Regional Anesthesia Versus General Anesthesia: Is There an Impact on Outcome After Major Surgery?

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The ability of neuraxial blockade, by either epidural or spinal analgesia, to provide excellent analgesia and to suppress some aspects of the stress response to surgery was established in the late 1970s. By 1982 Kehlet was suggesting that the neuroendocrine changes in surgery were detrimental and that obtunding or abolishing these changes could improve outcome (1). In other words, the hormonal and metabolic responses to surgery were an epiphenomenon and no longer necessary for survival in modern surgical practice but may instead be associated with major morbidity and even mortality. This persuasive hypothesis, although without scientific foundation, stimulated considerable research in the succeeding years. Some early small studies supported the notion that regional anesthesia (RA) improved morbidity and mortality. For example, in 1987 Yeager et al. (2) found a statistically significant improvement in mortality and morbidity in high-risk patients undergoing major surgery who received epidural anesthesia and analgesia. The results were so impressive that the study was terminated early because of the important benefits in the epidural patients. Enthusiasts for RA embraced the results with fervor. In 1991 further support for the advantages of epidural anesthesia was found in a study of patients undergoing revascularization of the leg; patients receiving general anesthesia (GA) plus epidural analgesia had improved cardiac morbidity and less early arterial thrombosis than patients receiving GA alone (3). These results were confirmed in 1993 by Christopherson et al. (4), who compared epidural analgesia alone with GA for lower extremity vascular surgery. Although there were no differences in cardiac outcomes, again there was a significant improvement in early graft patency in the RA group. The importance of obtunding the stress response to surgery was seemingly reinforced by a study in which high-dose sufentanil anesthesia was associated with improved mortality in pediatric cardiac surgery (5).

An authoritative review of the role of epidural anesthesia and analgesia in determining postoperative outcome was published in 1995 (6). The authors concluded that the ability of epidural analgesia to alter clinical outcome was unproven. There was, however, some evidence to suggest that perioperative coagulability was decreased with epidural analgesia with a resultant decreased incidence of arterial and venous thromboses. Additionally, there were short-term improvements in gastrointestinal motility (time to pass flatus), but it was unclear whether these benefits would be translated into more rapid functional recovery. Otherwise, evidence for clinically important improvements in morbidity involving other organ systems was insufficient to draw conclusions. Furthermore, they concluded that more studies were needed to determine if a relationship exists between the stress response and postoperative morbidity before the importance of decreasing the stress response with RA can be determined. The purpose of this article is to consider the key studies that have been published since 1995 on the effects of RA on outcome after major inpatient surgery.

Meta-Analyses

Many anesthesiologists hold the view that neuraxial blockade improves respiratory function after abdominal and thoracic surgery and so results in fewer pulmonary complications. Support for this opinion was provided in 1998 by a meta-analysis of randomized controlled trials examining the effects of RA on postoperative pulmonary function (7). Epidural local anesthesia decreased the incidence of pulmonary infections (relative risk [RR], 0.36; 95% confidence interval [CI], 0.21–0.65) and pulmonary complications (RR, 0.58; 95% CI, 0.42–0.80) and increased Pao_2 by 4.6 mm Hg (95% CI, 0.06–9.08) compared with systemic opioids. However, there were no differences, clinical or statistical, in surrogate measures of respiratory function such as forced expiratory volume in 1 s, functional vital capacity, or peak expiratory flow rate, suggesting that these measurements are of little use as predictors, or determinants, of postoperative pulmonary morbidity. The results of this review indicated that postoperative epidural analgesia decreased pulmonary complications but that other regional techniques, such as intrapleural block and intercostal nerve block, were ineffective. It is notable that the

main conclusions were based on a small number of studies with few patients (total, 200–250).

