 9 GA | GA: 25–50 $\mu$g/kg fentanyl/isoflurane | Death |
| | 12 IT | IT: GA/10 $\mu$g/kg IT morphine/25 $\mu$g fentanyl | Time to extubation<br>Morphine use |
| | | Postoperative analgesia: morphine intravenously as needed | Pain scores |
| Vanstrum *et al.*[37] | 14 GA | GA: 7 $\mu$g/kg sufentanil/isoflurane | Death |
| | 16 IT | IT: GA/0.5 mg IT morphine | Time to extubation<br>Morphine dose |
| | | Postoperative analgesia: morphine intravenously as needed | Pain scores<br>N/V<br>Pruritus |
| Zarate *et al.*[41] | 20 GA | GA: sufentanil (0.75 $\mu$g/kg then 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$) and desflurane | Death<br>MI: electrocardiogram/troponin |
| Mixed CABG/valve | 20 IT | IT: GA with remifentanil (0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$) instead of sufentanil/IT morphine 8 $\mu$g/kg | Time to extubation<br>Morphine use<br>Pain scores |
| | | Postoperative analgesia: intravenous PCA hydromorphone | |

GA = general anesthesia; IT = intrathecal analgesia; MI = myocardial infarction; N/V = nausea and vomiting; PCA = patient-controlled analgesia; TEA = thoracic epidural analgesia.

our meta-analysis. Both of these benefits would allow for early resumption of spontaneous respiration and effective pulmonary toilet.

*Intrathecal Analgesia*

Even fewer subjects have been enrolled in RCTs studying effects of IT on outcomes after CABG and mixed CABG–valve surgery. Thus, we had insufficient power to detect effects on mortality and myocardial infarction. IT may improve outcome by attenuating the stress response associated with cardiac surgery and cardiopulmonary bypass.[3] Consistent with this proposal, all the RCTs that measured perioperative stress hormones (catecholamines, cortisol, and glucose) observed some reduction in these hormones with use of IT.[30,33,35] However, the hemodynamic effects from this mild reduction in stress response were not readily apparent because none of the RCTs that also reported intraoperative hemodynamic changes and therapy noted a difference with IT.[24,27,30–32,37,39] Because these RCTs administered up to 4 mg intrathecal morphine, it is unlikely that any further effects would be gained by even larger doses of intrathecal opioids. Therefore, the lack of clinical effect from reduction in stress hormones in addition to relatively few subjects may explain the inability of IT to reduce mortality and cardiac morbidity in this meta-analysis.

Ability to extubate the trachea after cardiac surgery is dependent on a number of factors, including analgesia

and avoidance of respiratory depressant drugs. Intrathecal morphine is approximately 100 times more potent than systemic morphine, which well explains why the use of IT reduces systemic opioid consumption and improves analgesia. However, the absolute magnitude of analgesic benefit may be small, because analgesia seems to be already acceptable in the general anesthesia groups. The average (weighted by subjects) morphine use per day in the general anesthesia group was a modest 27 mg, and the average pain score was 22/100 mm. Changing practice in cardiac anesthesia may also narrow these differences as use of nonsteroidal antiinflammatory analgesics and cyclooxygenase-2 inhibitors are incorporated into current postoperative analgesia management after general anesthesia for CABG surgery.[48] The analgesic effects of intrathecal morphine are dose dependent, as are its respiratory depressant effects. Previous studies indicate that doses greater than 500 $\mu$g result in profound and prolonged respiratory depression.[49] This finding explains why only a subset of RCTs administering less than this dose reported significantly faster times until tracheal extubation. Because increased doses of intrathecal morphine do not seem to improve mortality or morbidity, the use of smaller doses to achieve faster tracheal extubation would be prudent. In the subset of RCTs using smaller doses of intrathecal morphine, the average (weighted by subject number) time until extubation with IT was 7.1 h. Recent publications using fast-track cardiac anesthesia report average times until extubation of 4.1 h.[45] Therefore, adoption of fast-track techniques may obviate the potential benefits of small-dose IT for CABG surgery.

### *Risk of Central Neuraxial Analgesia for CABG Surgery*

The primary concern with use of central neuraxial analgesia for CABG surgery is the potential for increased risk of spinal hematoma with systemic anticoagulation doses of heparin. No cases of spinal hematoma were reported in the included RCTs for this meta-analysis, but prediction of risk of such a rare complication remains difficult. Current guidelines from American Society of Regional Anesthesia and Pain Medicine estimate the risk of spinal hematoma in noncardiac surgery to be 1:150,000 with epidural anesthesia and 1:220,000 with spinal anesthesia.[50] These guidelines consider the risks and benefits of central neuraxial analgesia in the fully anticoagulated patient for cardiopulmonary bypass to be unclear and do not offer recommendations. The most recent publication using statistical modeling to predict the probability of rare events estimated the risk of a spinal hematoma in patients undergoing full anticoagulation for cardiopulmonary bypass to be 1:1,528 for epidural and 1:3,610 for spinal techniques (based on totals of 4,583 epidural and 10,840 spinal anesthetics reported without complications).[8]

## Conclusion

We could find no difference in rates of mortality or myocardial infarction after CABG. TEA significantly hastens time until tracheal extubation, reduces pain scores, and reduces risk of postoperative dysrhythmias and pulmonary complications. IT significantly hastens time until tracheal extubation when administered in small doses and reduces pain scores. The majority of these benefits may be reduced or eliminated with changing cardiac anesthesia practice using fast-track techniques, use of $\beta$ blockers or amiodarone, and nonsteroidal antiinflammatory analgesics and cyclooxygenase-2 inhibitors for postoperative analgesia. The risk of spinal hematoma due to central neuraxial analgesia in patients undergoing full anticoagulation for cardiopulmonary bypass remains uncertain.

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