Similar advantages for RA were found in a meta-analysis examining the effect of epidural analgesia on postoperative myocardial infarction (8). Eleven randomized controlled trials of 1173 patients were examined in which epidural analgesia had been continued for more than 24 h after surgery. The epidural patients had better analgesia for the first 24 h after surgery and RA was associated with a lower rate of myocardial infarction that just reached statistical significance ($P = 0.049$). The overall frequency of postoperative myocardial infarction was 6.3%. Subgroup analysis showed that thoracic epidural analgesia was associated with a decrease in infarction compared with systemic analgesia ($P = 0.04$) but that lumbar epidural analgesia had no effect. There was no difference between the groups for the in-hospital death rate.

A comprehensive meta-analysis of the effects of neuraxial blockade, with epidural or spinal analgesia, on postoperative mortality and morbidity was published in 2000 (9). This review assessed 141 trials of 9559 patients and concluded that the overall 30-day mortality was decreased significantly by 30% ($P = 0.006$) by neuraxial blockade (odds ratio [OR], 0.70; 95% CI, 0.54–0.90). Furthermore, there were reductions in the odds of deep vein thrombosis by 44%, pulmonary embolism by 55%, transfusion requirements by 50%, pneumonia by 39%, and respiratory depression by 59% (all $P < 0.001$). At last, there seemed to be clear evidence of an improvement not only in major morbidity, as had already been suggested by previous studies, but even on mortality. The authors concluded that the proportional reductions in mortality did not differ by surgical group, type of blockade (epidural or spinal), or in those trials in which neuraxial blockade was combined with GA compared with trials of neuraxial blockade alone. Unfortunately, in many instances the results do not support these conclusions.

Regional anesthesia only improved mortality in patients undergoing orthopedic surgery and had no effect in patients undergoing general, urological, and vascular surgery. Also the use of GA with neuraxial blockade negated the beneficial effect on mortality of RA alone. Analysis of the type of neuraxial blockade showed that although thoracic epidural and spinal analgesia significantly improved mortality, lumbar epidural analgesia was ineffective.

Close perusal of the studies presented to show improved mortality with RA reveals some interesting anomalies. In those studies in which the overall mortality was low (more than 7000 patients), there were no benefits of neuraxial blockade. Conversely, in the nine trials in which there were more than 10 deaths, in only two studies was RA shown to improve mortality. One of these studies was published in 1982, although most of the results had been presented in 1978, and the GA group had a mortality of 27%. The second study published in 1990 also had a high mortality in the GA group of 18%. If both studies are excluded then the benefits of RA are marginal. Some important issues are raised by this detailed appraisal. The historical nature of many of the trials used in this meta-analysis, with references cited from 1971, must cast doubt on the applicability of the findings in the 21st century. Furthermore, there is obvious distortion in favor of neuraxial blockade by the unusually high complication rate in the GA group in two studies. This is an under-recognized problem, and it is notable that, in the earlier work showing an effect of epidural anesthesia and analgesia on arterial thrombosis after revascularization of the leg, the incidence of early vascular occlusion in the GA groups was 20% (3) and 22% (4). This occlusion rate is twofold to threefold greater than most vascular surgical centers (10).

After a detailed dissection of Rodgers et al.'s review (9) the only tentative conclusion that can be drawn is that neuraxial blockade may improve outcome in orthopedic patients. The beneficial effects on transfusion requirements, deep vein thrombosis, and pulmonary embolism are consistent with earlier studies, but many were undertaken before routine thromboprophylaxis with low molecular weight heparin was introduced. Other studies published at a similar time to the meta-analysis of Rodgers et al. provide little support for the benefits of neuraxial blockade in orthopedic patients. A meta-analysis comparing GA versus RA for hip fracture surgery examined 15 trials of 2162 patients (11). The 30-day mortality was decreased in the RA group—6.4% RA versus 9.4% GA (OR, 0.66; 95% CI, 0.47–0.96) but this was not sustained at 3, 6, and 12 months (OR, 0.91, 1.05, and 1.10, respectively). Neuraxial blockade was associated with a decrease in deep vein thrombosis (OR, 0.41; 95% CI, 0.23–0.72), but this was not matched by a decreased incidence of pulmonary embolism (OR, 0.84), need for transfusion (OR, 1.02), or pneumonia (OR, 0.92). The overall incidence of pulmonary embolism was low, suggesting the widespread adoption of thromboprophylactic measures. More intraoperative hypotension was noted in the RA group (OR, 1.51; 95% CI, 1.12–2.02), a clinical problem not highlighted in previous work. O'Hara et al. (12) conducted a retrospective study of over 9000 patients undergoing repair of hip fracture under RA or GA between 1983 and 1993 and found no effect of the type of anesthetic on 7- and 30-day mortality, myocardial infarction, congestive heart failure, pneumonia, and postoperative mental status. Further studies examining long-term, as opposed to short-term, outcome after RA or GA for hip fracture repair for up to 24 months after surgery also found no differences between spinal and general anesthesia (13,14). Thus, the benefits claimed for RA in orthopedic patients by

Rodgers et al. have not been substantiated by larger studies.

There is no doubt that meta-analysis is a valuable means of combining data from similar studies. There are problems with this technique and these include excessive heterogeneity of patients and treatment, inclusion of older outdated studies, and the initial failure to publish negative studies (15,16). These factors increase the likelihood of finding an effect of treatment. Therefore, there remains the need for large, randomized controlled trials to examine the effects of RA on outcome.

Recent Randomized Controlled Trials

Randomized controlled trials comparing RA with GA for major surgery have failed to demonstrate any useful effect of RA on outcome. A study conducted in United States Veterans Affairs hospitals compared GA intraoperatively and parenteral opioids postoperatively with epidural bupivacaine analgesia and light GA intraoperatively and epidural morphine postoperatively in 1021 patients undergoing intraabdominal aortic, gastric, biliary, or colonic surgery (17). Overall, there was no significant difference in the incidence of death and major complications for up to 30 days after surgery between the groups. The RA group had better pain relief than the GA group and had needed significantly less postoperative analgesia. Subgroup analysis found that for aortic surgery the epidural group had fewer ($P < 0.01$) major complications (cardiovascular complications, respiratory failure, and stroke), but the number of deaths was similar in both groups and there was no difference in duration of hospital stay. The overall mortality rate from aortic surgery was low (9 of 374 patients). These effects were not found in the other surgical groups.

A detailed and complex study also examined the effects of RA in 168 patients undergoing abdominal aortic surgery (18). This double-masked randomized trial compared alternate combinations of intraoperative anesthesia and postoperative analgesia. There were, in essence, four groups: GA and IV patient-controlled analgesia (PCA) postoperatively, RA supplemented GA and IV PCA postoperatively, GA and epidural PCA postoperatively, and RA supplemented GA and epidural PCA postoperatively. Postoperative analgesia was continued for at least 72 h, and strict protocols were used to standardize perioperative medical management and preserve "masking" or blinding. Postoperative outcomes were similar among the four treatment groups with respect to death, myocardial infarction, myocardial ischemia, and renal failure. The only difference observed was a shorter time to tracheal extubation in the epidural PCA group. The in-hospital mortality rate of 5.4% is representative of many vascular surgical units.

The MASTER Anesthesia Trial (Multicenter Australian Study of Epidural Anesthesia) chose deliberately to study high-risk patients (19). The investigators argued that the failure to demonstrate an effect of RA in previous studies may have been the result of a lack of major postoperative complications in relatively healthy patients. Nine hundred and fifteen patients undergoing major abdominal surgery with one or more defined comorbid states were randomly assigned to intraoperative epidural anesthesia with GA and postoperative epidural analgesia for 72 h or a control group of GA and postoperative opioids for analgesia. The co-morbid states were: morbid obesity, diabetes mellitus, chronic renal failure, respiratory insufficiency, cardiac failure, recent acute myocardial infarction, exertional angina, myocardial ischemia, and severe hepatocellular disease. Epidural analgesia resulted in lower pain scores in the first three postoperative days. However, there was no difference in the 30-day mortality rate between the groups and only one major postoperative complication, respiratory failure, occurred less frequently in the RA group (23%) than in the GA group (30%) ($P = 0.02$). The authors concluded that most major postoperative complications in high-risk patients undergoing major abdominal surgery are not decreased by the use of combined epidural and GA and postoperative epidural analgesia for 72 h.

A secondary subgroup analysis of the same data set was published in 2003 and found no difference in outcome between RA and GA in subgroups at increased risk of pulmonary or cardiac complications, or undergoing aortic surgery (20). No differences were found in duration of hospital stay or intensive therapy unit stay. There was no relationship between frequency of use of epidural analgesia in routine practice outside the trial and benefit from RA in the trial. There was no indication that perioperative epidural analgesia significantly influenced serious morbidity and mortality after major abdominal surgery.

Present Position

Although there is some evidence from meta-analyses that there may be benefits from RA on postoperative pulmonary complications, postoperative myocardial infarction, and even mortality, these have mostly not been confirmed by recent randomized controlled trials. These trials have been criticized in terms of their protocol design, evolution and timeliness, and statistical analysis (21). Nevertheless, in most instances the management of epidural anesthesia and analgesia reflected common clinical practice but not necessarily best practice. The lack of generalizability of results derived from complex, highly labor-intensive studies advocated by enthusiasts of RA is a major handicap to their widespread clinical acceptance.

Could the results derived from meta-analyses be misleading? Some of the limitations of meta-analysis have been mentioned above and there is growing awareness of the problems resulting from the inclusion of older, outdated trials. Anesthetic and surgical practices evolve continuously with many small changes occurring concurrently. These include: new shorter-acting drugs, new monitoring standards, routine thromboprophylaxis, patient-care pathways with enhanced recovery, better preoperative assessment and optimization, and rapid mobilization. Specific changes in neuraxial blockade have been much less pronounced in the past 25 yr. It is therefore possible that recent improvements in GA have been sufficient to catch up to the standards set by RA in the 1980s and early 1990s.

Is Kehlet's hypothesis that obtunding the neuroendocrine response to surgery incorrect? There is no doubt that the introduction of laparoscopic and other minimally invasive surgical techniques has enhanced recovery and decreased hospital stay without any major change in anesthesia. Abdominal laparoscopic surgery evokes a similar neuroendocrine response to the same surgery undertaken by laparotomy, but the inflammatory response is markedly decreased (22). The obvious inference is that enhanced recovery is associated with decreased cytokine/inflammatory changes and that the neuroendocrine response does not influence outcome. It is tempting to speculate that in those integrated "packages" designed to achieve rapid recovery such as patient information, epidural anesthesia and analgesia, laparoscopically assisted surgery, early feeding, rapid mobilization and multimodal postoperative analgesia regimens—regional anesthesia has only a minor part to play. There are some data to support the concept that decreasing the size of the inflammatory response to surgical trauma is associated with more rapid recovery after major abdominal and orthopedic surgery (23,24).

Simple preoperative interventions can markedly improve the incidence of postoperative complications (25). Cessation or 50% reduction of cigarette smoking for 6–8 wk before orthopedic surgery resulted in a major complication rate of 18% in the intervention group compared with 52% in the control group ($P = 0.0003$). Wound-related complications decreased significantly from 31% to 5% ($P = 0.001$), cardiovascular complications from 10% to 0% ($P = 0.08$), and duration of hospital stay by 2 days. These are results that RA enthusiasts would be pleased to emulate.

In conclusion, the supposition that RA decreases morbidity and mortality after major surgery remains unproven. Epidural analgesia provides excellent pain relief after surgery, which alone is sufficient to justify its use. The exhortation of de Leon-Casasola in a recent editorial in *Anesthesia & Analgesia* (21) "do not throw away the Tuohy needles and epidural catheters just yet" must be based on the quality of analgesia rather than improved outcome.

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